pH Changes On the Surface of Brain and In Cisternal Fluid in Dogs in Cardiac Arrest

S. Javaheri, M.D., A. Clendening, B.S., N. Papadakis, M.D., and J.S. Brody, M.D.

SUMMARY We measured brain surface pH and cisternal cerebrospinal fluid (CSF) acid-base variables in Na-pentobarbital anesthetized dogs during KCl induced cardiac arrest. Electrocardiographically, an agonal rhythm occurred within seconds, presumably resulting in rapid fall in cerebral blood flow. The mean arterial blood pressure fell from 125 ± 22 (mean ± 1 SD) to 35 ± 28 mm Hg at 30 seconds and to 19 ± 3 mm Hg at 60 seconds after KCl injection. The mean brain surface pH (n = 8) dropped abruptly from 7.30 to 6.80 within 3 minutes after induction of cardiac arrest. Changes in cisternal CSF pH, however, occurred slowly with the mean pH falling from 7.33 to 7.27 at 4 minutes and to 6.99 at 10 minutes after induction of cardiac arrest. The fall in cisternal CSF pH was due to a rise in CSF concentration of organic acids as well as a rise in CSF P CO2; the mean cisternal CSF [HCO3] fell 3.6 mEq/l while the mean cisternal CSF lactate concentration and the mean CSF P CO2 rose, respectively, 2.1 mEq/l and 37.8 mm Hg 10 minutes after induction of cardiac arrest. We conclude that during acute ischemic anoxia pH disequilibria develop between brain extracellular fluid and cisternal CSF; analyses of the latter fluid provide unreliable information about brain metabolic status and its acid-base balance even up to ten minutes after induction of cardiac arrest.

Methods

General

Mongrel dogs (n = 16) weighing from 15–20 kg were anesthetized with intravenous injection of sodium pentobarbital (initially 30 mg/kg followed by 4.5 mg/kg 2 h later) and paralyzed by intramuscular injection of succinylcholine (40 mg initially and 20 mg every 2 h). Ventilation was maintained on oxygen through an endotracheal tube by a volume respirator adjusted to keep the arterial P CO2 (Pa CO2) normal. End tidal P CO2 (PETCO2) was recorded continuously using an infra-red CO2 analyzer. Two femoral arteries and one femoral vein were cannulated for monitoring arterial blood pressure, obtaining blood samples and intravenous injections. Through a midline incision atlanto-occipital membrane was exposed for obtaining cisternal cerebrospinal fluid. Rectal temperature was measured by a thermometer.

Fifteen minutes after stable PETCO2, simultaneous femoral arterial blood (3 ml) and cisternal CSF (2 ml) samples were collected for determination of gas tensions and pH and CSF potassium and lactate concentrations. If CSF was bloody the animal was not used.

Measurement of Brain Surface pH

Details of our technique for measurement of the brain surface pH have been described previously: a modified technique of Rapoport,4 Loeschcke and co-workers5, 6 and Fencl and associates7, 8 was used. Briefly, a small parietal craniotomy was performed and a combination pH electrode (Ingold Inc., Lexington, Mass.) was placed on the surface of the brain on the pia-arachnoid membranes where large vessels were absent. The flat surface of the pH electrode was round with a diameter of 4 mm. The reference electrode was either placed on the pia-arachnoid or on the adjacent dura. The weight of the electrode was balanced by a special lever. The pH electrode was connected to a pH electrometer (Model 213, Instrumentation Laboratory, Lexington, Mass.) and recorder. pH calibrations were performed at 37°C with precision buffers (pH = 6.840 and 7.340) before and after each experiment; there was essentially no shift.

Brain surface temperature was measured by a ther-
mocouple (Model 127, Bailey Instrument, Saddlebrook, New Jersey) with its tip in the fluid adjacent to pH electrodes. Brain surface was heated by a heating lamp when surface temperature fell to 36.5°C.

**Induction of Cardiac Arrest**

After obtaining baseline samples and recording a stable brain surface pH, cardiac arrest was induced by bolus injection of 35–40 ml of saturated KCl. Electrocardiogram was recorded continuously. Brain surface pH was measured in 8 animals; in these cisternal CSF samples were obtained only at 0 time and after 3 minutes of induction of cardiac arrest in order not to disturb the position of the pH electrodes on the brain. In the remaining 8 animals, however, CSF samples were obtained periodically throughout the experiment (see results). In this context, it is emphasized that KCl induced cardiac arrest is an extremely reproducible event.

**Measurements, Analysis and Calculation**

A four-channel recorder (Hewlett Packard, San Diego, California) was used for continuous recording of blood pressure, PECO2, and brain surface pH. Gases of known concentration were used to calibrate the infrared CO2 analyzer (LB—2 Bechman, Medical Gas Laboratory) at 37°C. P O2 and P CO2 electrodes were calibrated with humidified gases of known P O2 and P CO2.

All pH electrodes were calibrated with precision buffers (6.840 and 7.384 at 37°C). These calibrations were made repeatedly throughout the experiment before and after each measurement. Through the three-way-stopper a small amount of cisternal CSF was initially drawn into a dry glass syringe for flushing and filling of its dead space. Cisternal CSF was then obtained anaerobically for immediate measurement of P CO2 and pH. Arterial blood samples were obtained anaerobically by syringes whose dead space was filled with heparin. All arterial and cisternal gas tensions and pH measurements were corrected for the animal’s rectal temperature using respective correction factors.9,10 Cisternal CSF [HCO3−] was calculated from the Henderson-Hasselbalch equation using appropriate pK’values and CO2 solubility factors.9 All pH values were converted to [H+] for further calculations.

Lactate concentration in the cisternal cerebrospinal fluid was determined spectrophotometrically (Sigma Chemical Company, St. Louis, Missouri) and |K+| by flame photometry.

For comparison of two means, two tailed paired or unpaired t test (whichever appropriate) was used. Analysis of variance was used when comparison was made among more than two sample means. P values <0.05 were considered significant.

**Results**

Electrocardiographic abnormalities characterized by asystole ventricular fibrillation or an agonal rhythm occurred within seconds after KCl injection; the length of such periods, however, was variable with an average of 41 seconds (± 30, 1 SD; n = 8). Hemodynamically, there was a relatively abrupt and pronounced drop in the mean arterial blood pressure (table 1), resulting in cerebral ischemia.

**Table 1** Changes in the Mean Arterial Blood Pressure (MABP), Brain Surface [H+] and Cisternal Cerebrospinal Fluid (CSF) P O2, P CO2, and H+, HCO3—, Lactate and K+ Concentrations During Cardiac Arrest (Mean ± so)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0.0</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>125</td>
<td>35*</td>
<td>19*</td>
<td>8*</td>
<td>8*</td>
<td>8*</td>
</tr>
<tr>
<td>±22</td>
<td>±28</td>
<td>±3</td>
<td>±2</td>
<td>±2</td>
<td>±2</td>
<td></td>
</tr>
<tr>
<td>Surface [H+] (nmol/l)</td>
<td>50.3</td>
<td>55.2*</td>
<td>69.6*</td>
<td>129.8*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>±3.0</td>
<td>±6.0</td>
<td>±6.3*</td>
<td>±17.4</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Surface pH</td>
<td>7.30</td>
<td>7.26</td>
<td>7.16</td>
<td>6.89</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CSF [H+] (nmol/l)</td>
<td>46.3</td>
<td>47.5</td>
<td>48.5</td>
<td>49.5</td>
<td>54.1*</td>
<td>101.7*</td>
</tr>
<tr>
<td>±4.5</td>
<td>±6.2</td>
<td>±6.5</td>
<td>±5.9</td>
<td>±6.7</td>
<td>±20.3</td>
<td></td>
</tr>
<tr>
<td>CSF pH</td>
<td>7.33</td>
<td>7.32</td>
<td>7.31</td>
<td>7.31</td>
<td>7.27</td>
<td>6.99</td>
</tr>
<tr>
<td>CSF P O2 (mm Hg)</td>
<td>45.7</td>
<td>46.6</td>
<td>46.5</td>
<td>46.6</td>
<td>49.8*</td>
<td>83.5*</td>
</tr>
<tr>
<td>±3.7</td>
<td>±2.0</td>
<td>±2.3</td>
<td>±5.8</td>
<td>±3.0</td>
<td>±14.0</td>
<td></td>
</tr>
<tr>
<td>CSF [HCO3—] (mEq/l)</td>
<td>22.9</td>
<td>22.2</td>
<td>22.4</td>
<td>21.3</td>
<td>21.1</td>
<td>19.3*</td>
</tr>
<tr>
<td>±2.8</td>
<td>±2.9</td>
<td>±2.6</td>
<td>±1.8</td>
<td>±2.6</td>
<td>±1.6</td>
<td></td>
</tr>
<tr>
<td>CSF P CO2 (mm Hg)</td>
<td>124.0</td>
<td>111.0</td>
<td>100.0</td>
<td>96.0*</td>
<td>63.0*</td>
<td>34.0*</td>
</tr>
<tr>
<td>±22.0</td>
<td>±14.0</td>
<td>±28.0</td>
<td>±15.0</td>
<td>±12.0</td>
<td>±7.0</td>
<td></td>
</tr>
<tr>
<td>CSF K+ (mEq/l)</td>
<td>3.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3.5</td>
<td>5.5*</td>
</tr>
<tr>
<td>±0.2</td>
<td>±0.2</td>
<td>±0.7</td>
<td>±1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF lactate (mEq/l)</td>
<td>1.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.1</td>
<td>3.9*</td>
</tr>
<tr>
<td>±0.4</td>
<td>±0.2</td>
<td>±0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates statistical significance with p < 0.05 compared to values at time 0.0 (KCl injection). The brain surface pH had fallen to 6.80, three minutes after KCl injection in all animals studied (n = 8). For CSF values there are at least 5 measurements at each time. For comparison of surface and CSF [H+] see page 8.
brain surface pH and end-tidal P
CO2 (PECO2) vs time during cardiac arrest.

FIGURE 1. Changes in the mean arterial blood pressure, brain surface pH and end-tidal P
CO2 (PECO2) vs time during cardiac arrest.

Changes in the mean arterial blood pressure and PE
CO2, photographed from the original record of one animal. The initial segment of the pH recording demonstrates a Rapoport test. Intravenously infused NaHCO3 (10 ml, 1 M) resulted in a rise in P
CO2, and consequently brain surface pH fell; this was followed by a gradual return of the surface pH toward normal. These sequences of events suggested that the blood-brain barrier had remained intact.

Changes in the brain surface pH and blood pressure were noted within few seconds after KCl injection. The brain surface pH fell to 6.80 pH units within less than 3 minutes, a pattern seen in all 8 animals studied. In some cases we noted that the slope of the fall in brain surface pH was interrupted by a very small and transitory rise in pH lasting for few seconds (fig. 3). The reasons for this are not well understood; a similar alkaline shift in cerebellar ECF pH during ischemia has been observed by Kraig et al in rat.

Figure 2 shows changes in brain surface and cisternal CSF pH during cardiac arrest. The slopes of changes were profoundly different; the brain surface pH fell by 0.50 and CSF pH by 0.34 pH units, respectively 3 and 10 minutes after induction of cardiac arrest. The increments in the mean surface |H
+| were 4.9 ± 3.6 (SD), 19.3 ± 4.5 and 79.6 ± 18.0 nmol/l, respectively 30, 60 and 120 seconds after induction of cardiac arrest; respective values for changes in CSF |H
+| were 1.7 ± 4.5 (mean ± SD, paired values) 3.1 ± 4.8 and 3.4 ± 4.8 nmol/l and these values were lower than the respective values of surface |H
+| with p values of 0.09, <0.0001 and 0.0001, respectively (two tailed, unpaired t test). With time, however, cisternal CSF pH fell gradually (fig. 2; see later).

We emphasize that we did not measure the temperature in the suboccipital cistern and therefore we chose to correct all CSF pH values to the animal’s rectal temperature rather than brain surface temperature. Although the temperature correction factor is small the differences between surface and CSF pH values during cardiac arrest would have been more pronounced if we had used the lower brain temperature as the correction factor for CSF pH values.

Changes in cisternal CSF acid-base variables and |K
+| (table 1) were characterized by a slow and gradual rise in P
CO2 and H
+, K
+ and lactate concentrations and a fall in CSF P
CO2 and |HCO3
-| within the ten minutes after cardiac arrest. These trends were uniformly observed in all animals.

The mean arterial P
CO2 fell from 320 ± 70 torr (SD) to 63.3 ± 33 and the mean arterial blood |H
+| rose from 45.5 ± 4.2 to 53.5 ± 11.2 nmol/l after 10 minutes of cardiac arrest. The mean arterial P
CO2 fell from 35.5 ± 3.0 to 20.0 ± 3.0 torr and P
CO2 gradually fell and approached zero due to the high ventilation-perfusion ratio (unchanged mechanical ventilation with reduced venous return and cardiac output).

Discussion

The results of the present study demonstrate that extremely rapid and profound changes in the brain surface pH occur during cardiac arrest; most importantly, however, such pH changes are reflected very slowly in cisternal CSF. The latter grossly underestimated the severity of the metabolic events which occurred within the brain during acute anoxic ischemia.

The continuous recording of brain surface pH coupled with periodic measurements of cisternal CSF pH in this study, clearly demonstrated the time dependent pH disequilibria which might exist between brain and cisternal CSF during acute events. This observation makes measurement of the changes in the latter fluid a poor candidate for assessment of brain tissue acid-base balance under such circumstances.

Four minutes after induction of the cardiac arrest, the mean CSF P
CO2 and HCO3
-, K
+ and lactate concentrations had changed very little (table 1); the mean brain surface and CSF pH had fallen, respectively by about 0.5 and 0.2 pH units 3 minutes after cardiac arrest (fig. 2). We are not aware of any other studies in the literature to compare our data with, but the notable difference in pH changes between the two fluids should reflect the time-dependent diffusion processes occurring between CSF and ECF during cerebral ischemia; specifically this represents the delayed permeation of CO2 and organic acids into CSF from ECF as they diffuse into the latter compartment from within the brain cells. The rise in CSF P
CO2 as measured in the
present study and tissue \( P_{CO_2} \) as measured by Severinghaus and Feustel\(^{12} \) was mainly due to nonmetabolic \( CO_2 \) generation via titration of \( HCO_3^- \) with organic acids produced in excess during cerebral ischemia;\(^{13, 14} \) in this context it is noted that in cisternal CSF the fall in the mean \( | HCO_3^- | \) was 3.6 and the rise in lactate concentration was 2.1 mEq/l, 10 minutes after induction of cardiac arrest.

The development of rapid and profound brain surface acidosis measured by surface pH electrodes in the present study is similar to the previously reported pH changes during acute cerebral ischemia as measured by pH electrodes\(^{8-13} \) (see later) or biochemically.\(^{14} \) We have observed similar brain surface pH changes during Na-pentobarbital induced cardiac arrest in dogs.\(^{15} \) Such profound pH changes are due to excessive production of organic acids\(^{13, 14} \) (or their equivalents; see reference 18) as a result of anaerobic consumption of glucose during cerebral ischemia. Assuming that similar brain pH changes may occur in man, it is noteworthy that brain function can return to normal after 3 to 4 minutes of cardiac arrest.

It may be argued as to how accurately the changes in brain surface pH as measured in the present study as well as several other studies\(^{8-13} \) represent actual changes which occur within the brain tissue, particularly in view of the acute nature of the study\(^{16} \) and the potential influence of a slow or an asymmetric DC potential shift developing during cerebral ischemia and affecting the surface pH values. The latter argument i.e. the influence of asymmetric potential changes on pH is also applicable to pH measurements by microelectrodes when the reference barrel is not side by side to the actual pH barrel.

To this end, in one animal we simultaneously measured both brain surface fluid pH, by placing our surface electrode on one cerebral hemisphere, and brain ECF pH by inserting a double-barrelled microelectrode\(^{20, 21} \) 5 mm below the cortex into the other hemisphere. Although the steady state pH values were different, the slopes of changes were remarkably similar during induction of cardiac arrest (fig. 3).

The double-barrelled microelectrodes had a tip-diameter of 30 \( \mu M \) with the tip of the reference barrel (10 \( \mu M \)) next to the tip of the pH barrel (20 \( \mu M \)). The resemblance of the two pH tracings, therefore, suggests that the pH changes recorded by the surface electrodes were not affected by either artifactual cortical \( P_{CO_2} \) changes or asymmetric or slow DC potentials developing during cardiac arrest. Further studies using intracerebral ECF pH microelectrodes have shown similar pH changes during cardiac arrest (unpublished observations).

In conclusion, profound changes occurred in brain ECF pH during cardiac arrest and analyses of cisternal CSF provided unreliable information about the magnitude of the severity of brain metabolic derangements under such circumstances. We have also shown that time dependent pH disequilibria exist between cisternal CSF and brain surface fluid during respiratory arrest\(^{22} \) as well as during transients of acute metabolic acid base perturbations.\(^{1, 20} \) In this context, other investigators have shown that during ischemia or hypoxia rapid and pronounced changes occur in cerebral ECF electrolyte composition;\(^{23} \) specifically ECF K\(^+ \) and lactate concentrations have been shown to rise relatively abruptly\(^{24-27} \) while respective changes in CSF as shown in the present study (table 1) as well as by others\(^{24, 28} \) occur relatively slowly. Therefore, taken together, all these studies suggest that caution should be taken in relying on changes in cisternal CSF for an assessment of brain metabolic status during acute events.

References


21. de Hemptinne A. Intracellular pH and surface pH in skeletal and cardiac muscle measured with a double-barrelled pH microelectrode. Pflugers Arch 386: 121-126, 1980


PH changes on the surface of brain and in cisternal fluid in dogs in cardiac arrest.
S Javaheri, A Clendening, N Papadakis and J S Brody

Stroke. 1984;15:553-557
doi: 10.1161/01.STR.15.3.553

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/15/3/553

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at:
http://stroke.ahajournals.org//subscriptions/