Intrapulmonary Epinephrine During Prolonged Cardiopulmonary Resuscitation: Improved Regional Blood Flow and Resuscitation in Dogs

Sandra H. Ralston
William D. Voorhees
Charles F. Babbs

Purdue University, babbs@purdue.edu

Follow this and additional works at: http://docs.lib.purdue.edu/bmepubs

Part of the Biomedical Engineering and Bioengineering Commons

Recommended Citation
http://docs.lib.purdue.edu/bmepubs/110

This document has been made available through Purdue e-Pubs, a service of the Purdue University Libraries. Please contact epubs@purdue.edu for additional information.
Intrapulmonary Epinephrine During Prolonged Cardiopulmonary Resuscitation: Improved Regional Blood Flow and Resuscitation in Dogs

Sandra H Ralston, RN, PhD
William D Voorhees, PhD
Charles F Babbs, MD, PhD

Biomedical Engineering Center and School of Veterinary Medicine, Purdue University, West Lafayette, Indiana, USA.

ABSTRACT

Blood flow to vital organs was measured at five-minute intervals during 20 minutes of cardiopulmonary resuscitation (CPR) and ventricular fibrillation in two groups of anesthetized dogs (n = 15 per group). The relationship between organ blood flow and restoration of circulation after 20 minutes was assessed with no additional treatment in Group I and with intrapulmonary epinephrine in Group II. Cardiac output and organ blood flow did not vary significantly in Group I. In Group II, intrapulmonary epinephrine significantly improved blood flow to the myocardium, the brain, and the adrenal glands. A mean myocardial blood flow of less than 0.13 mL/min/g resulted in no survival, while a flow of greater than 0.16 mL/min/g resulted in survival. These studies show that a critical level of myocardial blood flow is required to restore ability of the heart to function as a pump after prolonged CPR, and that a drug that increases flow improves resuscitation efforts.

Key words: cardiopulmonary resuscitation, epinephrine, intrapulmonary, CPR, survival

INTRODUCTION

Survival following prolonged cardiopulmonary arrest remains poor despite the evolution of organized basic and advanced life support. Currently only about one-third of out-of-hospital victims respond to initial resuscitation efforts, while fewer than one-fifth survive long enough to leave the hospital. When cardiopulmonary resuscitation (CPR) is initiated within four minutes and when advanced life support is administered within eight minutes after cardiovascular arrest, long-term survival approaches 43%. Because survival is inversely related to the duration of CPR, it is possible that CPR becomes progressively less effective in providing artificial circulation to vital organs during prolonged periods of arrest. The first phase of this two-phase study was designed to measure blood flow to vital organs during prolonged CPR in dogs and to assess the relationship of organ blood flow to "resuscitability," the ease with which spontaneous circulation is restored.

The second phase of the study was designed to determine whether the observed pattern of regional blood flow during CPR could be altered favorably by drug therapy. Recent reports suggest that coronary flow is unacceptably low during CPR and that blood flow to the myocardium is more compromised than is the flow to the brain. One means of improving coronary flow is suggested by the work of Holmes et al, who showed that epinephrine triples coronary perfusion during CPR, perhaps through its combined alpha and beta adrenergic effects that lead to peripheral vasoconstriction, coronary vasodilatation, and increased diastolic arterial pressure. Accordingly, the second phase of this study tested the effectiveness of intrapulmonary epinephrine in improving coronary blood flow. The intrapulmonary route was selected as a convenient means of prolonging the duration of action of epinephrine.

METHODS

Animal Preparation

Thirty mongrel dogs of either sex, weighing 6.5 to 19 kg (mean, 11.2 kg) were studied in two sequential groups of 15 dogs each. They were anesthetized with pentobarbital sodium (30 mg/kg, IV) and intubated with the largest possible cuffed endotracheal tube. Intravascular catheters were inserted into the left ventricle for injection of microspheres; the left femoral artery for withdrawal of blood samples to calibrate regional blood flow measurements; the right brachial artery to monitor systemic arterial pressure; and the right atrium to monitor central venous pressure. Catheter tip position was confirmed by pressure recordings during placement and by pressure recordings and/or postmortem examination after the experimental procedure. Heparin (1 mg/kg, IV) was given to retard intravascular coagulation induced by the catheters or by blood stasis during CPR. Animals were placed in dorsal recumbency on a V-shaped board, and the limbs were firmly anchored to prevent lateral movement of the thorax during the procedure.

Physiologic monitoring was done on a Physiograph recorder (Narco Biosystems). Four channels of data were recorded: ECG lead II, brachial artery pressure, central venous pressure, and electrical impedance of withdrawn blood.
Fig. 1. Blood pressure response to epinephrine administered via the airways during ventricular fibrillation and CPR. (A) Epinephrine (0.2 mg/kg diluted in 10 mL saline) injected through the endotracheal tube into the trachea (arrow). (B) Epinephrine (0.1 mg/kg diluted in 10 mL saline) injected deep into the bronchial tree (arrow).
Fig. 2. Mean cardiac output at 5-minute intervals during 20 minutes of CPR in Group I (untreated) and Group II (intrapulmonary-epinephrine-treated) anesthetized dogs.

CPR Equipment

CPR was performed using a mechanical chest compressor and ventilator (Thumper®, Michigan Instruments, Inc). This instrument was powered by compressed oxygen, which served also as the ventilation gas. A 10- by 6-cm chest compression pad was positioned midline on the sternum 1 to 2 cm cranial to the xiphisternal junction. The pad was covered with a wire mesh, which served as one electrode for defibrillation. The second electrode was a V-shaped wire mesh placed under the shaved back of the animal. Both electrodes were covered with a low-resistance gel.

American Heart Association (AHA) standard CPR was used in these studies. The chest was compressed at a rate: of 60/min and the compression phase lasted 50% of each cycle. The force and pad placement were adjusted initially in each animal to maximize the end diastolic arteriovenous pressure difference. This pressure, which reflects the myocardial perfusion pressure, was convenient for on-line assessment. In these animals, the force ranged from 30 to 90 lb and, once set, remained constant throughout the experiment. Ventilation was interposed after every five chest compressions with a pressure of 20 cm H₂O.
**Microsphere Technique**

Radioactively labeled polystyrene microspheres (3M Co) with a mean diameter of $15 \pm 0.3 \, \mu m$ were used to determine regional blood flows and cardiac output during CPR according to the method of Heymann$^{11}$ as modified for CPR studies by Voorhees and coworkers.$^{12}$ Microspheres impregnated with one of four different gamma-emitting radionuclides ($^{141}\text{Ce}$, $^{85}\text{Sr}$, $^{95}\text{Nb}$, and $^{46}\text{Sc}$) and suspended in a 10% Dextran solution permitted determinations at four different times during the procedure.

One milliliter of a well-mixed microsphere suspension, containing approximately $5 \times 10^5$ microspheres, was injected into the left ventricle, followed by a 10-mL saline flush. Mixing of microspheres with the blood was aided by forcible injection of the microsphere suspension through the eight side holes near the distal end of the catheter. Simultaneously a reference blood sample from the lower abdominal aorta was collected with a motor-driven syringe at a constant flow rate (7.3 mL/min). Passage of the microspheres into the periphery was inferred by monitoring electrical impedance changes (caused by the saline flush solution) in the arterial blood passing into the motor-driven syringe. One could have confidence that when the impedance change due to the saline flush returned to baseline, a sampling from the entire microsphere injection had been collected. Sampling duration ranged from 2.5 to 3 minutes in these animals. At this time, the motor-driven syringe was turned off, the reference organ blood sample was preserved for counting, and an equal volume of lactated Ringer's solution was injected intravenously to maintain blood volume.

At the termination of the experiment, the animals were euthanized by fibrillation of the ventricles. Whole organ samples were removed, including the brain, heart, kidneys, adrenals, pancreas, and spleen, as were samples from the small intestine. These were placed in small plastic vials and the radioactivity measured in counts per minute (CPM) was obtained from a Beckman 8000 gamma spectrophotometer. Stripping of radioactivity resulting from the overlap of one nuclide on another was accomplished using a system of simultaneous equations.$^{12,13}$ Blood flow to the organs was then calculated from the following ratio:

$$\frac{\text{Organ Blood Flow (mL/min)}}{\text{Organ Activity (CPM)}} = \frac{\text{Reference Organ Blood Flow (mL/min)}}{\text{Reference Organ Activity (CPM)}}$$

By dividing the organ flow by its weight, the flow in mL/min/g was obtained. In a similar manner, cardiac output was determined from the ratio:

$$\frac{\text{Cardiac Output (mL/min)}}{\text{Total Activity Injected (CPM)}} = \frac{\text{Reference Organ Blood Flow (mL/min)}}{\text{Reference Organ Activity (CPM)}}$$
The cardiac output was divided by the weight of the animal and reported as mL/min/kg.

The accuracy of the microsphere technique was assessed under these low-flow conditions. First, blood flows to right and left paired organs were compared as a check of the uniformity of mixing of the microspheres with the blood. Second, cardiac output was calculated using microspheres and compared with the values obtained using the saline indicator dilution method.\textsuperscript{14}

Fig. 3. Mean tissue flows during 10 to 20 minutes of CPR to heart (HRT), brain (BRN), kidney (KID), adrenal (ADR), pancreas (PANC), spleen (SPL), and small intestine (SI). Each bar represents mean ± SE of pooled measurements made at 10, 15, and 20 minutes after onset of VF and CPR. With the exception of small intestine blood flow, all differences between Groups I and II are significant.
Experimental Protocol

The experiment began with a preliminary trial of ventricular fibrillation (VF) followed by immediate onset of CPR. Fibrillation was induced with 60 Hz electrical stimulation through the left ventricular catheter. During this brief trial period of less than two minutes, the Thumper® pad position and force of chest compression were adjusted to achieve a maximum diastolic arteriovenous pressure difference. The ventricles were defibrillated and blood pressure was allowed to recover to prefibrillation levels.

Ventricular fibrillation was again induced and confirmed by observation of the electrocardiogram and arterial blood pressure. After 30 seconds of documented VE mechanical CPR was begun for a period of 20 minutes, during which time the settings of the Thumper® were not changed. During this period radioactively labeled microspheres were injected at 5, 10, 15, and 20 minutes. The 15 animals in Group I received no supportive drugs. The 15 animals in Group II received intrapulmonary epinephrine (0.1 mg/kg diluted in 10 mL saline) at seven and 17 minutes after onset of VF and CPR.

Fig. 4. Organ blood flows at 5-minute intervals during 20 minutes of CPR in Group I (control) and Group II (epinephrine-treated) dogs. (Arrows indicate epinephrine injection. [*] Indicates statistical significance, P < 0.05.)
Intrapulmonary Epinephrine Technique

The deep intrapulmonary route was selected, rather than the endotracheal route reported by Greenberg\textsuperscript{15}, because pilot studies showed that epinephrine given by the endotracheal route, although effective when the heart was beating normally, was ineffective when administered during CPR (Figure 1). Intrapulmonary drug injection was done with a Swan-Ganz catheter. This catheter, with its balloon inflated to a diameter of 10 mm, was inserted through the endotracheal tube to a wedge position deep in the bronchial tree. Insertion of the catheter with its balloon already inflated eliminated the risk of puncturing the visceral pleura. With the balloon in the wedge position, epinephrine was rapidly injected through the catheter lumen.

Chest compressions were interrupted for a few seconds while the drug was being injected, after which three full maximal ventilations were blown through the endotracheal tube in rapid succession to help distribute the drug. Standard CPR was then resumed. To determine the effects of fluid in the lungs on gas exchange, arterial blood gases were drawn in the drug treated animals prior to fibrillation, and at 2, 8, 13, and 18 minutes after VF.

![Graph](image)

Fig. 5. Heart blood flow as a function of mid-diastolic arteriovenous pressure difference in Group I (control) and Group II (epinephrine-treated) animals. $S_{y,x}$ for Group I = 0.09 and for Group II = 0.13 ($P < .01$). There are four data points for each animal representing blood flow measurements at 5-minute intervals during 20 minutes of CPR.
Assessment of Resuscitability and Short-Term Survival

After 20 minutes of VF and CPR, defibrillation was accomplished using shocks ranging from 25 to 110 joules stored energy. Animals were grouped into three classes according to the efforts required for their resuscitation. Short-term survival was defined as return of pulsatile blood pressure for a period of at least 20 minutes after defibrillation. Class A (easy to resuscitate) animals regained spontaneous pulsatile blood pressure and respirations following electrical defibrillation alone. Class B (difficult to resuscitate) animals required some adjunctive therapy before pulsatile blood pressure returned. The protocol of adjunctive therapy included repeated defibrillation shocks with increasing shock strengths until defibrillation was achieved. When blood pressure pulses were weak or absent, additional chest compressions were administered. Following recommended AHA standards, drugs were injected into the left ventricle for electromechanical dissociation or asystole, including epinephrine (0.1 mg) which was repeated in larger doses as necessary, sodium bicarbonate (1 mEq/kg), and lidocaine (1 mg/kg). As a last resort, in some animals, calcium chloride (15 mg) was given. The animals in Class B recovered their circulatory function and survived. Class C (impossible to resuscitate) animals received all adjunctive therapy but did not recover circulatory function.
**Statistical Analysis**

Duncan's multiple range test was used to assess time-dependent changes in blood flow during CPR alone versus CPR with epinephrine. An unpaired Student's t test was used to compare variables between groups. When necessary, a logarithmic transformation of the data was performed before statistical tests were done to satisfy the assumptions of normality and homogeneity of variance. A P-value of < 0.05 was considered significant.

**RESULTS**

**Cardiac Output**

Cardiac output after five minutes of CPR averaged 26.7 ± 3.9 (SE) mL/ min/kg in Group I and 24.5 ± 3.6 mL/min/kg in Group II. Cardiac output did not vary significantly throughout the experiment in either animal group. However, in Group II (epinephrine treated), cardiac output tended to decrease following epinephrine injections at seven and 17 minutes (Figure 2). All animals with cardiac output greater than 30 mL/min/kg in Group I or 15 mL/min/kg in Group II survived for at least 20 minutes after defibrillation.

**Organ Blood Flow**

After five minutes of CPR and VF, organ blood flow did not differ significantly between animal groups. The blood flow to various organs is depicted (Figure 3). Each bar represents the average of three blood flow measurements at 10, 15, and 20 minutes after initiation of CPR and VF for animals in each group. Intrapulmonary epinephrine dramatically reduced blood flow to the kidneys and gastrointestinal tract, while improving heart, brain, and adrenal blood flow.

Changes in blood flow to vital organs over time are illustrated (Figure 4). In Group I, blood flow to the kidneys, brain, adrenals, and heart in the 15 animals did not vary significantly during the 20-minute period. In Group II, intrapulmonary epinephrine effectively increased perfusion of the heart, brain, and adrenal glands and decreased perfusion of the kidneys. Myocardial blood flow was correlated with the diastolic arteriovenous pressure difference in both animal groups (Figure 5). Diastolic pressures measured at the midpoint of the release phase of each cycle reflected the mean perfusion pressure for the coronary vasculature. Correlation coefficient (r) was 0.89 for the Group I (control) animals, and 0.85 for the Group II (epinephrine-treated) animals. In these studies, when mean diastolic arteriovenous pressure difference was greater than 15 mm Hg the animals survived; when this pressure was greater than 30 mm Hg, circulation was restored spontaneously following defibrillation.

Blood pressures before and during the experimental procedure are presented (Table 1). With only one exception, pressures in Group I did not vary significantly from Group II. During the pre-experimental trial fibrillation, systolic arterial pressures in Group I were greater than in Group II (P < 0.05).
Table 1: Hemodynamic data

<table>
<thead>
<tr>
<th></th>
<th>Beating Heart</th>
<th>Trial Fibrillation</th>
<th>5 Min CPR</th>
<th>10 Min CPR</th>
<th>15 Min CPR</th>
<th>20 Min CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I (Untreated)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial artery (Compression)</td>
<td>133.6 ± 10.0</td>
<td>58.53 ± 2.0*</td>
<td>66.9 ± 6.7</td>
<td>64.6 ± 7.7</td>
<td>64.3 ± 7.6</td>
<td>61 ± 7.6</td>
</tr>
<tr>
<td>Brachial artery (Release)</td>
<td>94.5 ± 7.8</td>
<td>17.47 ± 1.9</td>
<td>19.9 ± 3.2</td>
<td>21.1 ± 3.3</td>
<td>19 ± 3.1</td>
<td>16.7 ± 2.9</td>
</tr>
<tr>
<td>Right atrium (Compression)</td>
<td>2.13 ± 1.1</td>
<td>55.07 ± 8.3</td>
<td>75.6 ± 8.1</td>
<td>76 ± 8.4</td>
<td>74.3 ± 7.8</td>
<td>74.7 ± 7.8</td>
</tr>
<tr>
<td>Right atrium (Release)</td>
<td>-0.93 ± 0.4</td>
<td>1.47 ± 0.9</td>
<td>2.3 ± 0.8</td>
<td>2.6 ± 1.0</td>
<td>2.1 ± 0.8</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td><strong>Group II (Treated)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial artery (Compression)</td>
<td>136 ± 7.1</td>
<td>48.93 ± 2.6*</td>
<td>56 ± 5.0</td>
<td>69.7 ± 6.7</td>
<td>65.7 ± 5.1</td>
<td>71.1 ± 5.8</td>
</tr>
<tr>
<td>Brachial artery (Release)</td>
<td>99.2 ± 6.3</td>
<td>18.93 ± 2.1</td>
<td>18.2 ± 2.9</td>
<td>25.9 ± 4.2</td>
<td>21.1 ± 3.5</td>
<td>24 ± 3.7</td>
</tr>
<tr>
<td>Right atrium (Compression)</td>
<td>4.4 ± 0.9</td>
<td>41.6 ± 4.3</td>
<td>51.1 ± 5.0</td>
<td>61.3 ± 5.2</td>
<td>62.9 ± 5.2</td>
<td>63.7 ± 5.5</td>
</tr>
<tr>
<td>Right atrium (Release)</td>
<td>-0.67 ± 0.3</td>
<td>2.8 ± 0.8</td>
<td>3.7 ± 0.8</td>
<td>4.8 ± 0.7</td>
<td>4.4 ± 0.7</td>
<td>5.3 ± 0.7</td>
</tr>
</tbody>
</table>

*Paired t test significant at $P < .05$.

**Resuscitability**

The 15 animals in Group I (controls) included five Class A (easy), five Class B (difficult), and five Class C (impossible) animals. The 15 animals in Group II (epinephrine treated) included nine Class A (easy), three Class B (difficult), and three Class C (impossible) animals. All animals were defibrillated successfully. Death in Class C animals was due to electromechanical dissociation or asystole. Intrapulmonary epinephrine nearly doubled the fraction of animals that were easy to resuscitate (from 5/15 to 9/15), despite slightly lower initial myocardial blood flow after five minutes of CPR in the epinephrine-treated group.

The dependent variables in this study were compared to determine a possible relationship between organ blood flow and the resuscitability of the animals after 20 minutes of CPR. Mean blood flow to the heart during the 20-minute time interval correlated well with resuscitability (Figure 6), while blood flow to the brain showed little relationship to initial recovery (Figure 7). Adrenal blood flow in the Class A (easy) animals (1.22 ± 0.08 mL/min/g) was significantly greater than adrenal blood flow in the Class B and C (difficult and impossible) animals (0.42 ± 0.05 mL/min/g).
Fig. 7. Relationship between the animals’ response to resuscitation and blood flow to the brain. Each data point represents the mean of four blood flow determinations in one animal.
Fig. 8. Myocardial blood flow as a function of diastolic brachial artery pressure in Group I (control) and Group II (epinephrine-treated) animals. $S_{yx}$ for Group I = 0.09 and for Group II = 0.11 ($P < .001$).

**Blood Gases**

Blood gases were determined in 11 of the 15 epinephrine-treated animals (Table 2). An acid-base map was used to predict the contribution of respiratory and metabolic imbalances. Prefibrillation values on these anesthetized animals were suggestive of a combined respiratory and metabolic acidosis. After two and eight minutes of CPR, an arterial respiratory alkalemia existed. After 13 and 18 minutes, the values were consistent with a mixed metabolic acidosis and respiratory alkalosis. There is no clear evidence that the two intrapulmonary drug injections impaired gas exchange during CPR.
Table 2. Arterial blood gases and pH before and during 20 minutes of CPR with intrapulmonary epinephrine

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>pH</th>
<th>PCO₂</th>
<th>PO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>7.31 ± .03*</td>
<td>45 ± 4*</td>
<td>83 ± 5*</td>
</tr>
<tr>
<td>2</td>
<td>7.62 ± .04</td>
<td>13 ± 2</td>
<td>384 ± 23</td>
</tr>
<tr>
<td>8</td>
<td>7.48 ± .04</td>
<td>17 ± 2</td>
<td>388 ± 21</td>
</tr>
<tr>
<td>13</td>
<td>7.42 ± .05</td>
<td>14 ± 2</td>
<td>417 ± 22</td>
</tr>
<tr>
<td>18</td>
<td>7.29 ± .03</td>
<td>18 ± 2</td>
<td>312 ± 42</td>
</tr>
</tbody>
</table>

*Indicates breathing room air. Remainder on 100% oxygen.

Validation of Microsphere Technique

Comparing flow (mL/min/g) to the right versus left cerebral hemispheres for each microsphere determination in all 30 animals yielded a correlation coefficient of .97 with a slope of .96. Similarly flow to the right versus left kidney yielded a correlation of $r = .94$ with a slope of .99, providing evidence for uniform mixing of microspheres with the left ventricular blood. Cardiac output obtained with the saline dilution method was compared with cardiac output measured with microspheres in ten of the 15 control animals. The mean ratio of microsphere to saline cardiac output measurements was $0.91 ± 0.03$ (mean ± SE) in these animals, indicating substantial agreement.

DISCUSSION

Regional Blood Flow and Survival

In both groups of animals, blood flow to the myocardium was the one parameter most closely related to the resuscitability of the animals. In all animals, when myocardial blood flow was less than 0.13 mL/min/g, the animals did not survive. When myocardial blood flow was greater than 0.44 mL/min/g, the circulation was restored with electrical defibrillation alone. This result shows the critical level of coronary blood flow required to restore the heart's ability to function as a pump.

Intrapulmonary epinephrine after seven minutes of CPR enhanced coronary blood flow by raising diastolic arterial pressure and by redistributing cardiac output. Perhaps as a result, spontaneous circulation was established following defibrillation in 60% of the treated animals compared with only 33% of the control group, despite the fact that myocardial flow after five minutes of CPR was essentially the same in both groups.
Clinically it would be desirable to be able to assess blood flow to the heart during CPR. Because no quick, easy method currently exists to determine this parameter directly in human beings, one must rely on indirect indicators. Coronary flow has been shown to be related to central arteriovenous pressure differences during the diastolic or release phase of chest compression during CPR\textsuperscript{10}. In our study, diastolic brachial arterial pressure was as good a predictor of heart flow as was the arteriovenous difference (compare Figure 8 and Figure 5), for central venous pressures approaching zero when the chest compression was released. Epinephrine treated animals showed a tendency toward a greater myocardial flow for a given pressure compared with controls. This tendency suggests decreased resistance of the coronary vasculature.

Evidently epinephrine improves chances of immediate survival by augmenting perfusion of heart muscle during CPR. Interestingly epinephrine also improved blood flow to the adrenal glands. This action may provide a mechanism for additional, endogenous epinephrine release. In this study, all animals that were easy to resuscitate displayed significantly higher adrenal blood flow than did those that were difficult and impossible to resuscitate, suggesting that endogenous catecholamine and/or steroid release may play a significant role in the effectiveness of CPR.

**Intrapulmonary Epinephrine**

While some investigators have suggested advantages of the intrapulmonary route of drug administration\textsuperscript{17,18}, its use is not without risks. Epinephrine has been associated with recurrence of ventricular fibrillation\textsuperscript{19} and, conceivably, the sustained drug levels provided by the intrapulmonary depot could prolong this risk. In our study, however, only two of the drug treated and one of the untreated animals that were easy to resuscitate refibrillated during the first few seconds following initial defibrillation. Subsequent defibrillation was effective, and the animals survived with no further sequelae. Thus epinephrine did not appear to increase the incidence of refibrillation in these animals.

A second risk associated with the depot effect occurs when the circulation is first reestablished. Prolonged hypertension has been documented previously\textsuperscript{20}, and was noted to varying degrees in the surviving animals. Following defibrillation the depot of epinephrine in the lungs produced rapid increases in blood pressure, which declined to a steady state over periods ranging from four to 17 minutes. The anatomical site of drug injection into the lungs rather than the trachea appears to be important in determining the onset and duration of effects. Most previous studies have used an endotracheal site of administration\textsuperscript{17,18,20-22}, in which a drug depot was created effectively in the endotracheal tube and conducting airways. However, the importance of deep endobronchial drag instillation has been recognized by Elam\textsuperscript{17} and by Greenberg.\textsuperscript{23} In pilot studies, Greenberg demonstrated better drug delivery with endobronchial than with endotracheal injection (M. Greenberg, personal communication, April 1982). Our own pilot studies revealed delayed onset and severely decreased amplitude of drug effects with endotracheal compared with intrapulmonary epinephrine (Figure 1). These findings suggest that during a low-flow state, little absorption of the drug occurs across the thicker conducting airways, and that deep endopulmonary instillation is required for a clinically significant effect.
Despite the fluid injected into the alveolar bed, positive pressure ventilation with oxygen appeared to maintain adequate gas exchange. Blood gases observed in this study following deep intrapulmonary epinephrine were largely consistent with findings of others during CPR.\textsuperscript{24, 25}

**Accuracy of Microsphere Technique During Experimental CPR**

Recently two groups of investigators using microspheres have reported coronary and brain blood flow during CPR in dogs to be considerably lower than those measured in our study.\textsuperscript{7, 26} These discrepancies may be related to inaccuracy of microsphere measurement technique or actual differences in quality of CPR and in the resulting blood flow. The accuracy of microsphere technique depends on complete mixing of the microsphere suspension with the blood in the left ventricle, total expulsion of the injected microspheres into the peripheral circulation, and representative sampling of the microsphere population into the reference syringe. Comparable flow to the right and left cerebral hemispheres and right and left kidneys in this study is consistent with the assertion that adequate mixing occurred.

Evidence for the lack of sedimentation was provided by the agreement of saline and microsphere cardiac output measurements. This procedure served to compare an indicator in solution (saline) with an indicator in suspension (microspheres). If significant settling of the suspended microspheres occurred between the point of injection and the reference organ, one would expect cardiac output determined with microspheres to be falsely high compared to that determined using a soluble indicator. The saline cardiac output measurements were alternated with the microsphere injections and those measurements closest in time were paired. Although these were not simultaneous measurements, the stability of cardiac output during CPR in these animals allowed for valid comparisons. The ratio of less than 1.0 in this study (0.91) gives no evidence for settling of microspheres. Similar agreement between flows during CPR measured with microspheres and nonsedimentary indicators was obtained by Koehler.\textsuperscript{26}

Finally blood flow to the heart at a particular diastolic arteriovenous pressure difference was in agreement with those determined by Janicki\textsuperscript{27}, who measured coronary blood flow at controlled perfusion pressures in an isolated heart preparation. Indeed the relationship between coronary flow and perfusion pressure observed in this study is consistent with other studies that report much lower coronary perfusion during CPR.\textsuperscript{7,10, 26} From this evidence, we conclude that the microsphere technique of measuring blood flow is reasonably accurate, and that the differences in measured myocardial flow during CPR between our study and those of Luce, Koehler, and their coworkers are due to differences in CPR technique and in animal models,\textsuperscript{28} rather than inherent difficulties with the microsphere technique.
CONCLUSIONS

Standard CPR performed with uniform chest compressions and ventilation was capable of maintaining cardiac output during a 20-minute period, suggesting that prolonged CPR is not a futile effort. Adequate blood flow to the heart was essential for initial successful resuscitation. Therefore, efforts aimed at improving coronary blood flow, either by achieving higher total cardiac output or by redistributing available flow, may result in increased survival following cardiac arrest. Instillation of intrapulmonary epinephrine solution is one such approach that nearly doubled the percentage of animals in our study that were easy to resuscitate.

REFERENCES


