Pulmonary Ventilation/Perfusion Defects Induced by Epinephrine During Cardiopulmonary Resuscitation

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Background. Epinephrine has been shown to impair pulmonary excretion of CO₂ during resuscitation. This phenomenon was investigated in a rodent model of cardiac arrest and conventional resuscitation.

Methods and Results. The effects of racemic epinephrine were compared with the selective α₁-agonist methoxamine and with saline placebo during cardiac resuscitation in 15 Sprague-Dawley rats mechanically ventilated with gas containing 70% oxygen. Epinephrine and methoxamine but not saline placebo significantly increased coronary perfusion pressure from approximately 32 to 55 mm Hg. Following epinephrine, end-tidal PCO₂ decreased from approximately 10 to 5 mm Hg. This was associated with a time-coincident decrease in PAO₂ from approximately 130 to 74 mm Hg and an increase in PACO₂ from approximately 26 to 40 mm Hg. These changes indicated increases in alveolar dead space ventilation concomitant with increases in pulmonary arteriovenous admixture. No such effects were observed after administration of either methoxamine or saline placebo. Each of the 15 rats was successfully resuscitated. However, a significantly larger number of transthoracic countershocks were required after epinephrine compared with methoxamine or placebo before return of spontaneous circulation.

Conclusions. Epinephrine induced ventilation/perfusion during cardiopulmonary resuscitation as a result of redistribution of pulmonary blood flow. (Circulation 1991;84:2101–2107)

Epinephrine has been the preferred adrenergic amine for the management of human cardiac arrest for almost 30 years.1–3 The rationale for its use is supported by animal studies4–6 and anecdotal case reports on patients.7,8 There is persuasive evidence that restoration of spontaneous circulation is a result of its α-adrenergic effect, by which coronary perfusion is augmented. Redding and Pearson9 demonstrated that selective α₁-adrenergic agents such as phenylephrine and methoxamine were as effective as epinephrine for restoring spontaneous circulation after electrically induced ventricular fibrillation (VF) in dogs. To the contrary, isoproterenol, which is the prototype of β-agonists, decreased resuscitability.

However, several adverse effects of epinephrine have more recently been identified in the setting of cardiac resuscitation. These include increases in myocardial oxygen consumption10–12 and increased ventricular dysrhythmia due to reentrant and ectopic ventricular tachycardia.13–15 This becomes an issue of even greater moment when “mega” doses of epinephrine are administered after conventional doses fail to increase arterial resistance and therefore coronary perfusion pressure (CPP).5,16–19

See p 2199

Our group recently described a rat model for study of cardiac resuscitation.20 In exercising this model, we coincidentally observed that epinephrine administered during precordial compression decreased the end-tidal carbon dioxide (PETCO₂) excretion, an observation previously made by Paradis et al21 in patients. We further observed that there was a simultaneous decrease in PAO₂ and increase in PACO₂.22 Since epinephrine has been demonstrated to alter

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ventilation/perfusion (VA/Q) relations, we suspected that this was the mechanism operative in our rat model. We therefore undertook a controlled study in which we compared the effects of epinephrine with those of a more selective α-agonist, methoxamine, in the setting of cardiac resuscitation.

Methods

Preparation

The experiments were performed in a previously described rat model of cardiac arrest and cardiac resuscitation. Briefly, 15 Sprague-Dawley rats (455–565 g) were fasted overnight except for free access to water. The rats were anesthetized by intraperitoneal injection of 45 mg/kg pentobarbital sodium supplemented with additional doses of 10 mg/kg at hourly intervals, except that no pentobarbital was administered for 30 minutes before induction of cardiac arrest. The proximal trachea was surgically exposed at a site 1 cm caudal to the larynx, and a 14-gauge cannula (Quick-Cath, Viera Div., Travenol Laboratories, Dallas, Tex.) was advanced into the trachea for a distance of 1 cm. For measurement of \( P_{ETCO_2} \), the respiratory gas was sampled through a side manifold interposed between the tracheal cannula and the respirator at a rate of 200 ml/min. The \( P_{CO_2} \) was measured with a side-stream infrared \( CO_2 \) analyzer (model 200, Instrumentation Laboratories, Lexington, Mass.). Through the left external jugular vein, an 18-gauge polyethylene catheter (CPMS-401J-FA, Cook, Bloomington, Ind.) was advanced through the left superior vena cava into the right ventricle (RV). Guided by pressure monitoring, the catheter was slowly withdrawn into the right atrium to avoid adverse effects of ventricular arrhythmias and interference with the RV electrode. Right atrial pressure was measured with reference to the midchest with a high-sensitivity transducer (P-23-9b, Spectramed, Oxnard, Calif.). This catheter was also used to sample blood from the right atrium. Through the right external jugular vein, a 3F pediatric radial artery catheter (model C-PUM-301J, Cook) was advanced into the right atrium. A precurved guidewire supplied with the catheter was then advanced through the catheter into the RV until an endocardial ECG was observed. Through the right carotid artery, a Teflon catheter (UTX022, Becton Dickinson, Rutherford, N.J.) was advanced into the thoracic aorta for measurement of aortic pressure with a model TNF-R transducer (Abbott Critical Care, North Chicago, Ill.). Through the left femoral artery and the left femoral vein, catheters (UTX022, Becton Dickinson) were advanced into the abdominal aorta and into the inferior vena cava for sampling arterial blood and blood replacement. Rectal temperature was measured continuously with a rectal thermistor. Conventional lead II ECGs were recorded with skin electrodes (model E220, In-vivo Metric, Healdsburg, Calif.).

Experimental Procedure

The tracheal tube was connected to a volume-controlled ventilator as previously described. Ventilation was initially established at a tidal volume of 0.65 ml/100 g animal wt and a frequency of 100 breaths/min. The tidal volume was subsequently adjusted to compensate for the volume of gas sampled by the \( CO_2 \) analyzer so as to maintain \( P_{ETCO_2} \) between 30 and 35 mm Hg. The inspired \( O_2 \) fraction (\( FIO_2 \)) was 0.7. A progressive increase in 60-Hz current to a maximum of 8 mA was then delivered to the RV endocardium, and current flow was continued for 3 minutes. Four minutes after onset of VF, precordial compression was initiated and maintained for 5 minutes with a pneumatically driven mechanical chest compressor as previously described. Compression was maintained at a rate of 200 min\(^{-1}\) with equal compression–relaxation duration (i.e., 50% duty cycle). Compression depth was equivalent to 30% of the anteroposterior diameter of the chest and was adjusted to maintain CPP at 30–35 mm Hg. Compression and ventilation were synchronized so as to maintain two compressions for each ventilation.

After 2 minutes of precordial compression (i.e., 6 minutes of VF), 0.2 ml of either epinephrine (30 \( \mu g/kg \)) or methoxamine (750 \( \mu g/kg \)) or 0.2 ml of normal saline was bolus injected into the right atrium. After 5 minutes of precordial compression (i.e., 9 minutes of VF), a 20-J DC countershock was delivered between the anterior chest and the back. If VF was not reversed within 5 seconds, a second 20-J DC countershock was delivered. In unsuccessfully resuscitated rats, precordial compression was then resumed for another 30 seconds before delivery of a second sequence of countershocks. Resuscitated rats were monitored for an additional 30 minutes, after which they were killed by intravascular injection of 2 ml of saturated KCl solution. Autopsy was routinely performed to document position of catheters and identify adverse effects of the interventions on thoracic and abdominal organs.

Measurements

For blood transfusions, arterial blood (2 ml) from a donor rat of the same colony was injected into the inferior vena cava 30 seconds before blood sampling. One-milliliter aliquots of blood were then withdrawn from both the aorta and the right atrium. Measurement of \( P_{CO_2}, P_{O_2}, \) \( O_2 \) saturation (\( SO_2 \)), \( HCO_3^- \), hemoglobin, and \( O_2 \) content on these samples was by techniques previously described. At 6 and 8 minutes of VF and at 5 and 30 minutes after resuscitation, all measurements were repeated. Aortic and right atrial pressures were continuously recorded on a six-channel recorder (model 2600, Gould Inc., Rolling Meadows, Ill.) together with the ECG and \( P_{ETCO_2} \). The CPP was calculated as the difference between compression-induced diastolic aortic and time-coincident right atrial pressures.
The pulmonary venous admixture was calculated by conventional formula:

\[
\frac{Q_s}{Q_t} = \frac{(C_{co2} - C_{ao2})}{(C_{co2} - C_{vco2})} \times 100
\]  

(1)

In earlier studies, we observed no differences in the Cvo2 (or Pvco2) between right atrial blood sampled at a site immediately proximal to the RV and blood sampled from the pulmonary artery. Accordingly, measurements on blood from the right atrium were used for calculation of Cvo2.

The mean alveolar oxygen tension was calculated from the alveolar gas equation:

\[
P_{ao2} = P_{io2} - P_{aco2} \left[ F_{io2} + (1 - F_{io2}/R) \right]
\]  

(2)

The R was assumed to be 1 as it was in an earlier study.23

The pulmonary capillary oxygen content was assumed to be equivalent to blood equilibrated at the existing Pao2.

Statistical Analysis

The pressure, flow, and gas concentrations for epinephrine, methoxamine, and control were analyzed by analysis of variance (ANOVA), Scheffé multicomparison techniques, and paired t test. Comparisons between time-based measurements within each of the three groups were performed with ANOVA repeated measurements. Measurements are reported as mean±SD. A value of p<0.05 was considered significant.

Results

The control measurements did not differ significantly among the three groups.

After intra-atrial injection of epinephrine, CPP increased from 33±3 to 52±4 mm Hg (p<0.001) within 5 seconds. Comparable increases in CPP were observed with methoxamine (34±3 to 48±3 mm Hg, p<0.001). These pressure levels were maintained within ±2 mm Hg during the 5-minute interval of precordial compression. There was no increase in CPP after intra-atrial injection of saline placebo. After epinephrine, PETco2 was strikingly decreased, from 10±2 to 5±2 mm Hg (p<0.001) (Table 1). However, no such decreases in PETco2 followed injection of either methoxamine or saline placebo (Figure 1). The decrease in PETco2 that followed injection of epinephrine was associated with an increase in the estimate of pulmonary arteriovenous shunt from 12±2% to 27±3% (p<0.001). No such effects were observed after administration of methoxamine (12±3% versus 14±2%) or saline placebo (13±3% versus 13±2%) (Figure 2). There was a corresponding decrease in PaO2 from 130±9 to 74±6 mm Hg (p<0.001) and prominent increases in Paco2 from 26±4 to 40±5 mm Hg (p<0.001) after administration of epinephrine. However, there were no significant changes in arterial PVO2 or PVCO2 (Table 2) such that the arteriovenous gradient for O2 and CO2 was decreased after epinephrine.

**TABLE 1. Decrease in PETCO2 After Epinephrine**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (−5 minutes)</th>
<th>+6 / 8 Injection</th>
<th>+10</th>
<th>+14</th>
<th>+39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (5)</td>
<td>38±4</td>
<td>11±2</td>
<td>10±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (5)</td>
<td>39±3</td>
<td>10±2</td>
<td></td>
<td>5±2*</td>
<td></td>
</tr>
<tr>
<td>Methoxamine (5)</td>
<td>37±3</td>
<td>11±3</td>
<td></td>
<td>10±2</td>
<td></td>
</tr>
</tbody>
</table>

Minutes refers to start of ventricular fibrillation (VF). PETco2 given in mm Hg. In parentheses, number of animals in each group.

*p<0.001, epinephrine vs. control or methoxamine.

**FIGURE 1. Plots showing effects of epinephrine, methoxamine, or saline placebo on end-tidal PCO2 (PETco2) and coronary perfusion pressure (CPP). CO2 excretion decreased after epinephrine during cardiopulmonary resuscitation. Values are mean±SD.
Neither methoxamine nor saline altered Pao2 and PaCO2 (Figure 3). The Pao2 and the computed pulmonary arteriovenous admixture gradually returned to prearrest levels within 30 minutes after resuscitation. The increases in pulmonary arteriovenous admixture were highly correlated with decreases in PETCO2 (r=0.97) (Figure 4). Each rat was successfully resuscitated after transthoracic countershock. However, rats that received epinephrine required an average of 3.5±1.1 countershocks before successful defibrillation. Methoxamine- or placebo-treated rats were successfully defibrillated with 1.6±0.5 countershocks (p<0.05).

**Discussion**

These studies demonstrate that in the setting of cardiac resuscitation, epinephrine adversely affects pulmonary gas exchange with consequent reduction in Pao2, decreases in Pao,CO2, and increases in PaCO2. The selective α1-agonist methoxamine increased CPP without altering pulmonary gas exchange. We also observed that epinephrine-treated rats were more resistant to electrical countershock for conversion of VF to a viable rhythm with restoration of spontaneous circulation.

Epinephrine increased the alveolar–arterial Po2 difference, reflecting an increase in venous admixture from 12% to 27%. Although respiratory exchange ratio (R) was not measured, if R had ranged between 0.8 and 1.2, this would have altered the computation of venous admixture by less than 2%.25,26

Our observations are consistent with those of Berk et al,23 who documented a twofold increase in pulmonary venous admixture produced by infusion of epinephrine during spontaneous circulation in dogs. However, these effects of epinephrine have not been

**TABLE 2. Aortic and Right Atrial Blood Gases**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (−5 minutes)</th>
<th>VF (minutes)</th>
<th>Postresuscitation (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>+6</td>
<td>+8</td>
</tr>
<tr>
<td>pHa (units)</td>
<td>C 5</td>
<td>7.43±0.05</td>
<td>7.32±0.04</td>
</tr>
<tr>
<td></td>
<td>E 5</td>
<td>7.42±0.02</td>
<td>7.30±0.05</td>
</tr>
<tr>
<td></td>
<td>M 5</td>
<td>7.45±0.04</td>
<td>7.31±0.06</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>C 5</td>
<td>126±9</td>
<td>128±10</td>
</tr>
<tr>
<td></td>
<td>E 5</td>
<td>119±7</td>
<td>130±9</td>
</tr>
<tr>
<td></td>
<td>M 5</td>
<td>121±9</td>
<td>128±8</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>C 5</td>
<td>30±4</td>
<td>27±3</td>
</tr>
<tr>
<td></td>
<td>E 5</td>
<td>32±4</td>
<td>26±4</td>
</tr>
<tr>
<td></td>
<td>M 5</td>
<td>30±3</td>
<td>24±3</td>
</tr>
<tr>
<td>Pvo2 (mm Hg)</td>
<td>C 5</td>
<td>52±4</td>
<td>46±5</td>
</tr>
<tr>
<td></td>
<td>E 5</td>
<td>55±8</td>
<td>45±6</td>
</tr>
<tr>
<td></td>
<td>M 5</td>
<td>58±4</td>
<td>44±5</td>
</tr>
<tr>
<td>PvCO2 (mm Hg)</td>
<td>C 5</td>
<td>37±3</td>
<td>48±4</td>
</tr>
<tr>
<td></td>
<td>E 5</td>
<td>38±4</td>
<td>49±3</td>
</tr>
<tr>
<td></td>
<td>M 5</td>
<td>37±6</td>
<td>46±5</td>
</tr>
</tbody>
</table>

C, control; E, epinephrine; M, methoxamine; VF, ventricular fibrillation.
Minutes refers to start of VF. Values are mean±SD.
*p<0.001, epinephrine vs. control or methoxamine.
cited previously as an issue during cardiopulmonary resuscitation. The mechanism by which epinephrine increased venous admixture is not well established. Although pulmonary edema may occur during infusion of epinephrine, this effect is mediated through stimulation of \( \alpha_1 \) rather than \( \beta \)-adrenergic receptors.27,28

The absence of increased venous admixture following administration of the \( \alpha_2 \)-agonist methoxamine and the rapidity with which it occurred virtually exclude the possibility that increased venous admixture resulted from adrenergically induced pulmonary edema in the present studies. It is more likely that increased venous admixture reflects altered VA/Q with recruitment of lung units with low VA/Q ratios. This may also include opening of anatomic arteriovenous communications in the lung. Such communications have been demonstrated in humans and animals; however, their significance and potential contribution to altered pulmonary gas exchange remain poorly understood.29–35

The issue, however, is more complex. The increases in venous admixture were closely related in both time and magnitude with decreases in \( P_{ETCO_2} \). In earlier studies, we demonstrated that \( P_{ETCO_2} \) was highly correlated with \( PaCO_2 \) and, in turn, with the amount of pulmonary blood flow generated during precordial compression.36 In the present study, however, epinephrine decreased \( P_{ETCO_2} \) without a corresponding change in \( PaCO_2 \). Accordingly, epinephrine increased the alveolar−arterial \( P_{CO_2} \) gradient and therefore the alveolar dead space. Since tidal volume and respiratory rate were constant, these changes strongly suggest that epinephrine altered the distribution of pulmonary blood flow such that a large fraction of the lung became underperfused.37–39

A corresponding increase in flow through the remaining lung favored not only venous admixture but also the narrowing of the venoarterial \( P_{CO_2} \) gradient and therefore the increase in \( PaCO_2 \).

Since the alterations in gas exchange were not observed after administration of the selective \( \alpha_1 \)-agonist methoxamine, the stimulation of \( \beta \)-adrenergic receptors are implicated at least in part. Preliminary observations on a porcine model of cardiac arrest in our laboratory corroborate comparable decreases in \( PaCO_2 \) and \( P_{ETCO_2} \) and increases in \( PaCO_2 \) after epinephrine but not after methoxamine. Although stimulation of \( \beta \)-receptors has minimal effect on normal lungs,40–42 stimulation of \( \beta \)-adrenergic receptors of poorly ventilated lungs releases compensatory pulmonary vasoconstriction.43,44 This results in increased perfusion through poorly ventilated (oxygenated) areas and consequently in increases in venous admixture. This effect is reminiscent of the hypoxic effects of \( \beta \)-adrenergic agonists when administered during clinical states of asthma and chronic obstructive airway disease.45,46 \( \beta \)-Agonists are implicated because increases in pulmonary venous admixture may be completely blocked by pretreatment with nonspecific \( \beta \)-adrenergic blocking agents.47 It is also minimized by ventilation with 100% \( O_2 \).48

Accordingly, our studies suggest that epinephrine alters the distribution of blood flow within the pulmonary circuit. The stimulation of \( \alpha \)-adrenergic receptors, especially of well-ventilated areas, would shunt blood away from these well-ventilated areas (dead-space effect) and preferentially distribute blood flow toward poorly ventilated regions in which the \( \beta \)-adrenergic receptor action had released hypoxic vasoconstriction (venous admixture effect). The already altered pulmonary gas exchange during cardiac arrest and resuscitation would set the condition under which these unfavorable effects of epinephrine are manifested.49

There is little controversy that \( \alpha \)-adrenergic agonists facilitate cardiopulmonary resuscitation after asphyxial cardiac arrest in dogs.50 Moreover, \( \alpha \)-receptor blockade with phenoxybenzamine before injection of epinephrine decreased resuscitability. This contrasted with high levels of effectiveness when epinephrine was administered after \( \beta \)-receptor blockade with propranolol. Equivalent effectiveness was demonstrated after administration of a relatively pure \( \alpha \)-adrenergic agonist, phenylephrine. Otto et al.51 induced cardiac arrest by VF in dogs and confirmed that it was the \( \alpha \)-agonists that accounted for the effectiveness of epinephrine. Conversely, when
α-receptors were blocked or after administration of β-adrenergic isoproterenol, attempts at resuscitation of dogs after electrically induced VF failed.

The greater ease of electrical defibrillation after either saline or methoxamine in contrast to epinephrine would also support the notion that the β-adrenergic effects of epinephrine may adversely affect resuscitability. Whether these effects are caused primarily by ventricular dysrhythmias independently of or together with pulmonary venous admixture is not fully clarified.13,14,52–54 However, β-adrenergic stimulation of the fibrillating heart increases myocardial oxygen requirement such that for any given level of myocardial blood flow generated by precordial compression, the oxygen deficit is likely to be increased.10–12

The value of PEF2CO2 as a reliable hemodynamic monitor during cardiac resuscitability is also at issue.55–58 These experiments also confirm that PEF2CO2 may lose its predictive value after the administration of epinephrine.

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