Effect of Cerebral Blood Flow Generated During Cardiopulmonary Resuscitation in Dogs on Maintenance Versus Recovery of ATP and pH

Scott M. Eleff, MD; Hotack Kim, MD; D. Hal Shaffner, MD; Richard J. Traystman, PhD; Raymond C. Koehler, PhD

Background and Purpose: Cardiopulmonary resuscitation with external chest compression generates low perfusion pressures that may be inadequate for restoring cerebral metabolism and may worsen intracellular pH. We tested the hypothesis that cerebral reperfusion with a low perfusion pressure after arrest restores brain adenosine triphosphate (ATP) and pH to levels attained at the same perfusion pressure without preceding complete ischemia.

Methods: Brain ATP and intracellular pH were measured by magnetic resonance spectroscopy, and cerebral blood flow was measured with microspheres in anesthetized dogs. External chest compressions were begun in group A (n=6) immediately after the onset of arrest (ie, arrest time zero) and in group B (n=10) after 6 minutes of arrest (ie, arrest time 6 minutes). In both groups, mean cerebral perfusion pressure was regulated at 30 mm Hg for 70 minutes by adjustment of inflation pressure of a pneumatic thoracic vest.

Results: At 12 minutes of resuscitation, cerebral blood flow was 27±4 mL/min per 100 g in group A and 21±4 mL/min per 100 g in group B, but ATP in group B (58±10% of prearrest) was less than in group A (105±6%). With prolonged resuscitation, ATP deteriorated to near zero levels in dogs in group B, with blood flow less than 15 mL/min per 100 g. Dogs with greater blood flow never achieved complete metabolic recovery. In group B, intracellular pH was unchanged from the 6.3 value at the start of resuscitation, even in those dogs with extremely low blood flows.

Conclusions: Levels of cerebral perfusion pressure sufficient to maintain cerebral oxidative metabolism without complete ischemia during cardiopulmonary resuscitation are not sufficient to restore metabolism after complete ischemia during cardiopulmonary resuscitation. However, low "trickle" blood flow did not worsen intracellular acidosis. (Stroke. 1993;24:2066-2073.)

Key Words: • acidosis • cardiopulmonary resuscitation • cerebral blood flow • spectroscopy, nuclear magnetic resonance • dogs

Sudden cardiac arrest is a leading cause of brain damage and death.1 Many neurochemical changes based on decreased oxidative metabolism occur within the first several minutes of complete cerebral ischemia associated with cardiac arrest. Among these changes are depletion of brain adenosine triphosphate (ATP) and a fall in intracellular pH (pHi) from 7.1 to 6.3.2 Cardiopulmonary resuscitation (CPR) with external chest compression is intended not only to restore spontaneous circulation but also to generate cerebral blood flow (CBF) and thereby reverse or at least ameliorate neurochemical changes. Unfortunately, clinical resuscitation has variable success in restoring normal brain function after restoration of spontaneous circulation; it depends primarily on preceding arrest (no-flow) time and CPR (low-flow) time.3–4 External

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CPR basic life support (BLS steps A through C) very rarely restores consciousness before restoration of spontaneous normotension. When CBF was maximized during cardiac arrest with either cardiopulmonary bypass or vest CPR, 31P magnetic resonance spectroscopy (MRS) demonstrated good recovery of pH, and high-energy phosphates, a prerequisite for brain viability. Normal levels of cerebral perfusion pressure (CPP; mean arterial pressure minus intracranial pressure) were generated in those studies.5,6 In clinical CPR, in contrast, peak aortic pressures are typically 60 to 80 mm Hg during chest compression, with mean aortic pressures of only 30 to 50 mm Hg. The actual CPP is probably <30 mm Hg because intracranial pressure is about one third of aortic pressure.6,7 Such a low level of CPP in experimental CPR is associated with subnormal levels of CBF and poor outcome.8,9

In the present study, CPP was intentionally maintained at only 30 mm Hg to simulate the clinical situation. In the absence of previous complete ischemia, a CPP of 30 mm Hg is near the partial ischemic threshold for the onset of lactic acid production and reduced pH,
but above the CPP threshold associated with complete ATP depletion. However, once ATP and pH are reduced by complete ischemia, the level of CBF associated with a CPP of 30 mm Hg during reperfusion may be inadequate to restore ATP and pH. Thus, it is unclear whether the levels of ATP and pH attained at a CPP of 30 mm Hg after complete ischemia are similar to the levels attained without complete ischemia. We tested the hypothesis that the levels of brain ATP and pH, during reperfusion at a CPP of 30 mm Hg with CPR instituted after 6 minutes of cardiac arrest are not different from those attained at a CPP of 30 mm Hg when there is no delay in the onset of CPR. A 6-minute delay in CPR onset (arrest time) is sufficiently long for ATP depletion and steady-state reduction in pH but sufficiently short to allow significant neurological recovery after optimal CPP with good CBF levels. We performed CPR for a prolonged period of 70 minutes to permit adequate time for recovery.

Materials and Methods

All studies received approval of The Johns Hopkins Animal University Care and Use Committee. We studied 16 male mongrel dogs weighing 15 to 20 kg. All dogs were fasted overnight except for free access to water. Anesthetic consisted of sodium pentobarbital (10 mg/kg IV) and fentanyl (50 μg/kg IV). The trachea was intubated, and the lungs were ventilated with 100% inspired O2. Via femoral cannulation, catheters were inserted into the descending thoracic aorta, left ventricle, and right atrium. An axillary artery was cannulated for microsphere reference sampling. Temporalis muscle and skin were fully retracted from the skull to prevent contamination of the MRS spectrum. A midline burr hole was made in the skull, and a catheter was inserted into the sagittal sinus proximal to the confluence of the sinuses. A vest with an inflatable bladder that covered two thirds of the thoracic circumference was secured snugly around the thorax with Velcro straps. A warm-water-perfused blanket was wrapped around the abdomen. The animal was placed onto a copper-lined cradle with the head fixed in position by a stereotactic frame. Dogs received an additional 6 mg/kg per hour of sodium pentobarbital during the surgery. Pancuronium bromide (0.2 mg/kg IV) was administered to prevent movement. Lactated Ringer’s solution containing no glucose (30 mL/kg) was infused during the surgery to ensure adequate cardiac filling pressures during subsequent CPR.

Ventricular fibrillation was induced by passing a 60-Hz current through a pacing electrode catheter in the right heart. CPR commenced either immediately after arrest (group A, n=6) or after a 6-minute delay (group B, n=10). The thorax was compressed by cycling vest pressure as previously described. The level of pressure in the vest was adjusted by varying the pressure in the reservoir chamber. The rise time to achieve a stable level of vest pressure was 150 milliseconds. Compressions occurred at a rate of 60 per minute with a 40% duty cycle. The microprocessor also controlled a pressure-limited ventilator to deliver 98.5% oxygen and 1.5% CO2 at a variable airway pressure of 20 to 35 cm H2O interposed after every fifth chest compression to maintain arterial Pco2 near normal levels. All animals received a bolus of 40 μg/kg of epinephrine at the start of CPR, followed by 10 μg/kg per minute continuous intravenous infusion to maintain vascular tone without affecting cerebral metabolism. Saline was infused at a rate of 4 ml/min for 70 minutes of continuous CPR. Vest pressure was continuously adjusted to maintain a CPP of 30 mm Hg. Mean sagittal sinus pressure, which is within a few millimeters of mercury pressure of intracranial pressure during CPR in dogs, was used as the downstream pressure.

Spectra were obtained with a CSI MRS Spectrometer (General Electric, Freemont, Calif) with a 4.7-T horizontal superconducting magnet (Oxford Instruments, Oxford, UK). The magnet has a 40-cm bore with a sensitive volume of approximately 25 cm³ over which the magnetic field homogeneity is 0.1 ppm. An inductively coupled, two-turn, 7-cm-diameter copper surface coil double-tuned to 81 MHz (31P) and 200 MHz (1H) was placed directly over the skull. The field was shimmed on the water proton signal to better than 0.3 ppm. 31P MRS signals were collected every 3 seconds with a 110-microsecond, 80-W excitation pulse and a 2.9-second 1-W saturation pulse 10 ppm upfield from phosphocreatine. MRS data were averaged and stored as 1-minute blocks.

Each 1-minute spectrum was analyzed with the GENCAP least-squares best fit routine for amount of phosphocreatine, inorganic phosphate (P), and ATP. pH was calculated from the shift of P, by the formula of Petroff et al:

\[ \text{pH} = 6.77 + \log[(\alpha - 3.29)/(5.68 - \alpha)] \]

where \( \alpha \) is frequency difference from phosphocreatine to P, in parts per million. The data were then reanalyzed averaging five 1-minute scans centered around the time of microsphere injection because during CPR, that measurement of CBF is a time-weighted average over 5 minutes. The Fourier transformation of the sum of 100 free induction decays (data points, 1024; frequency range, 6.0 kHz) was performed after application of a 30-Hz exponential filter. Typical phosphocreatine line width was 45 Hz (0.6 ppm) with a signal-to-noise ratio of >30:1. The phosphocreatine peak of the control spectrum was chosen as zero offset. The stability of the system was such that there was no frequency shift of phosphocreatine during CPR. This offset value was used even in those time points in group B when individual animals had no measurable phosphocreatine. Intracellular brain bicarbonate was calculated from the Henderson-Hasselbach equation, a pKa of 6.12, a CO2 solubility coefficient of 0.0314 mmol/L/mm Hg, pH derived by MRS, and sagittal sinus Pco2 as a close approximation to intracellular Pco2.

Arterial and sagittal sinus blood samples were analyzed for pH, Pco2, and P02 with a Radiometer ABL3 electrode system. Oxygen content was measured by a Radiometer Hemoximeter OSM3. Blood glucose concentrations were analyzed with a Yellow Springs Glucose Analyzer (model 2300A).

Spheres 15 μm in diameter labeled with one of six isotopes (152Gd, 114mIn, 113Sn, 108Ru, 99mTc, 46Sc) (Dupont-NEN Products, Boston, Mass) allowed CBF to be measured at six times per animal. A dose of about 1.5 million spheres (prearrest) or 0.5 million spheres during CPR was injected into the left ventricle while an arterial reference sample was withdrawn with a Harvard syringe.
pump at a rate of 3.8 mL/min from the axillary artery for 2 minutes before arrest and at a rate of 1.9 mL/min and for 5 minutes during CPR to ensure full washout of spheres during the low-cardiac-output state with CPR. Use of microspheres during CPR has been previously validated in this laboratory. CBF and cerebral metabolic rate of O₂ (CMRO₂) were calculated as previously described.

All data were analyzed before arrest and at 12, 20, 35, 50, and 70 minutes of CPR. One-way analysis of variance (ANOVA) with repeated measures and the Fisher protected least significant difference test was used at a .05 significance level to analyze for intragroup changes in blood gases, blood flow, and MRS measurements from prearrest baseline and for changes during prolonged CPR from the 12-minute CPR value. Differences between groups A and B at individual time points were analyzed by preplanned t tests. However, post hoc inspection of the data in group B revealed a bimodal distribution in CBF, CMRO₂, and ATP. Therefore, group B was further divided into two cohorts based on the level of CBF during early CPR. Four dogs in group B with CBF <15 mL/min per 100 g at 12 minutes of CPR were placed in a low-flow cohort (L), whereas six dogs in group B with CBF >15 mL/min per 100 g were placed in a moderate-flow cohort (M). One-way ANOVA with repeated measures and the Fisher protected least significant difference test was performed on each cohort, and t tests were performed between cohorts at individual time points, to determine which measurements are affected differentially over two ranges of CBF during CPR. Values are reported as mean±SEM.

Results

In both groups, CPP was maintained near 30 mm Hg throughout 70 minutes of CPR (Fig 1). In group B, with 6 minutes of arrest time, CBF was less than prearrest levels, whereas in group A, with no arrest time, CBF at 20 minutes of CPR and thereafter was not different from prearrest levels and was greater than the corresponding levels in group B. However, CBF and the associated metabolic recovery in group B were observed to have a bimodal distribution. On the basis of CBF being greater or less than 15 mL/min per 100 g at 12 minutes of CPR, dogs in group B were further separated into moderate-flow (M; n=6) and low-flow (L; n=4) cohorts. The CBF value in cohort M (29±5 mL/min per 100 g) was distinctly greater than in cohort L (8±2 mL/min per 100 g) at 12 minutes of CPR and remained greater throughout CPR despite equivalent CPP levels of 30 mm Hg (Fig 1).

In group A, CMRO₂ was maintained at prearrest levels, whereas in group B, CMRO₂ was significantly reduced (Fig 2). CMRO₂ declined in both cohorts M and L, but the reduction in cohort L was substantially greater. Cerebral ATP was well preserved in group A for 50 minutes of CPR (Fig 2). In group B, ATP was undetectable at 6 minutes of arrest and never fully recovered during CPR. Separation of group B into moderate-flow and low-flow cohorts resulted in corresponding separation of ATP recovery. However, the level of ATP recovery of approximately 75% in cohort M was significantly less than the prearrest level.

During 6 minutes of arrest in group B, cerebral pH decreased to 6.3 and remained at this level throughout CPR (Fig 3). There was no recovery of pH in cohort M, nor was there worsening of the acidosis by the low CBF in cohort L during prolonged CPR. With no arrest time in group A, there was a progressive decline in pH from 7.11±0.03 to 6.32±0.24 over a period of 70 minutes of CPR. Values in groups A and B were not different by 50 minutes of CPR. The decline in pH in group A paralleled the progressive decline in sagittal sinus pH from 7.31±0.01 to 6.68±0.06 (Fig 3). With 6 minutes of arrest time in group B, there was also a progressive decline in sagittal sinus pH similar to that of group A.

Cerebral pH depends on metabolic acid titration of intracellular bicarbonate ([HCO₃⁻]) and on tissue PCO₂, which in turn depends on CBF. To help separate these effects, [HCO₃⁻] was estimated by using sagittal sinus PCO₂ as an approximation of tissue PCO₂. In group A, the progressive decrease in pH was associated with both an increase in sagittal sinus PCO₂ and a decrease in [HCO₃⁻], (Fig 4). In group B and in cohorts M and L, [HCO₃⁻] was initially reduced by 6 minutes of arrest and did not change significantly during CPR. Time-dependent increases in sagittal sinus PCO₂ occurred that were not different between groups A and B or between cohorts M and L. The [HCO₃⁻] level in group A eventually fell to that attained in group B, thereby
indicating a major contribution of decreased [HCO₃⁻], to the reduced pH in both groups.

Part of the increase in sagittal sinus PCO₂ was attributable to an increase in arterial PCO₂ when CPR was prolonged (Table 1). The marked reduction in arterial pH was associated with a reduction in arterial bicarbonate levels from 18±2 to 7±1 mmol/L in group A and from 19±1 to 5±1 mmol/L in group B over a period of 70 minutes of CPR. Arterial hemoglobin levels and O₂ saturation decreased approximately 20% by 70 minutes of CPR. However, there were no differences between groups A and B in arterial O₂ saturation, hemoglobin, pH, bicarbonate, or PCO₂, other than a lower PCO₂ in group B at 12 and 20 minutes of CPR (Table 1). When cohorts M and L were analyzed separately, there were no differences between cohorts in any of the above arterial measurements except O₂ saturation, which fell more in cohort L (86±9%) than in cohort M (92±4%) by 50 minutes of CPR.

Blood flow was also analyzed in other regions (Table 2). In brainstem and spinal cord, blood flow was maintained at or above prearrest levels in groups A and B. When analyzed separately, cohort M had higher flows than cohort L. Left ventricular blood flow was lower than prearrest levels, as expected, but did not deteriorate during 70 minutes of CPR in either group.

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**Discussion**

The major findings of this study are that (1) when CPR is instituted immediately upon cardiac arrest and CPP is maintained at 30 mm Hg, the level of CBF generated is sufficient to preserve global CMRO₂ and ATP for a prolonged period, but pH_i gradually declines in parallel with the progressive decline in arterial and cerebral venous pH and (2) generating a CPP of 30 mm Hg is inadequate for restoring pH_i and only partially restores cerebral ATP and CMRO₂ when the institution of CPR is delayed 6 minutes after arrest and ATP is already depleted. In the latter case, the degree of metabolic recovery among dogs varied substantially and cosegregated with levels of CBF above or below 15 mL/min per 100 g.

In the absence of complete ischemia, physiological and chemical markers of partial ischemia each have their own threshold over a wide range of reduced CPP and CBF. A CPP of 30 mm Hg is near the threshold at which brain lactate substantially increases, pH_i decreases, CMRO₂ decreases, and evoked potentials are suppressed. Small decreases in ATP are observed in some studies, although large decreases in ATP generally require lower levels of CPP than those required to cause acidosis. Therefore, the present
Fig 4. Graphs showing (A) sagittal sinus blood Pco2 and (B) estimated intracellular bicarbonate ion (HCO3−) concentration in cerebrum during 70 minutes of cardio-pulmonary resuscitation (CPR) after zero (group A) or 6 minutes (group B) of delay in CPR onset. There were no intergroup differences in sagittal sinus Pco2. The intergroup differences in intracellular pH were due to differences in brain bicarbonate. *P<.05 between groups A and B; there were no differences between cohorts M and L.

Results without complete ischemia in group A, in which a CPP of 30 mm Hg maintained CMRO2 and ATP, are consistent with these earlier studies using arterial hypotension or intracranial hypertension. Thus, use of chest compressions to generate CBF does not appear to adversely affect the brain’s ability to maintain metabolism at low CPP although chest compressions cause large phasic increases in cerebral venous pressure.7

The progressive decline in pH, in group A is also consistent with earlier studies indicating that a CPP of 30 mm Hg is near the threshold for brain lactic acid production.13,23 A second consideration for the decrease in cerebral pH without an accompanying decrease in global CMRO2 and ATP is that pH is a more sensitive marker of selectively ischemic cells attributable to heterogeneous microcirculatory blood flow at a low CPP. On theoretical grounds, the pH measurement is highly weighted by the compartment with the greatest P1, which, if there is ischemic heterogeneity, would be dominated by the most ischemic cells. A third explanation is that pH is also influenced by blood pH. Ordinarily, metabolic acidemia does not cause major changes in cerebral pH.27 However, at critically low levels of CPP, blood pH may affect brain pH. The parallel time course of intracranial and sagittal sinus pH in group A is consistent with this possibility. Therefore, the magnitude of the decrease in pH at low CPP may be specific for CPR because of the marked systemic metabolic acidosis associated with CPR and, in the case of the present study, the moderate respiratory acidosis. In addition, there was some decrease in arterial hemoglobin and oxygen saturation and a moderate hyperglycemia that could have amplified lactate acid production.

Results from group B in which the 6-minute arrest time caused ATP depletion and intracellular acidosis before CPR demonstrated the inability to recover normal metabolic parameters at perfusion pressures that are ordinarily sufficient for maintenance of oxidative metabolism. CBF, CMRO2, and ATP during CPR were not only significantly different from prearrest control but in many dogs actually continued to decrease throughout CPR after some initial recovery. Thus, a CPP of 30 mm Hg was sufficient to initiate but not maintain recovery, presumably because of several of the many phenomena associated with ischemia/reperfusion injury. This is in marked contrast to our previous study, in which a CPP of 70 mm Hg was associated with a

### Table 1. Arterial Blood Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Before Arrest</th>
<th>Duration of CPR, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Pco2, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>31±1</td>
<td>37±3</td>
</tr>
<tr>
<td>B</td>
<td>34±2</td>
<td>27±3*</td>
</tr>
<tr>
<td>pH</td>
<td>7.40±0.01</td>
<td>7.24±0.03†</td>
</tr>
<tr>
<td>B</td>
<td>7.37±0.02</td>
<td>7.20±0.04‡</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>14.5±1.1</td>
<td>14.4±1.3</td>
</tr>
<tr>
<td>B</td>
<td>15.0±0.7</td>
<td>14.5±0.5</td>
</tr>
<tr>
<td>O2 saturation, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>100±0</td>
<td>93±2</td>
</tr>
<tr>
<td>B</td>
<td>100±0</td>
<td>95±2</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>99</td>
<td>172</td>
</tr>
<tr>
<td>B</td>
<td>94</td>
<td>118</td>
</tr>
</tbody>
</table>

CPR indicates cardiopulmonary resuscitation and Pco2, partial pressure of CO2. Group A, no downtime; group B, 6-minute downtime.

*P<.05 from group A.
†P<.05 from prearrest values.
‡P<.05 from 12-minute CPR values.
TABLE 2. Regional Blood Flow (mL/min/100 g)

<table>
<thead>
<tr>
<th>Group</th>
<th>Before Arrest</th>
<th>12</th>
<th>20</th>
<th>35</th>
<th>50</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>A 30±3</td>
<td>33±6</td>
<td>47±11†</td>
<td>39±6</td>
<td>41±8</td>
<td>50±14†</td>
</tr>
<tr>
<td></td>
<td>B 37±3</td>
<td>53±16</td>
<td>36±5</td>
<td>27±6‡</td>
<td>29±8‡</td>
<td>27±7‡</td>
</tr>
<tr>
<td>Cervical spinal cord</td>
<td>A 15±3</td>
<td>21±4</td>
<td>32±8‡</td>
<td>26±4†</td>
<td>29±7†</td>
<td>25±7†</td>
</tr>
<tr>
<td></td>
<td>B 22±3</td>
<td>37±11†</td>
<td>28±5</td>
<td>21±5‡</td>
<td>24±7</td>
<td>22±7‡</td>
</tr>
<tr>
<td>Left ventricle (heart)</td>
<td>A 87±10</td>
<td>28±6†</td>
<td>40±13†</td>
<td>34±10†</td>
<td>26±7†</td>
<td>37±14†</td>
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<tr>
<td></td>
<td>B 112±21</td>
<td>19±4†</td>
<td>17±5†</td>
<td>18±6†</td>
<td>17±7†</td>
<td>16±7†</td>
</tr>
</tbody>
</table>

CPR indicates cardiopulmonary resuscitation. Group A, no downtime; group B, 6-minute downtime.

*P<.05 from group A.
†P<.05 from prearrest values.
‡P<.05 from 12-minute CPR values.

sustained recovery of 86% of brain ATP after a similar 6-minute arrest time before CPR, and the study by Angelos et al.,28 in which optimal CPR can restore consciousness even after 10 minutes of arrest time. This observation may partially explain the clinical observation of a strong inverse correlation between duration of resuscitative efforts and neurological outcome in the clinical situations where closed-chest massage generates only a subnormal level of ATP.39,40

The 6-minute arrest time group was subjected to a post hoc stratification based solely on whether the CBF was <15 mL/min per 100 g, a level associated with loss of electrical function.31,32 We expected a uniform scatter in CBF, since a CBF of 30 mm Hg is below the perfusion pressure associated with cerebral autoregulation.11,20

The surprising observation seen in Fig 1 is that dogs with an initially low level of CBF (cohort L) never improved and that dogs with moderate levels (cohort M) of CBF at 12 minutes maintained flows above 15 mL/min per 100 g throughout the study. The lack of metabolic recovery in cohort L as reflected in ATP and CMRO₂ recovery paralleled the lack of CBF recovery. Ordinarily, reductions in CBF below 10 to 15 mL/min per 100 g result in a large reduction in CMRO₂ and ATP.12,20 Thus, it is not surprising that reperfusion at such low levels of CBF is inadequate to restore CMRO₂ and ATP. In contrast, cohort M with CBF above 15 mL/min per 100 g demonstrated a rapid and sustained 70% recovery of ATP. CMRO₂ initially recovered to prearrest levels and then moderately decreased in parallel with modest decreases in CBF. It is not possible to state whether CBF declined in cohort M because of decreasing cellular metabolic requirements or whether CMRO₂ declined because of an inability to maintain CBF. The relatively high levels of sagittal sinus oxygen saturation in cohort M would tend to suggest that oxygen delivery was adequate and hence metabolism is controlling blood flow. This hypothesis is also supported by the observation that posts ischemic CMRO₂ decreases during early reperfusion, with normal levels of CPP before the onset of delayed hypoperfusion.32 Although brain temperature was not measured in the <6 dogs, subsequent preliminary data indicate that brain temperature slowly decreases about 1 to 2°C over the course of 1 hour of continuous CPR in the magnet and that early reductions in brain temperature are unlikely to account for the early reduction in CMRO₂.

The results of the present and previous2 studies at 12 minutes of CPR permit assessment of the CBF requirement for ATP repletion after 6 minutes of complete ischemia. In cohort L, with a CBF of 8±2 mL/min per 100 g, ATP recovery was 35±12%. In cohort M, with a CBF of 29±5 mL/min per 100 g, ATP recovery was 74±11%. In our previous study, with a CBF of 70 mm Hg, CBF at 12 minutes of CPR was 57±16 mL/min per 100 g and ATP recovery was 85±7%. Thus, early reperfusion with near-normal levels of CBF appears to be required to reestablish near-normal levels of ATP. This is in contrast to the no-arrest-time group, in which levels of CBF below normal (27±4 mL/min per 100 g at 12 minutes) were associated with ATP levels of 105±6% before arrest. The apparently greater CBF requirement for ATP repletion than for ATP depletion may be related to greater postischemic ATP utilization for restoring ionic gradients or to greater blood flow heterogeneity during reperfusion, resulting in a greater portion of underoxygenated cells.

The effect of CPR with a CBF of 30 mm Hg after 6 minutes of arrest on pH was remarkably different from our previous study with a CBF of 70 mm Hg.2 In the previous study, pH, rapidly returned to within 0.1 pH units of control by 35 minutes of CPR. This is in marked contrast to the present study, in which pH showed no recovery in the equivalent arrest time group B. Even in cohort M, with a 12-minute CBF value of 29±5 mL/min per 100 g, pH showed no significant recovery. An initial assumption might be that pH recovery is dependent on energy-requiring processes such as the sodium/potassium pumps and cannot be restored until ATP reaches a minimum threshold value.34 Restoration of these ionic gradients is necessary for proper functioning of Na⁺/H⁺ and HCO₃⁻/Cl⁻ antiporters.35 Thus, the 50% to 60% ATP recovery observed in group B as a whole and the 70% to 75% ATP recovery in cohort M may not have been sufficient to restore pH. Together, these studies suggest that CBF at or above normal levels is required to restore pH, during early reperfusion.

A major concern in the field of CPR research is whether trickle flow attained in some cases of CPR is worse than zero flow. This concern is based largely on experimental models of severe ischemia in which hyperglycemia worsens the acidosis and injury.36 The significant increase in arterial glucose in group A both over time and compared with group B (Table 1) may partially
explain the decrease in brain pH in group A. However, in cohort L, with low levels of CBF, a measurable amount of ATP was detectable during early CPR without a further decline in pH, or bicarbonate. Thus, in the absence of severe hyperglycemia, low flow does not worsen the acidosis beyond that attained with cardiac arrest. These data support the concept that early initiation of basic life support CPR does not worsen outcome. 27

The mechanism for extremely low CBF in some dogs was not addressed in the present study, but it could have important clinical implications. If cerebral edema is worse in some dogs, then intracranial pressure may exceed sagittal sinus pressure, and we may have overestimated CPP by using sagittal sinus pressure as the downstream pressure. However, increased intracranial pressure after CPR is not common except after very long arrest times. 28 A more likely mechanism is that a greater pressure gradient is required to reinitiate flow of stagnant blood cells than is required to maintain flow. Another possibility is interanimal variation in intravascular coagulation. In a previous study on heparinized dogs with comparable levels of CPP, CBF was maintained at 25 to 30 mL/min per 100 g whether or not there was a 5-minute arrest time. 29 Dogs in the present study received minimal amounts of heparin during flushing of the catheters. Thus, heparinization may be an important factor. Combined heparinization, hemodilution, and a brief bout of hypertension during early reperfusion is thought to ameliorate the no-reflow phenomenon. 30,31

In summary, this study underscores the difference in CBF required to maintain cerebral metabolism versus the level of CBF required to restore cerebral metabolism after cardiac arrest. In addition, the level of CBF attained after the onset of CPR is delayed is variable and not as well predicted by the level of CPP compared with no delay in instituting CPR. Such biological variability adds to the difficulty of evaluating therapy in clinical studies involving CPR.

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References


In humans, cardiac arrest and resuscitation produce a multifactorial neurological insult. After complete neurological ischemia (during cardiac arrest) of variable duration, the brain is subjected to incomplete cerebral ischemia of highly variable magnitude and duration during resuscitation and postresuscitation stabilization. Neurological outcome in patients in whom spontaneous circulation is restored also must be influenced by pre-arrest chronic health status and the common occurrence of hypoxia or hypotension preceding arrest. Not surprisingly, postresuscitation therapeutic strategies have been ineffective in improving neurological outcome. Clinical efforts to improve the pharmacological management of cardiopulmonary resuscitation also have failed to improve neurological outcome.

One promising approach to the identification and modification of physiological factors that contribute to poor neurological outcome is to develop better experimental models of cardiac arrest and resuscitation. The experimental strategy employed by Eleff and colleagues offers a unique opportunity to monitor brain bioenergetics on-line during cardiac arrest and resuscitation, while isolating and controlling critical physiological variables. In the present study, they have specifically examined the influence of 6 minutes of “downtime,” the interval of cardiac arrest and of complete global ischemia preceding cardiopulmonary resuscitation. Cardiopulmonary resuscitation was subsequently performed at clinically relevant levels of cerebral perfusion pressure. Predictably, cerebral blood flow and adenosine triphosphate levels were better preserved during resuscitation in animals that had no downtime.

However, this technologically demanding experiment, employing venous cardiopulmonary resuscitation during magnetic resonance spectroscopy, generated one unexpected and intriguing result. Animals in the group subjected to 6 minutes of cardiac arrest before resuscitation developed two distinctly different patterns of cerebral circulatory and metabolic responses. In 6 of 10 animals, cerebral blood flow, the cerebral metabolic rate for oxygen, and adenosine triphosphate levels were preserved nearly as well as in animals that had no intervening period of complete cerebral ischemia; in the other 4 animals, the same variables were profoundly reduced.

These observations, potentially important in improving understanding of the heterogeneous clinical outcomes after cardiac arrest, demand continued investigation. Perhaps the best explanation of the bimodal distribution of responses is simply variability among mongrel dogs. More optimistically, a central cerebral circulatory or biochemical mechanism can be proved to explain the divergent physiologic manifestations. If so, perhaps an interventional strategy can be developed that will be applicable to humans during cardiopulmonary resuscitation.

Donald S. Prough, MD, Guest Editor
Departments of Anesthesia and Neurology
The University of Texas Medical Branch
Galveston, Tex

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