Angiotensin II Administration Improves Cerebral Blood Flow in Cardiopulmonary Arrest in Swine

Charles M. Little, DO; Charles G. Brown, MD

Background and Purpose  Cerebral blood flow during cardiopulmonary resuscitation is inadequate to meet cerebral metabolic demand. Adrenergic agonists improve cerebral blood flow, but clinical trials of increased doses in adults have not shown improved outcome from cardiac arrest. This may be due to adverse β-agonist-mediated effects. The purpose of this study was to determine the effect of angiotensin II, a potent nonadrenergic vasopressor, on cerebral blood flow in cardiac arrest.

Methods  Eleven immature swine were anesthetized and instrumented for regional blood flow measurements with radiolabeled microspheres. A sagittal sinus catheter was placed for blood gas determination. A blood flow measurement was performed in normal sinus rhythm and ventricular fibrillation induced. After 10 minutes of ventricular fibrillation, cardiopulmonary resuscitation was begun and a blood flow measurement performed. Angiotensin II at a dose of 50 µg/kg was administered intravenously at 13 minutes of ventricular fibrillation. A blood flow measurement was performed and defibrillation attempted. A fourth blood flow measurement was obtained if return of spontaneous circulation occurred.

Results  Total cerebral blood flow was 46.4 mL/min per 100 g in normal sinus rhythm. This fell to 6.9 mL/min per 100 g with cardiopulmonary resuscitation alone and rose to 30.8 mL/min per 100 g after the administration of angiotensin II. The improvement following angiotensin II was statistically different (P=0.002). Cerebral blood flow further rose in the animals that had return of spontaneous circulation to 73.9 mL/min per 100 g.

Conclusions  Angiotensin II in a dose of 50 µg/kg significantly improves cerebral blood flow in this model of cardiac arrest. (Stroke. 1994;25:183-186.)

Key Words  • angiotensins • cerebral blood flow • cardiopulmonary resuscitation • heart arrest • pigs
with a tidal volume of 15 mL/kg at a rate of 16/min initially and adjusted to a Paco₂ of 35 to 45 mm Hg.

A fluid-filled catheter was placed through a drill hole into the cerebral superior sagittal sinus for pressure monitoring and blood gas withdrawal. Millar high-fidelity pressure transducers (model SPC-450, Millar Instruments, Houston, Tex) were placed in the ascending aorta and the right atrium through the femoral vessels. A pigtail catheter for microsphere injection was placed in the left ventricle through the axillary artery. An aortic reference withdrawal catheter was placed in the descending aorta through the femoral artery. A pacing catheter was placed in the right ventricle through the angiography port. The position of all catheters was confirmed by pressure waveform and fluoroscopy.

The animals were transitioned to α-chloralose 25 to 100 mg/kg and ventilated on room air for a minimum of 10 minutes to allow halothane washout. Continuous aortic and right atrial pressures were recorded on computer (Reason Technology 386, Minneapolis, Minn). Sagittal sinus pressure was recorded except during sagittal sinus blood gas withdrawal. Baseline normal sinus rhythm blood gases were obtained and a blood flow measurement made.

Ventricular fibrillation (VF) was induced with 25-mA, 60-Hz AC delivered through the right ventricular pacing wire. Ventilation was stopped and the pacing wire removed. VF was assumed to persist for 10 minutes, then CPR was begun with a mechanical resuscitator (Thumper, model 1004, Michigan Instruments, Grand Rapids, Mich) with a duty cycle of 50%, Fio₂ of 0.85, compression rate of 80/min, and ventilation rate of 16/min. The compression depth was adjusted to be 1.5 to 2 inches during the first 30 seconds of CPR, and then no further adjustments were made. A blood flow measurement was performed from 10.5 minutes of VF to 13 minutes. Blood gases were obtained at 12 minutes of VF. Angiotensin II at 50 μg/kg (human angiotensin II, Sigma Chemical Co, St Louis, Mo) was administered at 13 minutes of VF (3 minutes after CPR was begun) into the superior vena cava, followed by a 10-mL saline flush. A blood flow measurement was performed from 14 to 16.5 minutes of VF and blood gases obtained at 15 minutes of VF. Defibrillation was attempted at 16.5 minutes of VF with 3 J/kg. If unsuccessful, defibrillation was attempted at 4 and then 5 J/kg. If return of spontaneous circulation (ROSC) occurred, defined as a systolic blood pressure greater than 60 mm Hg for 2 minutes, a fourth blood flow measurement and blood gases were obtained.

Blood flow measurements were performed according to the technique of Heymann et al.¹⁹,²⁰ and validated in the setting of cardiac arrest. Timed aortic blood withdrawal was used as the reference organ. Microspheres with a mean diameter of 15±0.03 μm labeled with ⁵¹Cr, ⁹⁵Tc, ⁴⁰K, and ⁴¹Nb were used to allow spectral separation of four different blood flows. The microspheres were ultrasonicated and injected through the left ventricular catheter for each blood flow measurement. At the end of the experiment the brain was removed, sectioned in entirety, weighed, and placed into scintillation vials. The tissues were counted in a multichannel spectrometer (Packard 9042). After correction for spectral overlap and tissue height, tissue blood flows were calculated by the formula:

\[
\text{Tissue Blood Flow (ml/min)} = \frac{\text{Tissue Activity (cpm)}}{\text{Reference Organ Blood Flow (ml/min) x Reference Organ Activity (cpm)}}
\]

where cpm is counts per minute.

Blood gases were analyzed with Instrumentation Laboratories (Lexington, Mass) blood gas analyzer (model 1304) and co-oximeter (model 282).

Oxygen utilization indexes were calculated by the following formulas: O₂ content = O₂ saturation (g/dL) x hemoglobin (g/dL) x 1.39 + (0.003 x Pco₂); cerebral O₂ delivery = cerebral blood flow x aortic O₂ content; cerebral O₂ consumption = cerebral blood flow x (aortic O₂ content - sagittal sinus O₂ content).

Hemodynamic data were acquired to computer disk at 5 Hz. Gould (Cleveland, Ohio) software was used for data acquisition (ACQ 4600, version 2.04). These data were then averaged over 15-second intervals, and these average values were used for data analysis. Cerebral perfusion pressure is calculated as mean arterial pressure minus sagittal sinus pressure. Baseline cerebral perfusion pressure during CPR is the 15-second value immediately before the administration of angiotensin II. Cerebral perfusion pressure after angiotensin II administration is the 15-second time interval from 14.5 to 14.75 minutes of VF. This time is chosen to avoid interference from the blood gas drawn at 15 minutes.

For statistical analysis a paired, two-tailed t test was used to compare the preangiotensin CPR values with the postangiotensin CPR values, as well as paired organ flows for microsphere validation (SYSTAT version 5.03, Systat Inc, Evanston, Ill). Statistical significance was considered at \( P<.05 \).

Results

Microsphere validation data are listed in Table 1. Adequate microspheres per tissue sample were present.²⁰ Total cerebral blood flow was 46.4 mL/min per 100 g in normal sinus rhythm (Table 2). This fell to 6.9 mL/min per 100 g with CPR alone and rose to 30.8 mL/min per 100 g with the administration of angiotensin II. The improvement following angiotensin II was statistically different (\( P<.002 \)). Cerebral blood flow further rose in the animals that had ROSC (n=5) to 75.9 mL/min per 100 g.

Sagittal sinus catheters could be successfully placed in only eight of 11 animals. Oxygen utilization indexes from these animals are reported in Table 3.

Hemodynamic indexes of cerebral perfusion improved in conjunction with the increased cerebral blood flow after angiotensin II administration (Table 4).

Discussion

The average cerebral blood flow after angiotensin II administration of 30.8 mL/min per 100 g tissue is well above the value of 10 to 18 mL/min per 100 g estimated

**Table 1. Microsphere Validation Data**

<table>
<thead>
<tr>
<th>Cortical Cerebral Blood Flow, mL/min/100 g tissue</th>
<th>Left</th>
<th>Right</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSR</td>
<td>46.6±10.6</td>
<td>46.5±13.7</td>
<td>.90</td>
</tr>
<tr>
<td>CPR</td>
<td>7.1±7.5</td>
<td>6.4±7.1</td>
<td>.26</td>
</tr>
<tr>
<td>CPR+ANG</td>
<td>29.6±18.9</td>
<td>32.0±20.8</td>
<td>.32</td>
</tr>
<tr>
<td>ROSC</td>
<td>72.9±40.85</td>
<td>75.7±38.7</td>
<td>.27</td>
</tr>
</tbody>
</table>

Values are mean±1 SD. NSR indicates normal sinus rhythm; CPR, cardiopulmonary resuscitation (before drug); CPR+ANG, CPR plus angiotensin II (after drug); ROSC, return of spontaneous circulation; and LV, left ventricle.
Angiotensin II Effect on Cerebral Blood Flow

It has been postulated that the relative distribution of α- and β-receptors in the cerebral vasculature is important in the control of cerebral blood flow during CPR. α-Receptors are more dominant in the larger vessels, and β-receptors are prominent in the microvasculature. The better cerebral blood flow seen with epinephrine or norepinephrine as opposed to pure vasoconstricting agents was postulated to result from additional β-receptor stimulation and therefore vasodilatation of the microcirculation. However, in this study angiotensin II improved cerebral blood flow as well as that reported with epinephrine or norepinephrine. This suggests that β-adrenergic-mediated cerebral vasodilatation may not be an important factor in the improved cerebral blood flows seen with mixed adrenergic agonists.

The differentially better blood flow to the lower brain structures than the cortices seen in previous adrenergic agonist experiments is again demonstrated with angiotensin II. A similar pattern of distribution of blood flow has now been demonstrated in animal models during CPR without drug; with the adrenergic agents epinephrine, phenylephrine, norepinephrine, and methoxamine; and with the nonadrenergic agent angiotensin II. These findings suggest that cerebral vascular anatomic structure and local vascular influences affect regional cerebral blood flow more than circulating hormones, and that regional cerebral blood flow may be in fixed proportion to cerebral perfusion pressure during CPR.

Cerebral oxygen delivery improved after angiotensin II as expected given the large increase in cerebral blood flow. Cerebral oxygen consumption after angiotensin II, and also after ROSC, was above the value for normal sinus rhythm. Abnormalities of the blood-brain barrier are known to occur after cardiac arrest. Because angiotensin II is known to have receptors in the brain, a direct effect of angiotensin II on increasing cerebral oxygen consumption is possible. However, the increased cerebral oxygen consumption was measured 2 minutes after the angiotensin II was administered. As angiotensin is a peptide, it is unlikely to penetrate even an abnormal blood-brain barrier rapidly enough to account for the increase. It is more likely that an oxygen debt has developed during cardiac arrest and CPR, and the metabolic demands of the brain are now met by the improved cerebral oxygen delivery, allowing cerebral oxygen consumption to be more closely estimated.

Cerebral perfusion pressure improved during CPR after angiotensin II administration. After ROSC, cerebral perfusion pressure only increased an additional 16%, while the total cerebral blood flow more than doubled. This would suggest that increased cerebral vasodilatation accounted for the increased cerebral blood flow after ROSC instead of increased perfusion pressure. In contrast, the increased cerebral blood flow seen after angiotensin II administration before ROSC was paralleled by increased perfusion pressure. Because there are many local cerebral factors that would promote vasodilation after ROSC, any specific effect from angiotensin II would be difficult to detect. Additionally, the lack of an increased mean arterial pressure after ROSC suggests that the effect of angiotensin II on peripheral vasoconstriction was absent within 4 to 5 minutes of administration.

In conclusion, angiotensin II, at a dose of 50 μg/kg, significantly improved cerebral blood flow in this model of cardiac arrest.

### Table 2. Regional Cerebral Blood Flows

<table>
<thead>
<tr>
<th></th>
<th>NSR</th>
<th>CPR</th>
<th>CPR+ANG</th>
<th>ROSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CBF</td>
<td>46.4±12.0</td>
<td>6.9±7.2</td>
<td>30.8±19.7</td>
<td>73.9±19.7</td>
</tr>
<tr>
<td>Left cortex</td>
<td>46.7±10.7</td>
<td>7.1±7.5</td>
<td>29.6±18.9</td>
<td>72.9±40.8</td>
</tr>
<tr>
<td>Right cortex</td>
<td>46.5±13.7</td>
<td>6.4±7.2</td>
<td>32.0±20.8</td>
<td>75.7±38.7</td>
</tr>
<tr>
<td>Midbrain</td>
<td>47.5±23.6</td>
<td>10.7±11.9</td>
<td>60.5±38.0</td>
<td>123.6±30.1</td>
</tr>
<tr>
<td>Pons</td>
<td>47.4±22.1</td>
<td>13.5±13.7</td>
<td>56.9±29.7</td>
<td>102.6±38.5</td>
</tr>
<tr>
<td>Medulla</td>
<td>44.8±20.7</td>
<td>17.5±17.8</td>
<td>69.2±40.2</td>
<td>121.1±58.4</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>77.9±35.2</td>
<td>14.2±17.3</td>
<td>41.8±32.1</td>
<td>92.2±42.3</td>
</tr>
<tr>
<td>Cervical spinal cord</td>
<td>37.1±19.2</td>
<td>11.3±12.1</td>
<td>52.6±29.4</td>
<td>76.5±24.6</td>
</tr>
</tbody>
</table>

Values are mean±1 SD, expressed in milliliters per minute per 100 g tissue. NSR indicates normal sinus rhythm; CPR, cardiopulmonary resuscitation (before drug); CPR+ANG, CPR plus angiotensin II (after drug); ROSC, return of spontaneous circulation; and CBF, cerebral blood flow.

### Table 3. Cerebral Oxygen Indexes

<table>
<thead>
<tr>
<th></th>
<th>NSR</th>
<th>CPR</th>
<th>CPR+ANG</th>
<th>ROSC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CeDO₂</td>
<td>5.8±1.6</td>
<td>1.0±1.0</td>
<td>5.1±4.0</td>
<td>14.9±9.2</td>
<td>.009</td>
</tr>
<tr>
<td>CeVO₂</td>
<td>2.9±1.4</td>
<td>0.7±0.8</td>
<td>4.0±2.4</td>
<td>4.2±2.3</td>
<td>.006</td>
</tr>
<tr>
<td>Extraction ratio, %</td>
<td>51.3±21.5</td>
<td>79.4±13.9</td>
<td>72.8±9.5</td>
<td>40.3±20.9</td>
<td>.28</td>
</tr>
</tbody>
</table>

Values are mean±1 SD. Cerebral delivery of oxygen (CeDO₂) and cerebral oxygen consumption (CeVO₂) are expressed in milliliters of oxygen per 100 g tissue per minute. Extraction ratio=CeVO₂/CeDO₂. NSR indicates normal sinus rhythm; CPR, cardiopulmonary resuscitation (before drug); CPR+ANG, CPR plus angiotensin II (after drug); and ROSC, return of spontaneous circulation.
Table 4. Hemodynamic Pressures

<table>
<thead>
<tr>
<th>Pressure, mm Hg</th>
<th>NSR</th>
<th>CPR</th>
<th>CPR+ANG</th>
<th>ROSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial</td>
<td>97.2±13.6</td>
<td>35.0±8.6</td>
<td>60.1±27.0</td>
<td>69.4±10.2</td>
</tr>
<tr>
<td>Sagittal sinus</td>
<td>13.1±5.0</td>
<td>22.1±5.7</td>
<td>29.8±7.0</td>
<td>17.0±2.3</td>
</tr>
<tr>
<td>Cerebral perfusion</td>
<td>89.6±11.0</td>
<td>15.4±11.1</td>
<td>45.5±24.2</td>
<td>52.9±10.3</td>
</tr>
</tbody>
</table>

Values are mean±1 SD. Cerebral perfusion pressure equals mean arterial pressure minus sagittal sinus pressure. Values were calculated for each individual animal and then averaged; therefore, values in the table do not sum up. NSR indicates normal sinus rhythm; CPR, cardiopulmonary resuscitation (before drug); CPR+ANG, CPR plus angiotensin II (after drug); and ROSC, return of spontaneous circulation.

Acknowledgment
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References

Editorial Comment
Survival from cardiac arrest in adults is uncommon despite three decades of progress since the discovery of closed-chest cardiopulmonary resuscitation (CPR). Only a minority of adults who require CPR in the out-of-hospital (2% to 44%) or in-hospital (3% to 27%) setting survive to hospital discharge. Most disturbingly, as many as half of the survivors suffer permanent brain damage. Maintenance of systolic and diastolic arterial pressure is essential during CPR. Since flow to most vital organs (except the heart) occurs during systole, a minimal arterial systolic pressure of 50 to 60 mm Hg is usually required to resist arteriolar collapse. Diastolic pressure is also important because it is a critical determinant of the coronary perfusion pressure, which is one of the most important hemodynamic prerequisites to get the heart beating again in both animal models and humans. Conventional closed-chest CPR alone rarely restores spontaneous circulation or consciousness during resuscitation because it provides inadequate systemic pressure and flow levels to meet the metabolic needs of the heart or the brain.
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