Failure of Epinephrine to Improve the Balance Between Myocardial Oxygen Supply and Demand During Closed-Chest Resuscitation in Dogs

Roy V. Ditchey, MD, and JoAnn Lindenfeld, MD

Although large doses of epinephrine increase coronary perfusion pressure and flow during cardiopulmonary resuscitation, epinephrine also increases myocardial oxygen consumption during ventricular fibrillation. To test the hypothesis that epinephrine improves the balance between myocardial oxygen supply and demand during cardiopulmonary resuscitation, myocardial adenosine 5'-triphosphate (ATP) and lactate concentrations were measured before and immediately after 10 minutes of cardiopulmonary resuscitation in 10 control dogs and 10 dogs given intravenous epinephrine (1-mg bolus followed by 0.2 mg/min). Left ventricular myocardial blood flow during cardiopulmonary resuscitation was measured with radioactive microspheres and was significantly higher in the epinephrine group (48 ± 11 vs. 21 ± 4 ml/min/100 g, p<0.05). However, myocardial lactate concentration increased significantly (p<0.01) after cardiopulmonary resuscitation in both groups and tended to increase more in epinephrine-treated animals. Myocardial ATP concentration decreased significantly (p<0.05) and by comparable amounts in the two groups. These findings suggest that large doses of epinephrine may fail to improve the balance between myocardial oxygen supply and demand during cardiopulmonary resuscitation, even when they result in a substantial increase in coronary blood flow. (Circulation 1988;78:382–389)

Large doses of epinephrine often are administered during cardiopulmonary resuscitation (CPR), partly in an attempt to increase arterial pressure and coronary blood flow.1 Although recent studies have confirmed that pharmacological doses of epinephrine can increase coronary flow during CPR,2,3 epinephrine also increases myocardial oxygen requirements during ventricular fibrillation.4 It is not known whether epinephrine has a net beneficial effect on myocardial oxygenation during resuscitation from ventricular fibrillation.

The present study was designed to test the hypothesis that pharmacological doses of epinephrine improve the balance between myocardial oxygen supply and demand during CPR. The problem was approached by comparing changes in myocardial adenosine 5'-triphosphate (ATP) and lactate concentrations after a 10-minute period of CPR performed with and without epinephrine administration in separate groups of experimental animals.

Materials and Methods

Studies were performed in 20 mongrel dogs weighing an average of 23.7 kg (range, 18.2–35.0 kg). The dogs were anesthetized with morphine sulfate (2 mg/kg) and α-chloralose (100 mg/kg), intubated, and mechanically ventilated with 100% oxygen. Additional α-chloralose was administered if necessary. A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle.

Before obtaining prearrest biopsies, ventilation was adjusted to maintain arterial pH between 7.50 and 7.70 and arterial Po2 above 100 mm Hg. These conditions were chosen to approximate the range of pH values typically present during this type of experimental CPR and to ensure complete arterial blood oxygen saturation. This was done to minimize any potential effect of altered pH or arterial hypoxemia on observed changes in myocardial ATP and lactate concentrations after CPR. Two full-thickness biopsies of the left ventricular free wall were then obtained with a high-speed drill with a hollow bit under suction that delivers a core of...
tissue approximately 3.5 mm in diameter. Biopsies were expelled from the bit with compressed air, rinsed in saline, and immediately placed in liquid nitrogen. In six dogs, a third biopsy was obtained, rinsed, and held in room air for 30 seconds before freezing. Biopsy sites were closed with purse-string sutures, and the time required to obtain, rinse, and freeze each tissue sample was recorded. Each biopsy was divided into three approximately equal layers (representing endocardium, mesocardium, and epicardium) immediately after freezing. Each layer was placed in a separate container and resubmerged in liquid nitrogen until the end of the study. A fluid-filled catheter was placed in the left atrium through the atrial appendage, and a bipolar electrode was sutured to the left ventricular apex. The atrial catheter and electrode leads were exteriorized through small incisions in the chest wall, and the pericardial cradle was released. The chest was then closed and drained of air.

The dogs were placed in a supine position, and ventilation was adjusted to maintain arterial pH and PCO$_2$ in the normal range. Sodium bicarbonate solution was administered when necessary. In addition, each dog was given 5 ml/kg normal saline as an arbitrary correction for insensible fluid losses during the preceding thoracotomy. High-fidelity, micromanometer-tipped catheters (Millar, Houston, Texas), each with a separate lumen for recording fluid-filled pressures, were inserted through a femoral artery and vein and positioned in the ascending aorta and right atrium, respectively. In some cases, a second fluid-filled catheter was positioned in the right atrium for epinephrine infusion. Catheter position was confirmed by appropriate pressure recordings and, in most cases, fluoroscopically. An additional, fluid-filled catheter was inserted via the opposite femoral artery and positioned in the ascending aorta for withdrawal of arterial blood reference samples. The lumen of each high-fidelity catheter was connected to a Gould P23Db pressure transducer with zero reference set at the midsternal level. Pressures were recorded on a Beckman model R611 eight-channel recorder. Pressure transducers were calibrated with a mercury manometer, and end-plate release phase high-fidelity and fluid-filled pressures from each set of recordings during CPR were matched to correct for baseline drift. Hematocrit level was determined after instrumentation and fluid replacement.

Total and regional blood flow were estimated with radioactive microspheres labeled with $^{57}$Co, $^{51}$Cr, $^{153}$Gd, $^{95}$Nb, $^{103}$Ru, $^{46}$Sc, or $^{113}$Sn. The microspheres were suspended in a 10% dextran solution with 0.02% Tween 80 and agitated before injection. An aliquot of at least 2 million microspheres, followed by a 5-ml saline flush, was injected through the left atrial catheter for each measurement. The radioisotopes used and the order of injection varied between studies. Adequate microsphere mixing under the low-flow conditions of CPR has been documented in previous studies from this laboratory.  

The first injection of microspheres was made under prearrest conditions. Beginning slightly before injection, blood samples were withdrawn at a constant rate through a catheter positioned in the ascending aorta. Sequential 20-second collections were obtained in preweighed vials for 160–200 seconds, after which pressures were recorded with respiration temporarily suspended at end expiration.

Ventricular fibrillation then was induced by applying a low-voltage, alternating current to the epicardial electrode. The current was discontinued, and anteroposterior chest compression was begun immediately after confirming the onset of ventricular fibrillation. The chest was compressed 60 times/min for a total of 10 minutes with a force of approximately 140 lb and a compression duration equal to 50% of each cycle with a modified, pneumatic chest compression device (model x1004 Life Aid Cardiopulmonary Resuscitator, Michigan Instruments, Grand Rapids, Michigan). The release phase of the cycle was prolonged by 0.5 seconds every fifth compression to allow synchronized lung inflation to a peak inspiratory pressure of 20 cm H$_2$O. Ten dogs were given a 1-mg bolus of epinephrine at the onset of CPR, followed by a continuous epinephrine infusion at a rate of 0.2 mg/min through a right atrial catheter. The remaining 10 dogs were studied without intervention.

A second injection of microspheres was made early during the course of CPR, and aortic blood reference samples were collected for 8 minutes. Aortic and right atrial blood pressures were recorded during the 1st and 10th minutes of CPR. An arterial blood sample was obtained for gas analysis during the final minute of CPR.

After 10 minutes of CPR, chest compression was stopped, the chest was opened, and two additional left ventricular biopsies were obtained, rinsed in saline, and frozen in liquid nitrogen as rapidly as possible. The time interval between the termination of CPR and the placement of each biopsy in liquid nitrogen was recorded. The frozen biopsies were cut into three pieces as described above. After the study, biopsies were stored in a freezer at $-70^\circ$C until biochemical analyses could be performed.

At the conclusion of the study, the aortic blood samples were weighed, and the volume of each sample was calculated. The heart, brain, and kidneys were removed, and the right and left cerebral hemispheres and right and left kidneys were homogenized separately (cerebral samples were not obtained in one dog). The left ventricular free wall was divided into three approximately equal layers (representing endocardium, mesocardium, and epicardium). Three samples of each myocardial layer and each cerebral and renal homogenate were placed in vials, weighed, and counted for radioactivity along with each set of blood samples and a reference standard for each microsphere in a three-
channel, well-type gamma scintillation counter (model 5230 Auto-Gamma Spectrometer, Packard, Downers Grove, Illinois). Samples were counted for 4 minutes or a maximum of 2 million counts, with energy windows calibrated and adjusted for the peak emissions of the isotopes used in each animal. Specific blood and tissue activities were corrected for radioactive "cross-talk" between isotopes. Analysis of sequential aortic samples demonstrated an average residual blood radioactivity in the final sample of less than 5% of the peak level. In one epinephrine-treated dog, the microsphere withdrawal catheter clotted after a collection period of approximately 5 minutes. Analysis of sequential samples in this dog revealed a blood radioactivity in the final sample before clotting of less than 5% of the peak level, indicating near-complete inscription of the arterial blood radioactivity curve.

Total forward blood flow (ml/min) and tissue blood flow (ml/min/100 g) were calculated from the microsphere data by previously described methods. The concentrations of ATP and lactate in each layer of each myocardial biopsy were determined with fluorometric assays.

Aortic and right atrial pressures from each set of CPR recordings were averaged over 10 consecutive chest compressions. Myocardial blood flow and ATP and lactate concentrations were analyzed both individually for each tissue layer and in combination by a weight-corrected average. Either the ATP or lactate assay was technically inadequate in one or more tissue layers of a single biopsy in four dogs (four of 80 biopsies). In the remaining cases, the results of the two biopsies from each prearrest and post-CPR condition were averaged. Data are expressed as mean ± SEM. The statistical significance of differences between the two study groups was tested by the Student's t test for unpaired samples. A one-tailed test was used when comparing peak and mean aortic pressures, mean aortic-right atrial pressure differences, and myocardial blood flow during CPR. A two-tailed test was used for all other between-group comparisons (including changes in ATP and lactate concentrations). Differences between measurements within the same study group were tested by the two-tailed Student's t test for paired samples or analysis of variance with multiple comparison testing (Student-Newman-Keuls) when more than two measurements were compared. p<0.05 was considered significant.

**Results**

Prearrest pressures, blood flow measurements, and myocardial concentrations of ATP and lactate did not differ significantly between the two study groups. Aortic and right atrial pressures are summarized in Table 1. Peak and mean aortic pressures and the mean aortic-right atrial pressure difference generated during CPR tended to be higher in the epinephrine-treated group, although differences were statistically significant only for the first set of CPR measurements.

Blood flow measurements are summarized in Table 2. Left ventricular myocardial blood flow (based on a weight-corrected average of the three tissue layers) was 21 ± 4 and 48 ± 11 ml/min/100 g during CPR in control and epinephrine-treated dogs, respectively (p<0.05), and was significantly higher in the epinephrine group in all three tissue layers (Table 3). Prearrest myocardial blood flow tended to be highest in the endocardial layer, although differences between layers were statistically significant only for the control group (Table 3). This pattern was reversed during CPR, with significantly greater flow going to the epicardium than to the endocardium in both control and epinephrine-treated dogs. When the epinephrine-treated dog with an abbreviated arterial reference sample collection was excluded, mean myocardial blood flow in the epinephrine group was 42 ± 10 ml/min/100 g.
TABLE 2. Blood Flow Measurements

<table>
<thead>
<tr>
<th></th>
<th>Total forward blood flow (ml/min)</th>
<th>Left ventricular myocardium (ml/min/100 g)</th>
<th>Left cerebral hemisphere (ml/min/100 g)</th>
<th>Right cerebral hemisphere (ml/min/100 g)</th>
<th>Left kidney (ml/min/100 g)</th>
<th>Right kidney (ml/min/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prearrest</td>
<td>2,055 ± 163</td>
<td>97 ± 11</td>
<td>63 ± 11*</td>
<td>64 ± 11*</td>
<td>351 ± 29</td>
<td>361 ± 32</td>
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<tr>
<td>CPR</td>
<td>380 ± 101</td>
<td>21 ± 4</td>
<td>19 ± 3*</td>
<td>19 ± 3*</td>
<td>77 ± 20</td>
<td>74 ± 23</td>
</tr>
<tr>
<td>Epinephrine-treated group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prearrest</td>
<td>1,773 ± 208</td>
<td>93 ± 16</td>
<td>75 ± 14</td>
<td>82 ± 20</td>
<td>399 ± 41</td>
<td>385 ± 35</td>
</tr>
<tr>
<td>CPR</td>
<td>188 ± 44</td>
<td>48 ± 11†</td>
<td>29 ± 6</td>
<td>29 ± 6</td>
<td>1 ± 1†</td>
<td>1 ± 0‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Prearrest and CPR, measurements during prearrest and CPR conditions, respectively. CPR, cardiopulmonary resuscitation.
*p = 0.05; otherwise, n = 10.
†p < 0.05 vs. control group; ‡p < 0.01 vs. control group.

(p < 0.06 vs. control). Regional myocardial flow patterns also were similar when this dog was excluded, although in some cases, differences between layers or between study groups were no longer significant at the 0.05 level. Cerebral blood flow tended to be higher, total forward blood flow tended to be lower, and renal blood flow was significantly lower during CPR in epinephrine-treated dogs (Table 2). There were no significant differences between paired blood flow measurements to the right and left cerebral hemispheres or the right and left kidneys (Table 2).

Myocardial lactate concentration (based on a weight-corrected average of individual tissue layers) increased after CPR from 0.4 ± 0.1 to 4.3 ± 0.5 nmol/mg in the control group and from 0.6 ± 0.2 to 5.9 ± 0.7 nmol/mg in the epinephrine group (both, p < 0.01). There was a trend toward a greater increase in lactate concentration after CPR in the epinephrine-treated group (Figure 1). Myocardial ATP concentration decreased from 5.8 ± 0.8 to 4.2 ± 0.4 nmol/mg in the control group and from 7.7 ± 1.1 to 5.4 ± 0.5 nmol/mg in the epinephrine group (both, p < 0.05). Changes in ATP concentration after CPR did not differ significantly between groups. Myocardial ATP and lactate concentrations did not differ significantly between tissue layers before CPR in either group or after CPR in the control group (Table 4). In epinephrine-treated dogs, post-CPR lactate concentration tended to increase and ATP concentration decreased progressively from endocardium to epicardium. Both ATP and lactate concentrations tended to change less after CPR in the endocardium than in other tissue layers in both study groups, although most differences between layers were not significant at the 0.05 level (Table 4). Changes in ATP and lactate concentrations after CPR did not differ significantly between groups in any tissue layer, except for the increase in epicardial lactate concentration, which was greater in the epinephrine group. Due to a technical error, there was a delay of approximately 17 seconds from the onset of ventricular fibrillation to the first chest compression during CPR in one dog in the epinephrine group. However, this interval did not differ significantly between the two groups overall (3.4 ± 0.3 and 5.3 ± 1.4 seconds for control and epinephrine-treated dogs, respectively), and exclusion of this dog did not signifi-

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Bar chart of changes in myocardial adenosine 5'-triphosphate (ATP) and lactate concentrations after a 10-minute period of cardiopulmonary resuscitation (CPR) in control and epinephrine-treated dogs. There was a trend toward a greater increase in myocardial lactate concentration after CPR in epinephrine-treated dogs (p < 0.1). Decreases in myocardial ATP concentration after CPR did not differ between groups (p > 0.4).
FIGURE 2. Plot of individual levels of myocardial blood flow during cardiopulmonary resuscitation (CPR) in control and epinephrine-treated dogs. Myocardial blood flow during CPR overlapped levels present in the control group in five of ten epinephrine-treated dogs.

TABLE 4. Regional Myocardial ATP and Lactate Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Endocardium</th>
<th>Mesocardium</th>
<th>Epicardium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATP</td>
<td>Lactate</td>
<td>ATP</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prearrest</td>
<td>5.4 ± 0.9</td>
<td>0.5 ± 0.1</td>
<td>6.4 ± 0.9</td>
</tr>
<tr>
<td>CPR</td>
<td>4.5 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>3.7 ± 0.6</td>
</tr>
<tr>
<td>Δ</td>
<td>-0.9 ± 0.9</td>
<td>3.6 ± 0.5</td>
<td>-2.7 ± 0.6*</td>
</tr>
<tr>
<td>Epinephrine-treated group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prearrest</td>
<td>7.6 ± 1.2</td>
<td>0.7 ± 0.3</td>
<td>8.2 ± 1.3</td>
</tr>
<tr>
<td>CPR</td>
<td>6.2 ± 0.5†</td>
<td>5.7 ± 0.7</td>
<td>5.3 ± 0.6*</td>
</tr>
<tr>
<td>Δ</td>
<td>-1.4 ± 1.0</td>
<td>5.1 ± 0.7</td>
<td>-2.9 ± 1.0</td>
</tr>
</tbody>
</table>

Values are mean ± SEM
Endocardium, mesocardium, and epicardium are arbitrary designations for tissue samples obtained by dividing the left ventricular free wall into three approximately equal layers.

ATP and lactate, myocardial adenosine 5'-triphosphate and lactate concentrations, respectively (nmol/mg). Prearrest and CPR, measurements during prearrest and CPR conditions, respectively. Δ, change in myocardial ATP or lactate concentration after CPR (nmol/mg). CPR, cardiopulmonary resuscitation.

Overall differences between tissue layers were significant by analysis of variance for changes in both ATP and lactate concentrations after CPR in epinephrine group (p<0.05). However, multiple comparison testing did not identify any individual differences that were significant at the 0.05 level.

*p<0.05 vs. endocardium; †p<0.05 vs. control group; ‡p<0.05 vs. mesocardium.

cantly affect analyses involving changes in myocardial ATP or lactate concentrations after CPR.

There was considerable individual variability in the level of left ventricular myocardial blood flow achieved during CPR in both control and epinephrine-treated dogs (Figure 2). To exclude the possibility that the metabolic changes observed after CPR in the two study groups were biased by the results of biopsies obtained from dogs with relatively low levels of coronary flow despite epinephrine administration, metabolic changes in the five epinephrine-treated dogs with the highest levels of myocardial blood flow during CPR were compared with changes in the five control dogs with the lowest levels of myocardial blood flow during CPR (Figure 3). There were no significant differences between these two subgroups with regard to changes in average myocardial concentrations of either ATP or lactate after CPR, despite a nearly sevenfold greater level of myocardial blood flow in the epinephrine-treated dogs. Because coronary perfusion pressures decreased with time during CPR in epinephrine-treated dogs (Table 1), a further analysis was performed in which metabolic changes were compared between the five epinephrine-treated dogs with the highest and the five control dogs with the lowest mean aortic-right atrial pressure differences during the 10th minute of CPR. Mean aortic-right atrial pressure differences averaged 2 ± 2 and 20 ± 3 mm Hg in control and epinephrine-treated dogs, respectively (p<0.01), but changes in myocardial concentrations of ATP (-2.7 ± 0.2 vs. -2.2 ± 1.5 nmol/mg) and lactate (4.1 ± 0.3 vs. 4.3 ± 1.0 nmol/mg) after CPR did not differ significantly between the two subgroups.

FIGURE 3. Bar charts of myocardial blood flow during cardiopulmonary resuscitation (CPR) (left) and changes in myocardial adenosine 5'-triphosphate (ATP) and lactate concentrations after CPR (right) in the five control and five epinephrine-treated dogs with the lowest and highest levels of myocardial blood flow during CPR, respectively (see text for explanation).
The two study groups did not differ with regard to body weight, baseline hematocrit level, or time required to obtain and freeze either prearrest or post-CPR myocardial biopsies (Table 5). Table 6 compares prearrest and post-CPR ATP and lactate concentrations from six dogs with a third prearrest biopsy held for 30 seconds before freezing. This comparison demonstrates that the metabolic changes observed after CPR cannot be attributed to differences in the time required to obtain tissue samples for analysis. Arterial pH tended to be higher and PaO₂ was lower after CPR than at the time of baseline biopsies in both the control and epinephrine groups (Table 7), but there were no significant differences in pH, PaO₂, or PaCO₂ between groups.

Finally, studies were completed in two dogs not included in the final (20-dog) analyses. One control dog with a relatively high level of myocardial blood flow during CPR was excluded because of an unusually leftward-from-midline position of the chest compression piston during CPR, and one epinephrine-treated dog with relatively low flow during CPR was excluded because epinephrine mistakenly was infused into the inferior vena cava rather than the right atrium.

**Discussion**

Ventricular fibrillation can be conceptualized as a state in which myocardial fibers contract asynchronously and at a rapid rate. In isolated preparations, β-adrenergic stimulation with epinephrine increases both intraventricular pressure and myocardial oxygen consumption during fibrillation at constant volume by augmenting the contractile state of the fibrillating heart. Although the α-adrenergic effects of epinephrine significantly increase arterial pressure and coronary blood flow during CPR, the concept that epinephrine can improve the balance between myocardial oxygen supply and demand during resuscitation from ventricular fibrillation is unproven.

Livesay et al. found that coronary perfusion pressure and flow during open-chest CPR can be increased substantially by either epinephrine or methoxamine (a relatively pure α-adrenergic agonist). However, doses of epinephrine sufficient to raise arterial pressure from 40 to 65 mm Hg during constant flow conditions on cardiopulmonary bypass both increased myocardial oxygen consumption and decreased total and subendocardial myocardial blood flow during ventricular fibrillation. Methoxamine had none of these adverse effects. The increase in coronary vascular resistance after epinephrine was attributed to an increase in intramyocardial compressive forces. Although direct assessment of the net effects of epinephrine on the balance between myocardial oxygen supply and demand during CPR (either open- or closed-chest) was not attempted, it was concluded that inotropic drugs that increase the "vigor" of ventricular fibrillation may worsen myocardial ischemia during CPR by impeding subendocardial blood flow while simultaneously increasing myocardial oxygen demands.

In the present study, there was no evidence that epinephrine administration improved myocardial oxygenation during CPR. In fact, the increment in myocardial lactate concentration after CPR tended to be higher in epinephrine-treated dogs (Figure 1). Although the markedly elevated values of arterial pH present in this study may have influenced myo-

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**Table 5. Weights, Hematocrits, and Biopsy Times**

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg)</th>
<th>Hematocrit level (%)</th>
<th>Prearrest 1 (sec)</th>
<th>Prearrest 2 (sec)</th>
<th>CPR 1 (sec)</th>
<th>CPR 2 (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>23.7 ± 1.1</td>
<td>40.4 ± 1.5</td>
<td>9.0 ± 0.4*</td>
<td>9.5 ± 0.6</td>
<td>20.8 ± 1.1†</td>
<td>34.0 ± 1.9‡</td>
</tr>
<tr>
<td>Epinephrine-treated group</td>
<td>23.7 ± 1.6</td>
<td>39.5 ± 1.4</td>
<td>8.7 ± 0.4*</td>
<td>9.1 ± 0.7</td>
<td>20.4 ± 1.2†</td>
<td>34.0 ± 2.7‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Prearrest 1 and 2, and first and second biopsies obtained under prearrest conditions. CPR 1 and CPR 2, first and second biopsies obtained after CPR (times are from cessation of CPR). CPR, cardiopulmonary resuscitation.

There were no significant differences between control and epinephrine-treated groups.

*p = 9 (otherwise, n = 10).

†p<0.05 vs. both prearrest 1 and prearrest 2; ‡p<0.05 vs. CPR 1.

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**Table 6. Effects of Biopsy Time on Myocardial Adenosine 5′-Triphosphate and Lactate Concentrations**

<table>
<thead>
<tr>
<th></th>
<th>Prearrest 1</th>
<th>Prearrest 2</th>
<th>Prearrest 3</th>
<th>CPR 1</th>
<th>CPR 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ATP]</td>
<td>4.6 ± 0.7</td>
<td>4.8 ± 0.9</td>
<td>6.8 ± 1.3</td>
<td>3.6 ± 0.2*</td>
<td>4.6 ± 0.2*</td>
</tr>
<tr>
<td>[Lactate]</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>1.9 ± 0.1†</td>
<td>3.4 ± 0.6*</td>
<td>4.1 ± 0.6*</td>
</tr>
<tr>
<td>Time</td>
<td>8.7 ± 0.4</td>
<td>8.8 ± 0.9</td>
<td>30.0 ± 0.0†</td>
<td>18.6 ± 1.4*</td>
<td>33.3 ± 3.3†‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM; n = 6.

Prearrest 1 and 2 and CPR 1 and 2, first and second myocardial biopsies obtained under prearrest conditions and after CPR, respectively. Prearrest 3, third prearrest biopsy held in air for 30 seconds before freezing. [ATP] and [Lactate], myocardial adenosine 5′-triphosphate and lactate concentrations, respectively (nmol/mg). Time, time required to obtain and freeze each biopsy (sec). CPR, cardiopulmonary resuscitation.

*p<0.05 vs. prearrest 3; †p<0.05 vs. both prearrest 1 and prearrest 2; ‡p<0.05 vs. CPR 1.
TABLE 7. Arterial Blood Gases

<table>
<thead>
<tr>
<th></th>
<th>pH (mm Hg)</th>
<th>Po2 (mm Hg)</th>
<th>Pco2 (mm Hg)</th>
</tr>
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<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsies</td>
<td>7.61±0.02</td>
<td>190±18</td>
<td>21±3</td>
</tr>
<tr>
<td>Prearrest</td>
<td>7.37±0.01*</td>
<td>242±27</td>
<td>42±1*</td>
</tr>
<tr>
<td>CPR</td>
<td>7.73±0.04†</td>
<td>256±28</td>
<td>11±1*†</td>
</tr>
<tr>
<td><strong>Epinephrine-treated group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsies</td>
<td>7.60±0.02</td>
<td>200±20</td>
<td>17±2</td>
</tr>
<tr>
<td>Prearrest</td>
<td>7.39±0.01*</td>
<td>226±30</td>
<td>41±1*</td>
</tr>
<tr>
<td>CPR</td>
<td>7.67±0.05†</td>
<td>224±34</td>
<td>10±2*†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Biopsies, prearrest, and CPR, measurements made at the time of baseline biopsies, before prearrest blood flow measurements, and during 10th minute of CPR, respectively. CPR, cardiopulmonary resuscitation.

Statistical significance applies to comparisons within the same study group. There were no significant differences between control and epinephrine-treated groups.

*p<0.05 vs. biopsies; †p<0.05 vs. prearrest.

Cardiac metabolism to some extent,5,6 prearrest conditions were designed specifically to approximate those present during CPR, and arterial pH did not differ significantly between control and epinephrine-treated dogs at any time sampled (Table 7). A potentially more important methodologic consideration is the fact that myocardial blood flow measurements were based on a single injection of microspheres early during the course of CPR. Because coronary perfusion pressures did not differ between groups during the final minute of CPR, it is possible that coronary blood flow also did not differ during the latter portion of the CPR period. However, microsphere flow measurements are not instantaneous but are influenced by flow conditions present throughout the time required for inscription of the arterial blood-radioactivity reference curve. Furthermore, changes in myocardial ATP and lactate concentrations did not differ between the two study groups, even when the results were biased heavily in favor of a positive drug effect by comparing the five epinephrine-treated dogs with the highest to the five control dogs with the lowest measured levels of myocardial blood flow during CPR (Figure 3). This was true despite a nearly sevenfold greater level of flow in the epinephrine-treated dogs. With such marked measured differences, it seems unlikely that flow was equal in these two subgroups for any significant period of time. Finally, changes in ATP and lactate concentrations after CPR still did not differ significantly when the five epinephrine-treated animals with the highest were compared with the five control dogs with the lowest coronary perfusion pressures during the 10th (and final) minute of CPR.

A further consideration is the fact that we studied only one epinephrine regimen. However, because myocardial blood flow during CPR overlapped levels present in the control group in five of 10 epinephrine-treated dogs (Figure 2), it seems unlikely that a lower dose of epinephrine would improve myocardial oxygenation. Alternatively, even if one assumes that a higher total epinephrine dose1 or different method of administration could produce substantially higher and more sustained increments in myocardial blood flow than were found in our present study, analysis of the epinephrine-treated dogs with the highest levels of myocardial blood flow (Figure 3) and best-sustained coronary perfusion pressures during CPR suggests that metabolic improvement would be unlikely.

The observed effects of epinephrine on blood flow distribution during CPR (Table 2) are consistent with previous reports2,3 and support the concept that pharmacological α-adrenergic vasoconstriction can effectively redistribute blood flow to the heart and brain. However, the pattern of regional myocardial blood flow during CPR (with or without epinephrine) is indicative of global myocardial ischemia. In a beating heart, autoregulatory mechanisms distribute myocardial blood flow in accordance with regional differences in oxygen requirements, and flow generally is higher in endocardial than in epicardial layers.10 However, when flow is inadequate, autoregulatory mechanisms are maximally operative in all areas, and blood flow distribution reflects regional differences in vascular resistance that are independent of local metabolic control. Geometric considerations11 predict that intramyocardial wall tension and, therefore, extrinsic vascular compression during ventricular fibrillation are greatest in the subendocardium. As a result, epicardial flow is better maintained than endocardial flow during CPR, regardless of whether epinephrine is administered (Table 3). However, changes in regional myocardial ATP and lactate concentrations after CPR did not reflect this distribution of blood flow (Table 4). This finding was unanticipated and is of uncertain significance. It is possible that it reflects the metabolic consequence of greater (endogenous or exogenous) epinephrine delivery to the outer myocardial layers.

In conclusion, the results of the present study suggest that epinephrine administration is unlikely to improve the balance between myocardial oxygen supply and demand during CPR, even when it results in a substantial increase in coronary blood flow. This finding is not inconsistent with an overall beneficial effect of epinephrine during attempted resuscitation. It does suggest, however, that the apparent benefit of epinephrine may be due to factors other than improved myocardial oxygenation. In addition to primary electrophysiological effects, it is possible that epinephrine’s ability to increase coronary blood flow aids resuscitation by preventing stasis in the coronary circulation and washing out metabolic end products. It remains to be determined whether relatively pure α-adrenergic agents or alternative pharmacological interventions aimed at improving the balance between myocardial...
oxygen supply and demand during CPR can further increase the likelihood of successful resuscitation.

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References


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