Hypertension With Hemodilution Prevents Multifocal Cerebral Hypoperfusion After Cardiac Arrest in Dogs

Yuval Leonov, MD; Fritz Sterz, MD; Peter Safar, MD; David W. Johnson, MD; Samuel A. Tisherman, MD; and Ken-Ichi Oku, MD

Background: Improved neurological outcome with postarrest hypertensive hemodilution in an earlier study could be the result of more homogeneous cerebral perfusion and improved O₂ delivery. We explored global, regional, and local cerebral blood flow by stable xenon-enhanced computed tomography and global cerebral metabolism in our dog cardiac arrest model.

Methods: Ventricular fibrillation cardiac arrest of 12.5 minutes was reversed by brief cardiopulmonary bypass, followed by life support to 4 hours postarrest. We compared control group I (n=5; mean arterial blood pressure, 100 mm Hg; hematocrit, ≥35%) with immediately postarrest reflow-promoted group II (n=5; mean arterial blood pressure, 140–110 mm Hg; hypervolemic hemodilution with plasma substitute to hematocrit, 20–25%).

Results: After initial hyperemia in both groups, during the “delayed hypoperfusion phase” at 1–4 hours postarrest, global cerebral blood flow was 51–60% of baseline in group I versus 85–100% of baseline in group II (p<0.01). Percentages of brain tissue voxels with no flow, trickle flow, or low flow were lower (p<0.01) and mean regional cerebral blood flow values were higher in group II (p<0.01). Global cerebral oxygen uptake recovered to near baseline values at 3–4 hours postarrest in both groups. Postarrest arterial O₂ content, however, in hemodiluted group II was 40–50% of that in group I. Thus, the O₂ uptake/delivery ratio was increased (worsened) in both groups at 2–4 hours postarrest.

Conclusions: After prolonged cardiac arrest, immediately induced moderate hypertensive hemodilution to hematocrit 20–25% can normalize cerebral blood flow patterns (improve homogeneity of cerebral perfusion), but does not improve cerebral O₂ delivery, since the flow benefit is offset by decreased arterial O₂ content. Individualized titration of hematocrit or hemodilution with acellular O₂ carrying blood substitute (stroma-free hemoglobin or fluorocarbon solution) would be required to improve O₂ uptake/delivery ratio. (Stroke 1992;23:45–53)
cerebral organs. The results of several acute animal studies on global or focal brain ischemia by others concerning benefit from postischemic hypertension,12-15 or hemodilution,15,16-20 are consistent with our findings in cardiac arrest outcome studies.1,2

We hypothesize that increasing perfusion pressure and decreasing blood viscosity postarrest can mitigate the cerebral hypoperfusion and thereby improve brain O2 uptake/supply relationships and outcome. In this study, we used our established dog model2,21,22 to monitor for the first time the effect of postarrest hypertensive hemodilution on global, regional, and local CBFW. In exploratory subgroups, we also studied global cerebral oxygen uptake (CMRO2) in relation to cerebral arterial O2 delivery.

Materials and Methods

This project was approved by the Animal Use Committee of the University of Pittsburgh (Pa.). We used 10 healthy, custom-bred male coon hounds from the same breeding colony, mean age 10 (range, 8-12) months and mean weight 21 (range, 16-30) kg. Control group I (n=5) also served other studies.5,7,8 It was compared with a reflow-promoted group (n=5) with immediate hypertension plus delayed hypervolemic hemodilution. Both groups were studied in 1988-1989 by the same team over 3 weeks in randomized sequence. Placebo control of treatment was not possible.

Anesthesia was induced with ketamine (10 mg/kg i.m.) and maintained with 50:50% N2O/O2 plus 0.1-0.5% halothane by endotracheal intermittent positive-pressure ventilation, with paralysis by 0.2 mg/kg i.v. pancuronium as needed, and controlled normoxia and normocarbia. Sterile cutdowns were performed for monitoring and cardiopulmonary bypass.21,22 Control of extracerebral variables prearrest and post-arrest, from start of reperfusion with bypass of <5 minutes to resuscitation time at 4 hours, were the same in both groups.

We continuously monitored the electrocardiogram, heart rate, mean arterial blood pressure (MABP), central venous pressure, end-tidal CO2 and central venous (core) temperature. We intermittently monitored arterial blood gases and Hct. Ringer’s solution without glucose was infused intravenously. We controlled MABP at 100±10 mm Hg (mean±SD) by adjusting the halothane concentration before and by using norepinephrine or trimethaphan after cardiac arrest, central venous pressure at 5-15 mm Hg, PaCO2 at ≥100 mm Hg, PaO2 at ≥30-35 mm Hg, base excess at ±7 meq/L, blood glucose concentration at 100-175 mg/dl before arrest, and central venous temperature at 37.5±0.5°C. Cerebral ( tympanic membrane) Tc, not monitored here because it would interfere with CT, was equal to central venous temperature in other experiments.22 In preparation for the insult and during paralysis with pancuronium and intermittent positive-pres-
30-40 seconds after the start of xenon inhalation. Constancy of the CT slices was ascertained from the consistent position of bony landmarks. Resolution power in monkeys and humans seems to be \( \geq 5 \times 5 \times 5 = 125 \text{ mm}^3 \) regions. With the dog's head rigidly immobilized, we studied global CBF for the tissue volumes of two 5-mm-thick coronal slices located 10 mm apart. The anterior slice included the hippocampus and thalamus, and the posterior slice included the brain stem. Computer programs provided one CBF value for each voxel of \( 1 \times 1 \times 5 = 5 \text{ mm}^3 \). The CBF values of all voxels in each slice and in each selected anatomic region \((100-800 \text{ mm}^3 \text{ volume for each region})\) were averaged to determine global and regional CBF, respectively. We calculated local CBF as the percentage of voxels of each CT slice (percentage area) having specific flow ranges: no flow, 0-5 ml/100 cm\(^3\)/min; low flow, 11-20 ml/100 cm\(^3\)/min; normal flow, 21-40 ml/100 cm\(^3\)/min; hyperemic flow, >120 ml/100 cm\(^3\)/min. Because it interferes with xenon monitoring, \( \text{N}_2\)O was replaced by \( \text{N}_2\) and the analgesic effect was replaced by fentanyl given as a continuous intravenous infusion of 10 \( \mu \text{g/kg/hr} \), starting 1-2 hours before baseline CBF. About 10 minutes before starting xenon washin of the baseline CBF, halothane \((<0.5\%)\) was discontinued. No halothane was given during CBF measurements before cardiac arrest, and none at all after cardiac arrest. The inhaled gas delivered contained 67\% \( \text{O}_2/33\% \text{ N}_2\), which was switched to 33\% \( \text{Xe}/67\% \text{ O}_2 \) during CBF measurements. Two baseline CBF studies were performed before cardiac arrest. Additional CBF studies were performed at 10 and 30 minutes and 1, 2, 3, and 4 hours after reperfusion. Before each CBF measurement, MABP, \( \text{PaO}_2 \), \( \text{PaCO}_2 \), arterial \( \text{pH} \), base excess, Hct, and central venous temperature were controlled.

Two sham experiments without cardiac arrest reported in another article\(^6\) revealed stable reproducible global, regional, and local CBF values over time, autoregulation, and responsibility of CBF to lowered \( \text{PaCO}_2 \).

The \( \text{CMRO}_2 \) was determined in three dogs of each group. Through a sterile 2-cm craniotomy, a PE 50 nonocclusive catheter was inserted into the sagittal sinus with the catheter tip placed 1 cm rostral to the confluence of the sinuses. For each \( \text{CMRO}_2 \) determination, the catheter deadspace was cleared and arterial and sagittal sinus blood samples were drawn at a constant slow rate into heparinized syringes, cooled, and analyzed within 2 hours for \( \text{O}_2 \) content, using a Co-oximeter. Samples for arterial and sagittal sinus \( \text{O}_2 \) contents (\( \text{Cao}_2 \) and \( \text{CssO}_2 \), respectively) were taken just before each xenon inhalation without halothane. Global \( \text{CMRO}_2 \) was calculated as the global CBF of the posterior CT slice times the \( \text{Cao}_2 \) content gradient (i.e., global CBF \( \times \text{[Cao}_2 - \text{CssO}_2] \)).

The cerebral \( \text{O}_2 \) utilization coefficient was calculated as global \( \text{CMRO}_2/\text{arterial} \text{O}_2 \) delivery (i.e., global CBF \( \times \text{[Cao}_2 - \text{CssO}_2] \)/global CBF \( \times \text{Cao}_2 \); i.e., \( \text{[Cao}_2 - \text{CssO}_2]/\text{Cao}_2 \)). Although global CBF was calculated from only one CT slice and \( \text{Cao}_2 - \text{CssO}_2 \) from the entire cerebrum, relative changes of \( \text{CMRO}_2 \) were considered valid.

Data were analyzed for group differences within times and group interaction over time using a univariate repeated-measures analysis of variance. Scheffe's post hoc procedure was used for analyzing changes within each group over time (baseline versus postarrest). The \( \text{CMRO}_2 \) data were not statistically analyzed because of small numbers. Results are reported as mean±SD.

Results

All 10 dogs followed protocol to 4 hours postarrest. Before cardiac arrest there was no statistically significant difference between groups in central venous temperature, arterial \( \text{pH} \), \( \text{PaO}_2 \), \( \text{PaCO}_2 \), Hct, MABP, and central venous pressure. At 10 minutes postarrest, hemodilution fluid at room temperature in group II caused mean central venous temperature to decrease from 37.5°C (baseline) to 36.2°C. Spontaneous normotension was restored within a mean of 2 minutes and 37 seconds in group I, and a mean of 1 minute and 50 seconds in group II (NS). In group I, mild hemodilution from Hct 42±3% at baseline to 30±8% at 10 minutes postarrest, caused by cardiopulmonary bypass, was transient; Hct was 34±4% at 2 hours and 39±4% at 4 hours. In group II, Hct was reduced according to protocol from 45±3% at baseline to 22±1% at 10 minutes postarrest; Hct was 19±2% at 30 minutes, 17±1% at 1 hour and 22±2% at 4 hours \((p<0.01)\).

The hypertensive bout, immediately after restoration of spontaneous heartbeat, varied in both groups. According to protocol, it was higher in group II (182±42 mmHg; range, 120-250) than group I (112±24 mmHg; range, 90-200) \((p<0.01)\). At 30 minutes postarrest, MABP was 158±9 mmHg in group II versus 110±12 in group I \((p<0.01)\); thereafter, the difference was only numerical (NS). Central venous pressure was 3±1 mm Hg prearrest in group I and 3±3 in group II; central venous pressure was 14±2 mm Hg at 10 minutes postarrest in group I versus 13±7 in group II; and at 4 hours, central venous pressure was 5±3 mm Hg in group I versus 8±4 in group II (NS).

In each dog, the two baseline global CBF measurements were similar (approximately 50 ml/100 cm\(^3\)/min); there was a small SD within each group, and no significant difference between groups (Table 1 and Figure 1). Baseline regional CBF values (Figure 2) also were similar in both groups. Baseline local CBF values were also the same between groups, with essentially no voxels with local CBF <10 ml/100 cm\(^3\)/min (Figure 1).
During the initial transient hyperemia, neither group showed evidence of sustained no reflow foci. In both groups, hyperemia was more pronounced and lasted longer in midbrain and thalamus and less in neocortex, hippocampus, and white matter. During the hyperperfusion phase at 1–4 hours postarrest (Table 1 and Figure 1), mean global CBF was 51–60% of baseline in group I versus 85–100% of baseline in group II \((p<0.01)\).

In group I (Reference 7, Table 2), the first postarrest CBF measurement (at 3–22 minutes after restoration of heart beat) showed diffuse hyperemia with global CBF of about two times baseline (Table 1) and no voxels with CBF <20 ml/100 cm³/min (Figure 1A). During the hyperperfusion phase at 1–4 hours postarrest, mean global CBF was 55% of baseline. The percentage of voxels with a local CBF of 0–10 ml/100 cm³/min (no flow or trickle flow) was about 15%, whereas 40% of voxels had a local CBF of 0–20 ml (worse than baseline) \((p<0.01)\), 44% had a local CBF of 20–40 ml, and 16% had a local CBF of 40–120 ml/100 cm³/min.

In group II, the first postarrest CBF measurement (at 8–20 minutes after restoration of heart beat) showed the same diffuse hyperemia with global CBF of about two to three times baseline (Table 1) and also with no voxels with CBF <20 ml/100 cm³/min (Figure 1B). During the hyperperfusion phase at 1–4 hours postarrest, however, global CBF values were significantly higher than in group I \((p<0.01)\) and not significantly different from group II baseline values. At 1–4 hours postarrest, mean global CBF was 92% baseline (versus 55% in group I) (Table 1). The percentage of voxels with a local CBF of 0–10 ml/100 cm³/min was 4% (versus 15% in group I), while 15% of voxels had a local CBF of 0–20 ml (versus 40% in group I), 40% had a local CBF of 20–40 ml (similar to the 44% in group I); and 44% had a local CBF of 40–120 ml/100 cm³/min (versus 16% in group I). After blood was reinfused 2 hours postarrest, there was no worsening of CBF patterns, except in dog 29, which had a slight decrease in global CBF and an increase in low-flow voxels at 4 hours postarrest (Figure 1B).

Regional CBF values for all regions studied revealed the same flow advantages for group II as did global CBF values \((p<0.01)\); for hippocampus \(p<0.05)\) (Figure 2). All regional CBF values (except for the white matter in group I) were >20 ml/100 cm³/min. Throughout 1–4 hours postarrest, all regional CBF values for gray matter in both groups were >20 ml/100 cm³/min. In group II at 1–4 hours postarrest, all CBF values of predominantly gray matter regions were significantly higher than in group I \((p<0.01)\) and not significantly different from group II baseline values.

The \(Cao_2\) and \(C_{so2}\) values (Table 2) varied considerably between animals, but followed a consistent pattern within each dog over time. During the first postarrest CBF measurement ("10 minutes postarrest"), \(Cao_2\) decreased as a result of transient hemodilution by cardiopulmonary bypass. At 1–4 hours postarrest, with group II further hemodiluted by protocol, \(Cao_2\) in group II was about one half of that in group I. The baseline \(Cao_2–C_{so2}\) was 8.0±2.7 ml/dl in group I and 9.0±2.1 in group II; after transient decrease early postarrest, it increased (worsened) in group I to 12.2±2.3 at 4 hours and remained near baseline values of 7.5±1.3 at 4 hours in group II. The calculated \(O_2\) utilization coefficient also increased (worsened) similarly in both groups, from 0.4±0.1 prearrest to 0.7±0.1 at 3–4 hours postarrest. Thus, in group II the higher CBF was offset by the reduced \(Cao_2\).

Arterial \(O_2\) delivery (global CBF×\(Cao_2\) (Table 2) postarrest was approximately the same in both groups, since in the hemodiluted dogs (group II) the normalized global CBF was offset by a \(Cao_2\) of 60% of that in the control dogs (group I). The \(CMRO_2\) values (Table 2) prearrest in both groups combined ranged between 2.3 and 4.5 ml/100 cm³/min. Although global CBF at 1–4 hours postarrest was about 50% of baseline values in group I and similar to baseline values in group II (Table 1), \(CMRO_2\) values were similar in both groups at 1–4 hours (Table 2), recovering from very low levels immediately postarrest to near baseline values 4 hours

### Table 1. Global (Slice) Cerebral Blood Flow Before and After Cardiac Arrest in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Before arrest (−30 Min)</th>
<th>10 Min</th>
<th>30 Min</th>
<th>1 Hr</th>
<th>2 Hr</th>
<th>3 Hr</th>
<th>4 Hr</th>
<th>1–4 Hr</th>
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<tbody>
<tr>
<td>Control group I</td>
<td></td>
<td></td>
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<tr>
<td>(dogs 13, 16, 20, 33, 34)</td>
<td>gCBF*</td>
<td>47±6</td>
<td>106±18</td>
<td>48±10</td>
<td>28±2</td>
<td>26±3</td>
<td>24±4</td>
<td>26±4</td>
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<tr>
<td>% of baseline</td>
<td></td>
<td>100</td>
<td>227</td>
<td>104</td>
<td>60</td>
<td>56</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>Hypertensive hemodilution group II</td>
<td>gCBF*</td>
<td>43±5</td>
<td>90±24</td>
<td>37±9</td>
<td>39±7</td>
<td>40±8</td>
<td>43±6</td>
<td>36±6</td>
</tr>
<tr>
<td>% of baseline</td>
<td></td>
<td>100</td>
<td>210</td>
<td>87</td>
<td>90</td>
<td>93</td>
<td>100</td>
<td>85</td>
</tr>
</tbody>
</table>

Values are mean±SD in milliliters per 100 cm³ per minute for posterior coronal slices 5 mm thick. Values from anterior slices were similar. gCBF, global cerebral blood flow. *All values at 1–4 hours postarrest are different between groups \((p<0.01)\).
FIGURE 1. Two ventricular fibrillation cardiac arrest (VFCA) experiments to resuscitation time 4 hours. Dots are global cerebral blood flow (gCBF) of posterior computed tomographic (CT) slice. At same times as for gCBF, local CBF ranges in percent of voxels is quantitatively presented. Prearrest, there were essentially no voxels with local CBF <10 ml/cm<sup>3</sup>/min. Panel A: Representative dog (CT 16) of control group I. Postarrest normotension and normal hematocrit (Hct). The first CBF determination postarrest was at resuscitation time 3 minutes, immediately after defibrillation and restoration of spontaneous circulation; gCBF was about two times baseline with increased hyperemic voxels and no voxels with local CBF <20 ml/100 cm<sup>3</sup>/min. Up to 20% of voxels with no flow or trickle flow and 50% of voxels with <20 ml low flow, which were not present prearrest, appeared at resuscitation time 25 minutes. At resuscitation time 1-4 hours, there was continued gCBF at about 50% of baseline and increased percent voxels with low flow ranges.

Panel B: Representative dog (CT 29) of reflow-promoted group II. Postarrest hypertension and hemodilution. Baseline values are the same as control dog (panel A). At resuscitation time 10 minutes, hyperemia with gCBF was two times baseline. At resuscitation time 30 minutes, CBF returned to baseline values. At resuscitation time 1-4 hours, gCBF and local CBF patterns were the same as baseline. There was no postischemic hypoperfusion. No local CBF voxels in no-flow, trickle-flow, or low-flow ranges were in excess of baseline values. At resuscitation time 4 hours, reinfusion of shed blood caused a reduction of gCBF and increase in low-flow voxels.

Discussion

In this study of post–cardiac arrest CBF reduction to 50% baseline with standard life support to 4 hours, we achieved normalization of global, regional, and postarrest. Postarrest CMRO<sub>2</sub> values were similar in both groups, ranging between 1.4 and 2.1 ml/100 cm<sup>3</sup>/min at 1 hour and between 2.2 and 4.2 at 4 hours postarrest. There was no evidence of postarrest hypermetabolism in either group.
Table 2. Cerebral Metabolic Variables Before and After Cardiac Arrest in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Before arrest</th>
<th>After arrest</th>
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<tbody>
<tr>
<td></td>
<td>(-30 Min)</td>
<td>30 Min 1 Hr</td>
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<tr>
<td>Arterial O₂ content (ml/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>20.2±0.9</td>
<td>15.9±0.4</td>
</tr>
<tr>
<td>Group II</td>
<td>21.5±1.4</td>
<td>9.9±0.2</td>
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<tr>
<td>Sagittal sinus O₂ content (ml/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>12.2±2.7</td>
<td>11.1±2.1</td>
</tr>
<tr>
<td>Group II</td>
<td>12.1±3.6</td>
<td>7.7±0.3</td>
</tr>
<tr>
<td>Cerebral arterial O₂ delivery (ml/100 cm³/min)</td>
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<td></td>
</tr>
<tr>
<td>Group I</td>
<td>8.7±1.2</td>
<td>8.1±1.3</td>
</tr>
<tr>
<td>Group II</td>
<td>8.6±0.8</td>
<td>3.7±0.9</td>
</tr>
<tr>
<td>Cerebral O₂ uptake (ml/100 cm³/min) (i.e., gCMRO₂)</td>
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<td></td>
</tr>
<tr>
<td>Group I</td>
<td>3.3±0.8</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>Group II</td>
<td>3.5±0.8</td>
<td>0.9±0.3</td>
</tr>
</tbody>
</table>

Values are mean±SD. Group I, control dogs (nos. 20, 33, 34); Group II, dogs treated postarrest with hypertension and hemodilution (Hct 20–25%) (nos. 24, 28, 29); n2, values for two dogs.

Statistical analysis not appropriate (numbers per group too small).

local (multifocal) CBF values postarrest with a combination of immediately postarrest hypertension plus hypervolemic hemodilution from Hct 40% to 20%. In the 5–30 minutes postarrest CBF determinations there was no sign of protracted multifocal no reflow, with or without hypertensive hemodilution. Exploratory monitoring of CMRO₂ and related variables revealed that the flow-promoting treatment studied did not result in increased arterial O₂ delivery, because hemodilution reduced CaO₂ to less than 50% baseline. This offset the increase in CBF. We had found the same combination treatment in the same model to improve cerebral outcome2; an early hypertensive bout seemed more responsible for the improved outcome than the hemodilution, which gave only numerical benefit. Hypertension then might have improved outcome not via protracted improvement in O₂ delivery, but perhaps by overcoming the initial no reflow phenomenon.9 The remaining uncertainty about the beneficial effect of moderate hemodilution to Hct 20–25% after cardiac arrest might also explain why clinical hemodilution after acute stroke has not resulted in improvement of outcome, although CBF was improved.18 In our first cardiac arrest outcome study in dogs, done in 19741 and using a similar model but with external cardiopulmonary resuscitation, the beneficial effect of hypertensive hemodilution plus heparinization could have been the result of a hypertensive bout, the initial intracarotid flush with plasma substitute, or both. A similar intracarotid flush occurred in both groups in this study and in our previous outcome study with the same cardiopulmonary bypass model.2 The dog model2,21,22 and the xenon-enhanced CT method3–5,23,24 are discussed in detail elsewhere. Because of the computational and physical limitations of the xenon-enhanced CT method, the local CBF data on percentage of voxels in slice area with no-flow and trickle-flow ranges are only suggestive. The system noise and computational and physical limitations of the method are amplified when CBF is low. For regions smaller than 5×5×5 mm³, CBF values of <10 ml/100 cm³/min might be in part accounted for by methodological error.3,5,23,24 Available evidence on the method, however, suggests that the regional CBF values in the range of 10–20 ml/100 cm³/min are accurate. In previous studies4,5 we also found early postarrest normal global CBF accompanied by increased percent of trickle flow voxels.

The rationale for inducing hypertension includes the likelihood that the initial no-reflow phenomenon9 is in part caused by capillary compression and increased blood viscosity,25 both of which require initial high perfusion pressure to ameliorate. Outcome benefit from an induced hypertensive bout early postarrest had experimental support not only from our studies,1,2 but from others.12–15 When in an additional pilot experiment (dog 14), after normotensive reper-
fusion, we transiently induced hypertension (MABP, 190 mm Hg) without hemodilution at 1 hour postarrest, we found only transient mitigation of reduced CBF. Immediate postarrest hypotension resulted in more low-flow voxels during the hyperemic phase.4,5 In patients, immediate postarrest hypotension correlated with worse cerebral outcome.26 The effect of epinephrine-induced immediate postarrest hypertension on cerebral outcome in patients is now being investigated with our multicenter clinical cardiac arrest study (N. Abramson, P. Safar, K. Detre, unpublished observations).

The rationale for inducing hemodilution after cardiac arrest is based on the Hagen-Poiseuille equation: Blood flow is inversely proportional to blood viscosity. Blood viscosity increases in the microcirculation during stasis.16 Hematocrit is the main factor influencing blood viscosity, particularly in the microcirculation. During initial transient hyperemia, we saw no evidence of a persistent no-reflow phenomenon with or without hypertensive hemodilution. Both hypertension and hemodilution might increase microcirculatory blood flow if hypoperfusion postarrest is caused by vasospasm, blood sludging, or cell aggregates.19,27,28 The possibility of vasospasm as an important factor in the protracted cerebral postarrest hypoperfusion phase is supported by improved outcome with use of calcium entry blockers.29,30 The drugs and fluids used in group II could influence CBF and CMRO₂31 irrespective of MAP and Hct. These treatments, however, could not be provided clinically without drugs and fluids.

The rationale for improving cerebral arterial O₂ delivery during the postischemic hypoperfusion phase is based on our earlier observation of mismatched CBF to CMRO₂.10 In the present study, the baseline CMRO₂ values of 2.3–4.5 ml/100 cm³/min were low normal. The low halothane concentration of 0.1–0.5% used before, but not during, prearrest CBF measurements may have slightly increased CBF; higher concentrations seem required to reduce CMRO₂.31 In our study, CMRO₂ returned from very low early postarrest

![Graph of regional cerebral blood flow (ordinate) versus time before and after ventricular fibrillation cardiac arrest (VFCA) (abscissa) in control dogs (group I, n=5) and hypertension plus hemodilution-treated dogs (group II, n=4). Values of each region (100–800 mm³ tissue volume) were calculated from local cerebral blood flow values of 1×1×5=5 mm³ voxels. All regional cerebral blood flow values of group I followed hyperemia-hypoperfusion pattern of global cerebral blood flow (Figure 1 and Table 1). There were significant group differences in regional cerebral blood flow values in cortex, white matter, midbrain and thalamus (p<0.01), and hippocampus (p<0.05). In group II, all postarrest regional cerebral blood flow values were the same as baseline values. Postarrest, regional cerebral blood flow values <20 ml/100 cm³/min only in white matter of control (group I).]
levels to baseline levels by 3–4 hours postarrest, while CBF was still 50% baseline (Table 2). This delayed CMRO_2 to CBF mismatching was missed by Michenfelder and Milde_32 whose observations to only 90 minutes postarrest suggest matching of CBF to CMRO_2. The very low Cso_2 values in our study and very low Psso_2 values in another study_8 also suggest an O_2 demand/supply uncoupling several hours postarrest. More work is needed to resolve this question. For improving O_2 delivery, the hemodilution to Hct 20% in this study was apparently too severe, since the associated reduction of CaO_2 to almost one half baseline offset the improvement in CBF and left arterial O_2 delivery unchanged (Table 2). For clinical application, both MABP and Hct manipulations will have to be titrated against continuously or frequently monitored arterial and cerebral venous (superior jugular bulb) O_2 values.

Once postarrest hyperperfusion was established, lowering Hct seemed more effective than hypertension for improving CBF. We conducted pilot experiments at 4–5 hours postarrest. When in four dogs (CT Nos. 9, 13, 14, and 17) we increased MABP from between 110 and 125 mm Hg to between 160 and 190 mm Hg at 4–5 hours postarrest, global CBF and percent low-flow voxels remained essentially unchanged. When in another four dogs (CT Nos. 22, 25, 26, and 27), we lowered Hct from between 35% and 50% to 25% at 4–5 hours postarrest, global CBF increased from 20–27 ml/100 cm^3/min to 34–41 ml/100 cm^3/min after hemodilution, which decreased the percentage of voxels with low CBF <10 ml/100 cm^3/min in these four dogs from 5% to 3%, 15% to 6%, 11% to 2%, and 22% to 4% of voxels, respectively. In other pilot experiments at 4 hours postarrest, we tested acetazolamide (dogs CT 13 and 15) or hypercarbia of PacO_2 50–70 mm Hg (dogs CT 14, 17, and 18); both treatments increased global and local CBF transiently. Such acidification, however, could impair chemical recovery of neurons. These observations suggest that the delayed protracted hyperperfusion is not caused by a fixed obstruction, such as edema or thrombosis, but perhaps by mediator-induced vasospasm or transient blood cell aggregates that yield to flow-promoting manipulations.

We conclude that after prolonged cardiac arrest, the combination of immediate hypertension plus hypervolemic hemodilution from Hct 45% to 20–25% (a rather aggressive therapy), which improved outcome in previous studies_1_2 can normalize the otherwise reduced global, regional, and local (multifocal) CBF. This degree of hemodilution, however, does not improve the O_2 uptake/delivery ratio postarrest, because it reduces arterial O_2 content to less than 50% of baseline, which offsets the positive flow effect. Improving the O_2 uptake/delivery ratio would require individualized titration of MABP and Hct to optimize arterial–cerebrovenous O_2 content differences. Postarrest improvement of cerebral O_2 uptake/delivery ratio might be achieved by reducing Hct with an acellular O_2 carrying blood substitute, such as a stroma-free hemoglobin or fluorocarbon solution.

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**References**

14. Nemoto EM, Erdman NW, Strong E, Rao G, Moosy J: Regional brain PO_2 after global ischemia in monkeys: Evi-

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Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs.
Y Leonov, F Sterz, P Safar, D W Johnson, S A Tisherman and K Oku

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