Cerebrospinal Fluid Acidosis Complicating Therapy of Experimental Cardiopulmonary Arrest

By Kalman J. Berenyi, M.D., Michael Wolk, M.D., and Thomas Killip, M.D.

SUMMARY
Cardiopulmonary resuscitation (CPR) may be followed by slow recovery of brain function. The possible role of bicarbonate therapy was assessed by analysis of arterial blood and cerebrospinal fluid (CSF) in 20 dogs during cardiac arrest and CPR. Samples were taken in the control period and every 5 minutes post-arrest for 20 minutes. Group I received no post-arrest CPR. Arterial pH fell from 7.37 to 7.31 (P < 0.01) and CSF pH from 7.34 to 6.94 (P < 0.001). Arterial pCO2 rose from 39 to 65 mm Hg (P < 0.005) and CSF pCO2 increased from 47 to 123 (P < 0.02). With CPR alone (group II) arterial pH decreased from 7.39 to 7.19 (P < 0.005), while arterial PCO2 and CSF pH and pCO2 were unchanged. CPR with bicarbonate therapy (mEq = weight × 0.43 × 1.1 mEq/min of arrest) given every 5 minutes (group III), resulted in a rise in arterial pH from 7.41 to 7.81 (P < 0.02). Excess bicarbonate administration during CPR may result in a marked dissociation between arterial and CSF pH as a consequence of rapid CO2 diffusion across the blood-brain barrier. Large amounts of NaHCO3 given during CPR may contribute to post-CPR cerebral depression.

IT IS COMMONLY OBSERVED that brain function may remain depressed for many hours following apparently successful restoration of the circulation after cardiopulmonary resuscitation. Although little information is available in man, one possible explanation is the development of divergent changes in H+ ion concentration in blood and cerebrospinal fluid (CSF) following therapy of cardiac arrest. In support of this premise is the observation that prolonged encephalopathy follows rapid correction of diabetic ketoacidosis with intravenous sodium bicarbonate. In the few patients studied in detail, hydrogen ion concentration has been shown to rise in CSF and simultaneously fall in arterial blood. This disparity has been attributed to differences in permeability of the blood-brain barrier to carbon dioxide and bicarbonate.

To evaluate the possibility that disparate acid-base relationships could develop during cardiac arrest, the present study was designed to measure arterial and CSF acid-base parameters following experimental cardiac arrest in the presence or absence of effective resuscitative measures. Particular attention was focused on the effect of bicarbonate administration on H+ ion concentration in an attempt to understand the mechanisms of post-arrest encephalopathy.

Methods
Twenty mongrel dogs weighing 20–25 kg were anesthetized with intravenous sodium pentobarbital (25 mg/kg). Following intubation with a cuffed endotracheal tube, the animal was attached to a Harvard Apparatus respirator and ventilated with room air. Tidal volume and respiratory rate were adjusted to maintain arterial pH (7.35–7.45), pCO2 (36–42 mm Hg) and pO2 (above 75 mm Hg) within normal range.

CSF was obtained through an 18 gauge × 2½ inch Beckton-Dickinson tellon catheter inserted into the suboccipital cisternal sac through the atlanto-occipital membrane. After clearing of catheter dead space, 0.75 to 1.0 ml samples of CSF were obtained and immediately analyzed for pH, pCO2, and pO2 with a Radiometer-Astrup blood gas analyzer. Simultaneously, heparinized arterial samples were drawn, placed in ice and analyzed within 30 min. Bicarbonate values were calculated from the Henderson-Hasselbalch equation, assuming an arterial carbonic acid pK of 6.10 and CO2 solubility factor of 0.0301. Similar calculations were made for cerebrospinal fluid using a carbonic acid pK of 6.15 and CO2 solubility factor of 0.0324.6

Aortic blood pressure was measured with a P23Db Statham transducer. Rectal temperature was monitored with a telemetry lead. II of the scalar electrocardiogram was recorded throughout each study. Total intravenous infusion was restricted to less than 250 ml of 0.9% sodium chloride.

Control samples were obtained during a steady state following preparation of the animal. Ventricular fibrillation was then induced by rapid electrical stimulation of the right ventricle via a bipolar pacing wire previously inserted under fluoroscopic control. With the onset of fibrillation ventilation was discontinued. Cardiopulmonary arrest was main-
tained for four minutes following which the animals were divided into three groups.

Group I (six dogs) received no therapeutic intervention for an additional 20 min. Animals in group II (seven dogs) were ventilated 20 times/min with oxygen enriched (2 L/min) air and received closed chest cardiac massage (CCCM) 60 times/min. Each compression was performed with the animal in the right lateral decubitus position.1,8 Peak aortic pressures averaged 80 mm Hg and mean pressures averaged 45 mm Hg. After 20 min of cardiopulmonary resuscitation (CPR) defibrillation was attempted.

The protocol for Group III (seven dogs) was similar to group II, but in addition, intravenous NaHCO₃ was administered at the conclusion of the four minute arrest period and at 5, 10, 15 and 20 min during CPR. NaHCO₃ was administered according to Astrup's formula for man, as modified by Ledingham9 for dogs: NaHCO₃ in mEq = body weight in kg × 0.43 (extracellular fluid space in dogs) × 1.1 per minute of cardiac arrest. This formula was chosen because it has been demonstrated in clinical situations to effectively correct acute or chronic acidosis and frequently culminate in metabolic alkalosis. In all groups, blood and CSF samples were obtained after four minutes of cardiopulmonary arrest and at 5, 10, 15 and 20 min following intervention.

The influence of frequency and volume of CSF sampling on the measured parameters was evaluated in three additional dogs. These animals were maintained in a steady state under anesthesia with intact circulation and artificial ventilation. Sampling was carried out in an identical time sequence to that described above. Acid-base parameters remained unchanged throughout. The pH ranged from 7.39 to 7.41 in blood and from 7.37 to 7.41 in CSF. Arterial pCO₂ varied between 38 and 43 mm Hg while CSF pCO₂ ranged from 44 to 46 mm Hg. The changes were random and not directional, suggesting lack of influence by frequency and volume of sampling.

Statistical analysis was performed in a Sigma III computer programmed for Student's paired and unpaired t-tests.

**Results**

Four minutes of cardiopulmonary arrest in the twenty animals resulted in modest but significant changes in several of the measured arterial and CSF variables reflecting hypoxia and acidosis (table 1). Thus, pCO₂ rose and pO₂ fell significantly in both fluids. CSF pH fell and bicarbonate rose in blood. Arterial pH was unchanged probably secondary to the absence of circulation at the sampling site.

Changes in acid-base parameters of arterial blood and CSF are summarized in table 2 and table 3, respectively. The P values in these tables reflect significance of difference of means compared to values after four minutes of cardiac arrest.

**Group I**

After 24 minutes of cardiopulmonary arrest in the untreated animals (fig. 1) mean arterial pH had fallen from the pre-arrest level of 7.37 to 7.31 (P < 0.01) while arterial pCO₂ rose from 39 to 65 mm Hg (P < 0.005). As arterial pCO₂ increased during the initial four minutes of cardiac arrest, arterial bicarbonate rose from a mean of 22 to 27 mEq/L (P < 0.05). During the ensuing 20 minute period bicarbonate did not change significantly, probably a reflection of a co-existing metabolic (lactic acidosis) and respiratory acidosis as indicated by the increasing pCO₂ and the fall in arterial pH. Relatively more pronounced changes occurred in CSF where pH fell from a pre-arrest average of 7.34 to 6.94 (P < 0.001) as pCO₂ increased from 47 to 123 mm Hg (P < 0.02).

**Group II**

Continued circulatory support beginning four minutes after arrest was associated with a fall of mean arterial pH from the control value of 7.39 to 7.19, (P < 0.001) after 20 minutes (fig. 2). Arterial carbon dioxide tension was unchanged indicating adequate ventilatory support. CSF pCO₂, pH and HCO₃ did not change significantly during 20 minutes of CPR. Arterial bicarbonate levels fell from 22.0 mEq after 4 minutes of circulatory arrest to 12.4 mEq by 20 minutes of CPR (P < 0.002) indicating severe, progressive metabolic acidosis. No significant changes in arterial or CSF PO₂ occurred during resuscitation. Four of seven animals were successfully defibrillated at the end of CPR but only one maintained an adequate circulation.

**Group III**

After four minutes of cardiac arrest, bicarbonate administration at five minute intervals during subse-

---

**Table 1**

**Influence of Four Minutes of Cardiopulmonary Arrest on Cerebrospinal Fluid and Arterial Acid-Base Status** *(N = 20)*

<table>
<thead>
<tr>
<th></th>
<th>Arterial blood</th>
<th>Cerebrospinal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-arrest</td>
<td>Post-arrest</td>
</tr>
<tr>
<td>pH</td>
<td>7.30 ± 0.05*</td>
<td>7.40 ± 0.05</td>
</tr>
<tr>
<td>pCO₂ (mm Hg)</td>
<td>37.5 ± 6.7</td>
<td>43.1 ± 9.7</td>
</tr>
<tr>
<td>HCO₃ (mEq/L)</td>
<td>22.0 ± 3.5</td>
<td>25.7 ± 5.7</td>
</tr>
<tr>
<td>pO₂ (mm Hg)</td>
<td>100 ± 32</td>
<td>88 ± 33</td>
</tr>
</tbody>
</table>

*Mean ± 1 SD of 20 determinations.

NS = not significant.

Circulation, Volume 52, August 1975


**Table 2**  

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 6) No CPR</th>
<th>Group II (N = 7) CPR</th>
<th>Group III (N = 7) CPR and Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH pCO₂ (mm Hg) HCO₃⁻ (mEq/L)</td>
<td>pH pCO₂ (mm Hg) HCO₃⁻ (mEq/L)</td>
<td>pH pCO₂ (mm Hg) HCO₃⁻ (mEq/L)</td>
</tr>
<tr>
<td>Pre-arrest</td>
<td>7.37 ± 0.06 39 ± 5.9 22</td>
<td>7.39 ± 0.06 36 ± 9.1 21</td>
<td>7.41 ± 0.03 38 ± 5.0 24</td>
</tr>
<tr>
<td>Arrest, 4 min</td>
<td>7.37 ± 0.04 48 ± 3.8 27</td>
<td>7.42 ± 0.07 35 ± 6.4 22</td>
<td>7.40 ± 0.04 48 ± 1.0 28</td>
</tr>
<tr>
<td>CPR, 5 min</td>
<td>7.35 ± 0.04 55 ± 7.1 28</td>
<td>7.43 ± 0.18 29 ± 16.3 17</td>
<td>7.58 ± 0.17 38 ± 13.5 34</td>
</tr>
<tr>
<td>CPR, 10 min</td>
<td>7.35 ± 0.05 58 ± 9.2 31</td>
<td>7.33 ± 0.14 32 ± 17.7 15</td>
<td>7.65 ± 0.17 53 ± 24.0 35</td>
</tr>
<tr>
<td>CPR, 15 min</td>
<td>7.33 ± 0.05 57 ± 9.2 30</td>
<td>7.23 ± 0.12 36 ± 20.1 14</td>
<td>7.69 ± 0.17 62 ± 19.5 72</td>
</tr>
<tr>
<td>CPR, 20 min</td>
<td>7.31 ± 0.06 65 ± 10.2 32</td>
<td>7.19 ± 0.10 35 ± 17.2 12</td>
<td>7.81 ± 0.31 64 ± 28.3 120</td>
</tr>
</tbody>
</table>

*Mean = 1 s.d.
†P value, significance of difference of means compared to value after 4 minutes of cardiac arrest.

**Table 3**  

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 6) No CPR</th>
<th>Group II (N = 7) CPR</th>
<th>Group III (N = 7) CPR and Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH pCO₂ (mm Hg) HCO₃⁻ (mEq/L)</td>
<td>pH pCO₂ (mm Hg) HCO₃⁻ (mEq/L)</td>
<td>pH pCO₂ (mm Hg) HCO₃⁻ (mEq/L)</td>
</tr>
<tr>
<td>Pre-arrest</td>
<td>7.34 ± 0.06 47 ± 14.6 23</td>
<td>7.38 ± 0.04 36 ± 6.3 19</td>
<td>7.37 ± 0.03 44 ± 7.3 24</td>
</tr>
<tr>
<td>Arrest, 4 min</td>
<td>7.30 ± 0.06 53 ± 15.8 24</td>
<td>7.36 ± 0.06 33 ± 11.1 17</td>
<td>7.35 ± 0.03 51 ± 6.7 26</td>
</tr>
<tr>
<td>CPR, 5 min</td>
<td>7.21 ± 0.07 70 ± 20.7 26</td>
<td>7.30 ± 0.05 43 ± 4.3 20</td>
<td>7.23 ± 0.12 62 ± 15.2 24</td>
</tr>
<tr>
<td>CPR, 10 min</td>
<td>7.10 ± 0.09 111 ± 31.3 31</td>
<td>7.32 ± 0.09 40 ± 5.2 19</td>
<td>7.18 ± 0.10 73 ± 16.3 26</td>
</tr>
<tr>
<td>CPR, 15 min</td>
<td>7.00 ± 0.08 116 ± 31.3 26</td>
<td>7.35 ± 0.15 38 ± 11.3 18</td>
<td>7.23 ± 0.12 67 ± 25.2 25</td>
</tr>
<tr>
<td>CPR, 20 min</td>
<td>6.94 ± 0.12 123 ± 44.4 24</td>
<td>7.35 ± 0.19 40 ± 15.3 20</td>
<td>7.24 ± 0.17 81 ± 27.0 32</td>
</tr>
</tbody>
</table>

*Mean = 1 s.d.
†P value, significance of difference of means compared to value after 4 minutes of cardiac arrest.
Changes in acid-base parameters in arterial blood and cerebrospinal fluid in group I (six dogs), with no cardiopulmonary resuscitation after the initial 4 minutes of cardiac and ventilatory arrest. Note progressive fall of pH and rise of pCO₂ in cerebrospinal fluid. P value indicates the significance of difference of means compared to value after the initial 4 minutes of cardiac arrest.

Figure 1

Arterial blood changes indicate a progressive disparity of acid-base status between CSF and arterial blood (fig. 3). Mean arterial pH increased from 7.40 after four minutes of cardiac arrest to 7.81 (P < 0.02) after 20 minutes of CPR, while mean arterial pCO₂ rose from 48 to 64 mm Hg. Despite the severe metabolic alkalosis in arterial blood, a striking decrease was noted in CSF pH at 5 minutes (7.23, P < 0.05), 10 minutes (7.18, P < 0.005) and 15 minutes (7.23, P < 0.05) when compared to the CSF pH of 7.35 at the beginning of CPR. By 20 minutes CSF pH had risen to 7.24, a value considerably lower but not significantly different from that obtained before bicarbonate administration. Arterial and CSF pH were significantly different at each sampling interval after the control period (fig. 3). Mean CSF pCO₂ rose from 51 to 81 mm Hg (P < 0.02) after 20 minutes of CPR.

With NaHCO₃ administration a progressive increase in arterial HCO₃ concentration, as anticipated, was noted after initiation of CPR at 5 (NS), 10 (P < 0.02) and 20 minutes (P < 0.05). CSF bicarbonate was unchanged over the study period although the 20 minute value was the highest detected.

Arterial and CSF pO₂ were maintained above 70 mm Hg during CPR. Defibrillation at 20 minutes was successful in all animals although none maintained an adequate circulation.

Discussion

The introduction of CCCM by Kouwenhouwen initiated a more aggressive approach to CPR. Recent CPR experiences, on open hospital floors indicate long-term survival rates ranging from 6 to 19.1%. Other studies from coronary care units where immediate CPR is feasible report survival rates over 50%. Attempts to further improve the efficacy of CPR involved organization of rescue teams, physician retraining in CCCM and studies of hemodynamic and metabolic events following cessation of adequate circulation.

In spite of intensive effort, many patients surviving cardiopulmonary arrest appear lethargic and at times progress to coma. These events have been attributed...
to cerebral anoxia although in many instances prolonged arterial hypoxemia could not be documented. Cerebral dysfunction clinically quite similar to post-arrest encephalopathy has been observed following rapid correction of diabetic ketoacidosis with sodium bicarbonate. This condition has been attributed to a rapid decline in CSF pH when arterial blood was rendered alkalotic.

The present study has investigated the relationships between CSF and arterial blood acid-base balance during experimental cardiopulmonary arrest and subsequent resuscitation. Attention was focused on over-correction of acidosis in order to evaluate the influence of alkalois induction by NaHCO₃ upon CSF acid-base status. Several points appear pertinent. During four minutes of cardiopulmonary arrest the increase in arterial pCO₂ was paralleled by a similar rise in CSF pCO₂ which resulted in a slight but significant fall in CSF pH. There was no change in CSF HCO₃, whereas arterial HCO₃ increased significantly.

The lack of change in arterial pH at the conclusion of the four minute arrest period reflects the problem of sampling arterial blood from a relatively large noncirculating pool not in equilibrium with body tissues. Since CSF was obtained from the suboccipital cisterna, it is likely to more closely reflect intracellular events in the central nervous system than fluid obtained from more distal sites.

CPR without bicarbonate administration (group II) prevented respiratory acidosis and maintained CO₂ tensions within normal range in both blood and CSF. Thus, CSF pH never fell below 7.30 during CPR although the metabolic component of post-arrest acidosis became progressively evident as arterial pH fell. The accumulation of intravascular H⁺ ion most likely reflects the post-arrest washout of metabolic byproducts of tissue acidosis following reinstitution of circulation. It is probable that an altered distribution of a decreased systemic blood flow contributed also. Constancy of CSF pH despite the progressive systemic acidosis suggests that CSF acid-base status is relatively stable in metabolic acidosis as long as a rise in CSF pCO₂ is avoided.

Administration of intravenous NaHCO₃ and CPR prevented the development of systemic metabolic acidosis following cardiac arrest. Although the dosage of administered HCO₃ was determined from an established formula, a marked arterial metabolic alkalosis ensued. In contrast, hydrogen ion concentration rose in the CSF. We postulate that the administered HCO₃, combined with acid radicals released from tissues, forms carbonic acid with subsequent dissociation to CO₂ and H₂O. CO₂ accumulated in arterial blood despite a level of ventilatory support that was adequate for group II in the absence of extrinsic NaHCO₃. The excess CO₂ so generated moved rapidly into CSF where buffering capacity is low. Thus, CSF pH fell dramatically creating a marked disparity between blood and brain.

The tendency to accumulate H⁺ ions in CSF is attributed to the marked permeability of the blood-brain barrier to CO₂ whereas it is relatively impermeable to HCO₃⁻ ion. Furthermore, in contrast to blood with its large buffer reservoir CSF is practically unbuffered toward CO₂ because nonbicarbonate buffer systems such as proteins and phosphates are virtually absent.

Bicarbonate diffuses across the blood-brain barrier slowly and is not immediately available to augment the limited CSF buffering capacity in the face of an increase in CO₂ tension. In the present experiments, CSF HCO₃ and pH began to increase only toward the end of the 20 minute intervention period.

Our results suggest the possibility that excessive accumulation of H⁺ in CSF could result from bicarbonate administration in man during resuscitation. Data depicting the acid-base status of CSF in man during and following cardiac arrest are presently not available. However, Posner and Plum and others have observed cerebral dysfunction to follow treatment with bicarbonate of metabolic acidosis from other causes. They documented a marked disparity between arterial and CSF pH and suggested that a CSF pH below 7.2 is associated with impaired consciousness. Such a fall in CSF pH has been demonstrated in the present study following bicarbonate administration, and may play a role in post-arrest cerebral dysfunction in man. The data must be interpreted with caution, however, since cisternal fluid may not accurately reflect intracellular events in the brain. Furthermore, post resuscitative behavior of animals could not be observed in the present protocol.

While extrapolation from animal studies may be premature, the present data stress the importance of early correction of the respiratory component of post-arrest acidosis by adequate ventilatory support. Since both acidosis and alkalosis are clearly detrimental to cardiac function, the dose of NaHCO₃ must be judiciously chosen. Frequent rapid analysis of blood acid-base parameters is highly desirable during resuscitation. It is of interest that the recent recommendations of the National Academy of Sciences emphasize this point and also sharply reduce the suggested dosage of bicarbonate in man. Further studies are indicated to define the role of NaHCO₃ therapy following cardiopulmonary arrest in man to evaluate the significance of alterations in CSF acid-base balance.
Acknowledgment

We are grateful to Dr. Jerome Posner for a critical review of the manuscript. We are indebted to Mr. James Ellison for his help with the laboratory experiments; to Mr. Stuart Gordon for the statistical part of this work; and to Mrs. Carmen Retz and Miss Carol Webster for preparing the manuscript.

References

20. Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 227 (suppl): 834, 1974
Cerebrospinal fluid acidosis complicating therapy of experimental cardiopulmonary arrest.

K J Berenyi, M Wolk and T Killip

*Circulation*. 1975;52:319-324
doi: 10.1161/01.CIR.52.2.319

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/52/2/319

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/