Organ Blood Flow and Somatosensory-Evoked Potentials During and After Cardiopulmonary Resuscitation With Epinephrine or Phenylephrine

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Pure α-adrenergic agonists, such as phenylephrine, and mixed α- and β-adrenergic agonists, such as epinephrine, raise perfusion pressure for heart and brain during cardiopulmonary resuscitation (CPR). However, with the high doses used during CPR, these drugs may directly affect vascular smooth muscle and metabolism in brain and heart. We determined whether at equivalent perfusion pressure, continuous infusion of phenylephrine (20 μg/kg/min) or epinephrine (4 μg/kg/min) leads to equal organ blood flow, cerebral O₂ uptake, and cerebral electrophysiologic function. During 20 minutes of CPR initiated immediately upon ventricular fibrillation in anesthetized dogs, left ventricular blood flow was similar with epinephrine (45±9 ml/min/100 g) or phenylephrine (47±8 ml/min/100 g) infusion. The ratio of subendocardial to subepicardial blood flow fell equivalently during CPR with either epinephrine (1.23±0.06 to 0.70±0.05) or phenylephrine (1.32±0.07 to 0.77±0.05) administration. At similar levels of cerebral perfusion pressure (44±3 mm Hg), similar levels of cerebral blood flow were measured in both groups (27±3 ml/min/100 g). Cerebral O₂ uptake was maintained at prearrest levels in both groups. Somatosensory-evoked potential amplitude was modestly reduced during CPR, but it promptly recovered after defibrillation. During CPR and at 2 hours after resuscitation, there were no differences between drug groups in the level of regional cerebral or coronary blood flow, cerebral O₂ uptake, or evoked potentials. Therefore, with minimal delay in the onset of CPR and with equipotent pressor doses of phenylephrine and epinephrine, we found no evidence that one agent provides superior coronary or cerebral blood flow or that epinephrine by virtue of its β-adrenergic properties adversely stimulates cerebral metabolism at a critical time that would impair brain electrophysiologic function. Moreover, epinephrine did not preferentially impair subendocardial blood flow as might be expected if it enhanced the strength of fibrillatory contractions. (Circulation 1989;79:1332–1342)

Epinephrine has been the primary choice of pressor agents used during cardiopulmonary resuscitation (CPR), although agents with pure α-adrenergic agonism have also been advocated.1-4 Epinephrine is known to improve blood flow to the heart and brain during external chest compression CPR by elevating perfusion pressure through peripheral vasoconstriction.5,6 Pure α-adrenergic agents also increase arterial pressure,2,3 but whether they increase coronary and cerebral blood flow is unclear.7-9

However, each class of drugs may have other specific effects on heart and brain. For example, α-adrenergic vasoconstriction unopposed by β-adrenergic vasodilation could result in lower coronary and cerebral blood flow with phenylephrine than with epinephrine despite similar increases in arterial pressure with each agent. In addition, agents with β-adrenergic agonism decrease the counter-shock energy required for defibrillation.10 On the
other hand, epinephrine can increase the strength of fibrillatory contractions and myocardial O₂ demand while limiting subendocardial blood flow. In contrast, methoxamine increases the ratio of subendocardial to subepicardial blood flow during open-chest CPR. With regard to the brain, cerebral O₂ demand may also be stimulated by central β-adrenoceptors if sufficient epinephrine crosses the blood-brain barrier. Stimulation of O₂ demand at a time when blood flow is limited could have an adverse effect on recovery, but a recent study contrasting the effects of epinephrine and phenylephrine administration in dogs 9 minutes after fibrillation failed to detect differences in neurologic deficit 24 hours later. However, the limited number of surviving animals largely remained behaviorally impaired at 24 hours, which made it difficult to show that one particular drug had an adverse effect on cortical function.

The purpose of this study was to determine whether equal levels of myocardial and cerebral blood flow would be achieved at equipotent pressor doses of epinephrine and phenylephrine during a 20-minute period of CPR after a short arrest period. We determined whether subendocardial blood flow differed with each pressor and whether myocardial blood flow was adequate for successful cardioversion. In addition, we evaluated whether cerebral O₂ uptake would be maintained at a level critical for normal brain electrophysiologic function as assessed by somatosensory-evoked potentials. At equivalent levels of cerebral perfusion pressure during CPR, we examined whether epinephrine administration increased cerebral O₂ uptake more than phenylephrine administration, and if so, whether this is reflected in differences in somatosensory-evoked potentials during CPR and the immediate, 2-hour postresuscitation period. We used simultaneous compression-ventilation CPR in dogs to generate stable levels of perfusion pressure that are sufficiently high to test for drug specific effects independent of perfusion pressure.

Methods

Preparation

All experiments were performed on large mongrel dogs, ranging in weight from 18 to 23 kg. The dogs were anesthetized with fentanyl (1 mg i.v.) and pentobarbital (195 mg i.v.), then ventilated with a Harvard respirator (S. Natick, Massachusetts) through an endotracheal tube secured by a tracheostomy. Fractional inspired O₂ was 0.3–0.5. Endtidal CO₂ was monitored continuously throughout the prearrest period to maintain arterial CO₂ tension (Paco₂) at 35–40 mm Hg. If the animals began to move, additional anesthetics were administered. Generally, additional doses of fentanyl, 1 mg i.v., and pentobarbital, 65–195 mg i.v., were required during a 2-hour period to maintain a depth of anesthesia adequate for surgery. Saline-filled catheters were advanced through two femoral arteries and one vein into the thoracic aorta, left ventricle, and right atrium, respectively. Catheters were passed through the right axillary artery into the proximal subclavian artery for microsphere withdrawal and through the right axillary vein for infusion of drugs. A catheter was passed into the sagittal sinus with the catheter tip lying 1–2 cm anterior to the confluence of the sinus for sampling cerebral venous blood and for measuring sagittal sinus pressure. A straight ventricular catheter (Cordis, Miami, Florida) was placed through a burr hole into the left lateral ventricle for measurement of intracranial pressure. A 4F pacing catheter was passed into the right heart through a femoral vein to induce ventricular fibrillation. A brass screw was inserted into the skull 1 cm to the right of midline for recording cortical somatosensory-evoked potentials. The reference screw electrode was placed over the left parietal lobe. A needle electrode was placed in apposition to the second cervical vertebrae (C2) to ensure that peripheral nerve transmission remained intact. A stimulating needle electrode was placed under the volar surface of the left foreleg. The left foreleg was otherwise free of surgical manipulation. The threshold required for the stimulating voltage to elicit a motor response from the paw was evaluated. The animal was then paralyzed with pancuronium (0.1 mg/kg). Heparin (4,000 units) was given before cardiac arrest was induced.

Experimental Protocol

Ventricular fibrillation was induced by passing a 60-Hz alternating current through a pacing wire in the right heart. CPR was begun 10 seconds after fibrillation. Animals were randomly assigned to receive either epinephrine or phenylephrine. Epinephrine or phenylephrine was given as a 1-mg bolus into the left ventricle for rapid distribution at the onset of CPR. Central intravenous infusion of epinephrine at the rate of 4 μg/kg/min or phenylephrine at the rate of 20 μg/kg/min both diluted in saline was continued throughout the duration of CPR. The volumetric rate of infusion was 6.8 ml/min in both groups. Epinephrine has a greater affinity for vascular α-adrenergic receptors than phenylephrine. Pilot experiments indicated that the higher dose of phenylephrine consistently produced an arterial pressure equivalent to that of epinephrine. The epinephrine dose is the same as that used previously in dogs. This dose produces high, stable levels of perfusion pressure.

External chest compression was performed over the sternum with a pneumatic chest compressor (Thumper; Michigan Instruments, Grand Rapids, Michigan). The Thumper and ventilator were controlled by a microprocessor. Chest compressions were performed at a rate of 40/minute with a compression duration of 50% of the total cycle time. Compression force was set at 110–120 N to produce a cyclic sternal displacement equivalent to 15–20% of the anteroposterior diameter. Simultaneous ven-
tillation at high airway pressure (75–95 mm Hg) was provided by a pressure-limited ventilator during the first 40% of each cycle. The animals were ventilated with a mixture of 95% O₂ and 5% CO₂ during CPR to prevent hypoxia and to avoid the hypocapnia associated with simultaneous compression-ventilation CPR.

CPR was performed continuously for 20 minutes after fibrillation. At 18 minutes of CPR, sodium bicarbonate (20 meq) was administered into the right atrium. At 20 minutes, cardioversion was attempted with a defibrillator with standard adult chest paddles (Lifepak 6s, Physio-control, Redmond, Washington). Up to five attempts to defibrillate were made at 150–200 W·sec. If the animal could not be resuscitated after five attempts, the animal was considered a failure to resuscitate, and an autopsy was performed. Resuscitation was considered a success if aortic systolic pressure was greater than 75 mm Hg immediately after defibrillation. Ventilation was adjusted to maintain end-tidal CO₂ near normal, and additional sodium bicarbonate was administered if the pH was less than 7.20 with Paco₂ equal to 30–40 torr. The infusion of epinephrine or phenylephrine was slowed incrementally every 1 minute when the mean aortic pressure was greater than 90 mm Hg. With this criterion, the infusion was stopped by 8 minutes after cardioversion in all animals.

**Measurements**

Pressures were recorded from the intrathoracic aorta, right atrium, lateral ventricle, and sagittal sinus with Statham 23Db transducers (Cleveland, Ohio) all referenced to the level of the right atrium. To measure regional blood flow, radiolabeled microspheres were injected before arrest, 7 and 15 minutes after ventricular fibrillation was induced, and 10, 60, and 120 minutes after defibrillation. Arterial and sagittal sinus blood samples were also obtained simultaneously for analysis of blood gases and pH with Radiometer ABL electrodes and analyzer system (Copenhagen, Denmark) corrected for body temperature. Oxygen contents and hemoglobin levels were measured on a CO-Oximeter (Model 282; Instrumentation Laboratory, Lexington, Massachusetts). To measure arterial plasma epinephrine and norepinephrine levels, 5-ml samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and spun, and plasma was stored at −70°C. Samples later underwent an alumina purification procedure before high-pressure liquid chromatography with electrochemical detection for catecholamine analysis.¹⁶

Radiolabeled microspheres (16±0.5 μm diameter; DuPont, Wilmington, Delaware; and New England Nuclear, Boston, Massachusetts) were injected into the left ventricle. Use of microspheres during CPR has been previously validated.¹⁷ The vials of microspheres were dispersed with a vortex mixer and by ultrasonic agitation. Approximately 2.5×10⁶ microspheres were injected before arrest and after defibrillation, and 1×10⁸ microspheres were injected for each CPR measurement. The order of radiolabels (¹⁵³Gd,¹¹⁴In,¹¹⁵Sn,¹⁰³Ru,¹⁰⁹Nb, and ⁸⁶Se) was randomly assigned for each experiment. Reference blood samples were withdrawn from the axillary artery catheter with a syringe pump at a rate of 3.8 ml/min for 2 minutes after the injections were made before arrest and after defibrillation and at a rate of 1.9 ml/min for 5 minutes after the injections were made during CPR. This combination of injection doses and withdrawal rates ensured that there were at least 2,000 microspheres in the reference sample during sinus rhythm and 10,000 microspheres during CPR. Vials of blood and tissue were counted on a multichannel autogamma scintillation spectrometer (Minaxi Model 5200, Packard Instruments, Downers Grove, Illinois). Spectra from pure isotope standards were used to correct the overlap of counts among isotopes in the tissue by the method of simultaneous equations.¹⁸ Tissue blood flow (Qₜ) was calculated from the product of corrected tissue counts (Cₜ) and arterial withdrawal rate (Qₐ) divided by the corrected counts in the reference withdrawal blood sample: (Cₜ)/Qₚ = Cₙ/Cₚ.

Somatosensory-evoked potentials were recorded before arrest at 3-minute intervals during CPR and then after defibrillation at 10-minute intervals for 30 minutes and every 30 minutes thereafter. The left foreleg was stimulated percutaneously under the volar surface at a rate of 5.9/sec with a voltage set at twice motor threshold. Voltages were recorded from spinal cord and cortex electrodes for 80 msec after each stimulus with bandpass filters set at 5 and 1,500 Hz. The sum of 128 responses was averaged for each determination. Duplicate measurements were made before arrest and after defibrillation. Summations of recorded voltage also were made without peripheral stimulation before arrest and during CPR to validate that the generated waves during stimulation were not due to artifact.

At the end of each experiment, postmortem examination was performed to confirm catheter positions. The entire heart and brain were removed, and multiple tissue samples of kidney, jejunum, cephalic muscle, cephalic skin, and tongue were obtained. The heart was cut into left ventricular free wall, interventricular septum, right ventricular free wall, and left and right atria. The left ventricular free wall and interventricular septum were sectioned into three layers, and the right ventricular free wall was sectioned into two layers. The brain was dissected into medulla, pons, midbrain, cerebellum, diencephalon, the primary supply territories of the middle cerebral and posterior cerebral arteries, the watershed areas between the anterior and middle cerebral arteries and between the middle and posterior cerebral arteries, and the residual cerebral hemispheres. Cerebral O₂ uptake was calculated as the product of the arterial-sagittal sinus O₂ content difference and blood flow to the cerebrum.
Statistical Analysis

Vascular pressures, organ blood flows, and blood sample measurements were compared between drug groups by use of two-way analysis of variance having a split-plot design with repeated measures over time within each group. When the F value indicated a significant overall effect of drug treatment or a significant interaction between drug treatment and time, mean values were compared by Duncan’s new multiple-range test. To determine whether there were regional variations in blood flow within brain and heart during the course of the experiment and whether such variations depended on drug treatment, three-way analysis of variance was performed with drug treatment as a between-subject factor and with region and time as within-subject factors. Values are mean±SEM, and the level of statistical significance was set at p<0.05 in all tests.

Results

Seven of 10 animals were successfully defibrillated in the epinephrine group, and eight of 11 animals were successfully defibrillated in the phenylephrine group. Thus, the success rate was 70% in the epinephrine group and 73% in the phenylephrine group (overall success rate was 71%). The number of defibrillation attempts was 3.1±0.6 in the epinephrine group and 2.5±0.5 in the phenylephrine group. None of the resuscitated animals died during the 120-minute postresuscitation period.

Heart

Similar levels of peak and mean aortic pressures were achieved during the chest compression phase of the CPR cycle in the epinephrine and phenylephrine groups throughout 20 minutes of stable CPR in the animals that were successfully resuscitated (Figure 1). During the relaxation phase of the CPR cycle, the aortic-right atrial pressure gradient, which is important for myocardial perfusion, was 26±2 mm Hg in the epinephrine group and 28±3 mm Hg in the phenylephrine group. There was also a modest positive gradient during the chest compression phase of 17±4 mm Hg in the epinephrine group and 10±5 mm Hg in the phenylephrine group.

After defibrillation, aortic systolic blood pressure increased to a maximum level similar in both drug groups; 196±14 mm Hg in the epinephrine group and 220±7 mm Hg in the phenylephrine group. All animals were weaned off drug infusion between 4 and 8 minutes after defibrillation. After weaning and without further blood pressure support, the transient rise in mean aortic pressure remained elevated for a longer duration in the phenylephrine group (Figure 1). By 30 minutes after resuscitation, aortic pressure was no longer significantly higher in the phenylephrine group.

In the six animals that could not be successfully resuscitated, mean aortic pressure (47±4 mm Hg) and the aortic-right atrial pressure gradient during the chest relaxation phase (15±3 mm Hg) were lower at 15 minutes of CPR than that in the two groups that were successfully resuscitated. Moreover, in the nonresuscitated animals, left ventricular free wall blood flow was only 16±5 ml/min/100 g at 15 minutes of CPR.

In those animals that were successfully resuscitated, left ventricular blood flow was 45±9 and 47±8 ml/min/100 g with epinephrine and phenylephrine infusions, respectively (Figure 2). At 10 minutes after resuscitation, blood flow increased by similar amounts in both groups (Figure 2), even though arterial pressure was higher in the phenylephrine group (Figure 1). At 60 minutes, ventricular blood flow returned to prearrest levels in both groups. Mean aortic pressure also returned to prearrest levels, but a sustained tachycardia developed (Table 1). At 120 minutes, blood flow remained at prearrest levels in the phenylephrine group, but it rose in the epinephrine group even though the drug infusion ceased 2 hours before the measurement.
### Table 1. Arterial Blood Analyses and Heart Rate

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Prearrest</th>
<th>Cardiopulmonary resuscitation (min)</th>
<th>Postresuscitation (min)</th>
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<tr>
<td></td>
<td></td>
<td>7</td>
<td>15</td>
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<td>pH</td>
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<td>7.16±0.02*</td>
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<td>PaCO₂ (torr)</td>
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<tr>
<td>1</td>
<td>35±1</td>
<td>34±1</td>
<td>36±2</td>
</tr>
<tr>
<td>2</td>
<td>37±2</td>
<td>35±2</td>
<td>36±2</td>
</tr>
<tr>
<td>PaO₂ (torr)</td>
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<td></td>
<td></td>
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<td>1</td>
<td>194±8</td>
<td>484±11*</td>
<td>450±30*</td>
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<td>2</td>
<td>188±19</td>
<td>430±23*</td>
<td>434±29*</td>
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<td>Hemoglobin (g/dl)</td>
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<td>14.5±0.6*</td>
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<td>2</td>
<td>13.1±0.6</td>
<td>14.2±0.6*</td>
<td>14.1±0.5*</td>
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<td>CaO₂ (ml O₂/dl)</td>
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<td>19.7±0.8*</td>
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<td>17.3±0.9</td>
<td>19.6±0.7*</td>
<td>19.4±0.7*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
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<tr>
<td>1</td>
<td>116±18</td>
<td>118±20</td>
<td>173±9*</td>
</tr>
<tr>
<td>2</td>
<td>128±18</td>
<td>125±15</td>
<td>177±7*</td>
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<td>Norepinephrine (ng/ml)</td>
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<td>0.4±0.1</td>
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<td>Epinephrine (ng/ml)</td>
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<td>436±22*</td>
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</table>

Values are mean±SEM.

PaCO₂ and PaO₂, arterial partial pressure of carbon dioxide and oxygen, respectively; CaO₂, arterial oxygen content.

Drug group 1 received epinephrine; group 2 received phenylephrine.

*p<0.05 from respective prearrest values.

The decrease in left ventricular blood flow during CPR and the hyperemia 10 minutes after defibrillation was more pronounced in the subendocardium than in the subepicardium. Consequently, the ratio of subendocardial to subepicardial blood flow decreased below one during CPR and increased immediately after resuscitation before returning to prearrest levels (Figure 3). These transmural changes occurred in both groups. Although the transmural blood flow gradient was altered, three-way analysis of variance revealed no significant interaction of drug treatment with either transmural region or time or both.

As a percentage of prearrest levels, blood flow was lower during CPR in the left ventricular free wall (62±8%) and interventricular septum (63±9%) than in the right ventricular free wall (104±16%). Right ventricular blood flow was unchanged from 43±7 to 39±7 ml/min/100 g in the epinephrine group and from 38±4 to 36±5 ml/min/100 g in the phenylephrine group. Moreover, a large decrease in the transmural blood flow gradient was not evident in the right ventricle as it was in the left ventricle during CPR (Figure 3). Total flow to the septum decreased similarly in both groups during CPR from 56±4 to 38±8 ml/min/100 g in the epinephrine group and from 75±5 to 46±8 ml/min/100 g in the phenylephrine group. Within the interventricular septum, blood flow decreased more on the left side than on the right side during CPR. Consequently, the transmural gradient seen in the septum with spontaneous circulation was abolished during CPR (Figure 3). Analysis of variance indicated that these effects on transmural septal blood flow were independent of the particular pressor agent. At 10 minutes after resuscitation, blood flow in all myocardial regions

![Figure 3](image-url)
was elevated. In the right ventricle, coronary flow remained elevated for 120 minutes in both groups.

**Brain**

In both drug groups, mean sagittal sinus pressure increased by 14 mm Hg during CPR (Figure 1). This increase in sagittal sinus pressure is equivalent to 35% of the increase in mean right atrial pressure and is in agreement with previous work. After resuscitation, sagittal sinus pressure initially remained elevated for 10 minutes before decreasing to prearrest levels in both groups. Throughout CPR, cerebral perfusion pressure (mean aortic pressure minus sagittal sinus pressure) was 44±3 mm Hg in both groups. At 10 minutes after resuscitation, cerebral perfusion pressure was higher in the phenylephrine group because of the higher mean aortic pressure. Thereafter, cerebral perfusion pressure was equivalent in both drug groups. In half of the animals, intracranial pressure was concurrently measured. Mean intracranial pressure was greater than mean sagittal sinus pressure by 8.6±2.2 mm Hg before arrest, by 2.1±3.6 mm Hg during CPR, and by 5.4±2.6 mm Hg at 120 minutes after resuscitation. Thus, the changes in sagittal sinus pressure tracked the changes in intracranial pressure, and sagittal sinus pressure closely approximated the downstream pressure for cerebral perfusion pressure calculations in these experiments.

Prearrest cerebral blood flow was 32±4 and 31±3 ml/min/100 g in the epinephrine and phenylephrine groups, respectively. During CPR, cerebral blood flows in the two groups were similar, averaging 27±2 and 23±2 ml/min/100 g, respectively. When the animals that were not eventually resuscitated are included in this comparison, likewise, cerebral blood flow between the epinephrine (25±2 ml/min/100 g) and phenylephrine (22±2 ml/min/100 g) groups were similar. Ten minutes after defibrillation, cerebral blood flow increased to 41±7 ml/min/100 g in both groups and then decreased to prearrest levels by 60 minutes after resuscitation (Figure 4). Blood flow to thalamus, cerebellum, and brain stem regions generally followed the same pattern as the blood flow in the cerebrum during CPR and after resuscitation. Hypoperfusion occurred 60 minutes after resuscitation in all of the individual regions of the epinephrine-treated group. However, analysis of variance indicated no significant interaction of drug treatment on these temporal changes in regional cerebral blood flow. Moreover, blood flow to watershed regions bordering the primary supply regions of major cerebral arteries was not selectively impaired during CPR in either group.

Cerebral O₂ extraction increased during CPR to maintain cerebral O₂ uptake at prearrest levels (Figure 4). Cerebral O₂ extraction declined when cerebral blood flow increased at 10 minutes after defibrillation, again maintaining cerebral O₂ uptake. Thus, cerebral O₂ uptake remained unchanged at all time points. There were no significant differences of either O₂ extraction or uptake between drug groups at any time point.

**Evoked Potentials**

Somatosensory-evoked potentials were recorded sequentially during CPR and after resuscitation (Figure 5). High-quality waves were obtainable during CPR because the peripheral nerve stimulation rate was out of phase and not a harmonic frequency of the chest compression rate and because screw electrodes were secured in the skull with the muscle retracted to minimize motion artifact. The example in Figure 5 illustrates that when the peripheral nerve is not stimulated, the summation of 128 epochs of 80 msec at a rate of 5.9/sec averages out to a flat line. This indicates the lack of synchronous artifact.

Baseline latency to the peak of the negative cortical wave (N1) was 21.0±0.6 and 20.8±0.7 msec in the epinephrine and phenylephrine animal groups, respectively. During CPR, cortical wave latency increased by 11% in the epinephrine group and by 10% in the phenylephrine group and then returned to baseline levels by 1 hour after resuscitation in both groups (Figure 6). Latency to C2 spinal cord was not significantly changed throughout the experiment. Amplitude as a percentage of baseline was reduced as much as 30% at 15 minutes.
in the epinephrine group but not significantly in the phenylephrine group (Figure 6). However, analysis of variance indicated no interaction with drug treatment. In addition, the wave was not flat in any animal. After defibrillation, amplitude returned to prearrest levels.

Other Organs

Blood flow to cephalic muscle, cephalic skin, tongue, jejunum, and kidney decreased proportionately more than blood flow to brain and heart during CPR in both drug groups (Table 2). After resuscitation, jejunal blood flow returned to prearrest levels, whereas renal blood flow remained depressed. Cephalic and abdominal organ blood flow responses during CPR and after resuscitation were similar between drug groups.

Blood Analyses

There were no significant differences between animal groups with respect to arterial pH, PaCO₂, PaO₂, O₂ content, or hemoglobin level (Table 1).

Paco₂ was maintained constant during the experiment in both groups by adding CO₂ to the inspired gas during CPR and by adjusting the ventilator after defibrillation. Arterial pH decreased during CPR and then returned to prearrest levels by 120 minutes after resuscitation in both groups. Cumulative doses of 2.2±0.4 and 2.3±0.2 meq/kg sodium bicarbonate were given in the epinephrine and phenylephrine groups, respectively. All animals were hyperoxic during CPR due to the increased inspired oxygen and were normoxic throughout the postresuscitation period. Arterial O₂ content and hemoglobin concentration increased during CPR and returned to prearrest levels after resuscitation. Arterial plasma epinephrine levels increased two and a half orders of magnitude when epinephrine was infused; levels were higher at 7 minutes than at 15 minutes of CPR (Table 1). When phenylephrine was infused, epinephrine and norepinephrine increased by approximately one-half order of magnitude.

Discussion

There are several major findings of this study. First, phenylephrine produces high levels of myocardial blood flow equivalent to that attained with epinephrine when the perfusion pressure generated

FIGURE 5. Tracings of somatosensory-evoked potentials from one representative animal (treated with epinephrine) before arrest, at 4, 8, and 16 minutes of cardiopulmonary resuscitation (CPR), and at 4, 10, 30, and 120 minutes after resuscitation. Latency was measured to the first negative wave (N1) (negative voltage is upward). Vertical dashed line is a reference for control N1 latency. Amplitude of the primary cortical wave complex was measured from the first positive wave deflection (P1) to the peak of N1. Waveform collected during CPR without foreleg stimulation shows lack of artifact.
during 20 minutes of CPR is equivalent. The corresponding success rate of cardiac resuscitation depended on the level of blood flow attained and not on the particular pressor agent. Second, alterations in the transmural gradient of myocardial blood flow seen during CPR in fibrillating hearts are not specific for epinephrine but also occur when phenylephrine is used as the pressor agent. Third, at equivalent cerebral perfusion pressures during CPR, high-dose epinephrine does not increase cerebral \( O_2 \) uptake or cerebral blood flow compared with phenylephrine when the initial duration of ischemia is short. Fourth, the level of cerebral blood flow and \( O_2 \) uptake was sufficient to restore somatosensory-evoked potentials at near-control values after the onset of ventricular fibrillation and after defibrillation.

We used the simultaneous compression-ventilation mode of CPR because high levels of intrathoracic pressure can be generated\(^{17}\) that result in levels of perfusion pressure that are sufficiently high to test for specific effects of each pressor agent on vital organ perfusion, brain metabolism, and electrophysiologic function independent of perfusion pressure. With conventional CPR in dogs, perfusion pressures are too low to test for such effects.\(^5\) With conventional CPR in pigs, the other commonly used species for experimental CPR studies, perfusion pressures are not stable and rapidly decay.\(^{21}\) Whether or not the heart is directly compressed with conventional CPR in humans, large cyclic variations in intrathoracic vascular pressures occur on both the arterial and venous sides of the circulation.\(^{22,23}\) Thus, the characteristics of the arterial and venous pressure variations seen by cerebral and coronary vessels are not grossly dissimilar from those produced by simultaneous compression-ventilation CPR in dogs. We believe that the present results are of some relevance for establishing any potential drug-specific effects directly on brain and heart in the presence of large arterial and venous pulse pressures typical for external CPR and in a model with stable vascular pressures. However, because CPR was begun within 10 seconds of cardiac fibrillation and pressor agents were infused immediately, brain and heart were not rendered completely ischemic. Therefore, potential differences between agents in their direct effects on heart and brain cannot be excluded for the more clinically relevant situation of delayed CPR.

Epinephrine infusion has previously been shown to produce selective vasoconstriction in noncerebral, peripheral vascular beds and thereby to maintain higher aortic pressures for perfusing the heart and brain for prolonged periods. When no pressor agent was infused, arterial pressure declined while CPR was prolonged, and consequently, coronary and cerebral blood flow eventually fell to low levels.\(^6\) Phenylephrine, with its \( \alpha \)-agonist properties, would be expected to be as effective as epinephrine during CPR.\(^4\) In the present study, we found that high, stable levels of arterial pressure can be sustained with continuous infusion of phenylephrine. Moreover, the high level of myocardial and cerebral perfusion and low level of abdominal visceral and noncerebral cephalic perfusion were equivalent with phenylephrine and epinephrine. Thus, our data support the premise that epinephrine benefits cerebral and myocardial perfusion by \( \alpha \)-adrenergic vasoconstriction of noncerebral peripheral vascular beds, thereby raising perfusion pressure for heart and brain.

Our results differ from recent studies that showed higher cerebral blood flow with epinephrine compared with phenylephrine or methoxamine administration during conventional CPR in pigs.\(^8,9\) The experimental protocol in those studies differed from the present study in that a longer ischemia time of 10 minutes occurred before commencing CPR. In addition, drugs were administered as a bolus, and blood flow was measured 1 minute later during the transient blood pressure change. The low cerebral blood flow achieved with either 0.2 mg/kg\(^{24}\) or 1 mg/kg\(^8\) phenylephrine compared with 0.02 mg/kg epinephrine\(^{25}\) is probably due to the lower aortic pressure with these doses of phenylephrine. When a higher dose of 10 mg/kg phenylephrine was used,\(^8\) aortic pressure and cerebral blood flow were similar to that of 0.2 mg/kg epinephrine, although the actual level of cerebral blood flow was only 8 ml/min/100 g. We also used a greater milligram per kilogram dose of phenylephrine than epinephrine. However, the cumulative dose that our animals received dur-

### Table 2. Blood Flow to Other Organs

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Prearrest</th>
<th>Cardiopulmonary resuscitation (min)</th>
<th>Postresuscitation (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
<td>383±38</td>
<td>4±2*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>399±55</td>
<td>14±4*</td>
</tr>
<tr>
<td>Jejunum</td>
<td>1</td>
<td>26±2</td>
<td>2±1*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>27±3</td>
<td>7±1*</td>
</tr>
<tr>
<td>Cephalic muscle</td>
<td>1</td>
<td>6.9±1.7</td>
<td>1.6±0.6*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.0±0.6</td>
<td>1.0±0.2*</td>
</tr>
</tbody>
</table>

Values are mean±SEM expressed as ml/min/100 g. Drug group 1 received epinephrine; group 2 received phenylephrine.

\(^*p<0.05\) from respective prearrest values.
ing the 20-minute CPR period was only 0.13 mg/kg epinephrine and 0.45 mg/kg phenylephrine, yet the level of cerebral blood flow was three times higher in our study. Differences in conclusions between us and Brown et al.24 on whether epinephrine provides superior vital organ perfusion may be related to differences in the animal model and experimental protocol.

Our observation that the success rate for defibrillation is equivalent with epinephrine and phenylephrine agrees with the work of others.2-4 Left ventricular blood flow at 15 minutes of CPR was less than 21 ml/min/100 g in five of the six animals not successfully resuscitated and greater than 19 ml/min/100 g in 13 of the 15 animals that were resuscitated. Therefore, data with both drugs are consistent with previous work showing a 20 ml/min/100 g threshold for successful resuscitation when the heart is not stunned by a delayed onset of CPR.

The ratio of left ventricular subendocardial to subepicardial blood flow fell below one during CPR. The left to right transmural blood flow ratio in the interventricular septum also decreased. These decreases were reversed after resuscitation. Because no differences were seen between drug groups, these decreases were not likely to be due to a β-agonist effect of epinephrine infusion. In support of this conclusion, Downey26 found that isoproterenol infusion did not affect the decrease in the endocardial to epicardial blood flow ratio during fibrillation in maximally dilated, constant-perfused coronary bed. However, this conclusion differs from that of Livesay et al.11 who reported lower ratios with epinephrine than with methoxamine when open-chest cardiac massage was applied or when cardiopulmonary bypass was instituted. The reason for this different conclusion is unclear other than mechanical differences in the way perfusion pressure was generated. It is possible that in patients with restricted subendocardial flow reserve, transmural flow differences between drugs would be manifested.

In contrast to the left ventricle, the subendocardial to subepicardial blood flow ratio in the right ventricle did not decrease during CPR, and blood flow to the right side of the septal wall did not decrease as much as that to the left side. Elevation of ventricular pressure impairs subendocardial flow in both fibrillating and nonfibrillating hearts.26,27 Differences in right and left chamber pressures may contribute to differences in transmural blood flow during CPR independently of the type of agent used to elevate aortic pressure.

During the first 10 minutes after defibrillation, mean aortic pressure was greater in the phenylephrine group. Although drug infusion had been discontinued, a longer circulating half-life of phenylephrine may have accounted for the transient hypertension. Unexpectedly, left ventricular blood flow was not correspondingly higher in the phenylephrine group. Whether metabolic demand was equivalent in the two groups at this time or whether α-adrenergic coronary vasoconstriction with phenylephrine was competing with metabolic vasodilation cannot be ascertained from these experiments.

In brain, we found no statistical evidence for an interaction of drug treatment with blood flow, O2 uptake, or electrical function. We postulated that epinephrine or phenylephrine could have direct effects in the brain if they gain access across the blood-brain barrier. Disruption of the barrier could occur from the large pulsation of cerebral venous and arterial pressures during chest compression or to the surge of arterial pressure in a maximally dilated bed after ventricular defibrillation.28 In this case, phenylephrine may cause vasoconstriction and decrease cerebral blood flow. Epinephrine may vasoconstrict or vasodilate cerebral vessels depending on the balance between α- and β-adrenergic effects.29 In addition, epinephrine may stimulate cerebral O2 uptake by its β-agonist activity.12,13 Under conditions of this experiment in which cerebral ischemia was very brief at the onset of ventricular fibrillation, we found that epinephrine had a similar effect on cerebral blood flow and O2 uptake compared with phenylephrine. With a longer delay in the onset of CPR and consequent cerebral ischemia, the blood-brain barrier may be more prone to disruption, and significant amounts of high circulating adrenergic agonists may gain access to the brain. Also, cerebral O2 uptake may have transiently increased at the start of CPR by a β-adrenergic mechanism before the first measurement was made at 7 minutes.

This is the first study in which somatosensory-evoked potentials were measured during the CPR period itself. Evoked potentials rapidly disappear after cardiac arrest. We determined whether the level of cerebral blood flow generated with each pressor drug was adequate to restore brain electrophysiologic function. We found some prolongation of somatosensory-evoked potential latency in both groups during CPR, but the waves were not flat in any animal, and they rapidly normalized after return of spontaneous circulation. Somatosensory-evoked potentials become depressed when cerebral blood flow falls below 20 ml/min/100 g during graded focal ischemia, or in the case of hypoxia, when cerebral O2 uptake falls.30,31 In addition, metabolism in subcortical white matter can be selectively disturbed in particular models of incomplete cerebral ischemia and thereby influence somatosensory-evoked potentials.32 Thus, the increased central conduction time we observed may reflect incomplete restoration of white matter metabolism after the brief transient ischemia that occurred before commencing CPR. After resuscitation, evoked potentials rapidly normalized, and any subtle effects of a particular drug treatment on regional flow and metabolism did not appreciably affect cortical electrophysiologic function.
In conclusion, a number of important aspects of CPR have been elucidated in this study. We have shown that phenylephrine in sufficient doses can be as effective as epinephrine in generating adequate myocardial and cerebral blood flow. The high level of myocardial blood flow achieved with either drug was associated with successful defibrillation after 20 minutes of continuous CPR. Left ventricular subendocardium was underperfused relative to the subepicardium during CPR, but this transmural gradient did not depend on the particular pressor agent. The high level of cerebral blood flow achieved during CPR maintained cerebral O₂ uptake at pre-arrest levels with either pressor agent. Conduction of somatosensory-evoked potentials was slowed somewhat during CPR, but it rapidly returned with the restoration of spontaneous circulation. The rapid normalization of evoked potentials indicates that somatosensory cortex did not suffer an irreversible functional insult. Therefore, we did not find any evidence that epinephrine or phenylephrine is superior to the other agent in overall cerebral metabolism, cerebral function, or hemodynamic stability in normal dogs when complete myocardial and cerebral ischemia was avoided by rapidly applied CPR.

Acknowledgments
We thank Dr. Robert McPherson for his assistance in the interpretation of somatosensory-evoked potentials, Dr. Kenneth Kubos for running the high-performance liquid chromatography assays, Karen Dwyer for her expert technical assistance, and Ms. Nikki Womer for her fine secretarial assistance in preparing the manuscript.

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KEY WORDS • cerebral blood flow • cerebral oxygen consumption • coronary blood flow • dogs
Organ blood flow and somatosensory-evoked potentials during and after cardiopulmonary resuscitation with epinephrine or phenylephrine.
C L Schleien, R C Koehler, H Gervais, I D Berkowitz, J M Dean, J R Michael, M C Rogers and R J Traystman

_Circulation_. 1989;79:1332-1342
doi: 10.1161/01.CIR.79.6.1332

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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