Attenuation of decompressive hypoperfusion and cerebral edema by superoxide dismutase

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This study tested the hypothesis that ischemia-reperfusion injury initiated by the superoxide anion radical is a major component of postdecompression hypoperfusion and cerebral edema, and could be attenuated by superoxide dismutase (SOD). A supratentorial extradural balloon was placed in 20 fasting, lightly anesthetized, mechanically ventilated dogs and inflated in 0.5-ml increments (0.07 ml/sec) at 15-minute intervals. The endpoint of balloon expansion was the onset of an isoelectric electroencephalogram, near-arrest of hemispheric cerebral blood flow (CBF) (measured by H₂ clearance), and the appearance of a suprainfratentorial intracranial pressure gradient, which was held for 15 minutes. The in vivo development of brain edema was detected by measuring brain elastic response (BER) extradurally, and was correlated with postmortem measurement of brain water content (gravimetry); blood-brain barrier integrity was tested by Evans blue dye given after the insult. After decompression, the dogs were randomly assigned to one of four treatment groups: Group I received hyperventilation (PaCO₂ 28 ± 1 mm Hg, mean ± standard deviation); Group II received furosemide (2.4 mg/kg) and pentobarbital (10 mg/kg) every 8 hours; Group III received 20% mannitol in a 1.4-gm/kg bolus plus furosemide, 0.5 mg/kg; and Group IV received SOD, 15,000 U/kg every 15 minutes for 3 hours. At 4 hours of decompression Group IV had significantly greater recovery in local CBF and BER than Groups I, II, and III (p < 0.05). The 24-hour survival rate was 20% for Group I, 60% for Group II, 80% for Group III, and 100% for Group IV. The survival rate appeared to correlate with a variable degree of postmortem intraparenchymal hemorrhages, blood-brain barrier disruption, and moderate to severe brain edema for Groups I, II, and III. In contrast, Group IV had the least brain edema (p < 0.05) and Evans blue dye extravasation (p < 0.05) and the fewest intraparenchymal hemorrhages. These data support the hypothesis that, under the experimental conditions described here, the superoxide anion plays a major role in the pathophysiology of postdecompression ischemic edema.

KEY WORDS: reperfusion injury, superoxide dismutase, cerebral edema, superoxide radical, dog

DECOMPRESSION of a supratentorial mass lesion, such as the evacuation of a subdural hematoma, may be complicated by a sudden increase in brain volume, intracranial hypertension, cerebral edema, and coma, and may occasionally lead to a fatal outcome. Although these processes have been attributed to brain congestion (hyperemia), the pathogenesis remains obscure. In the laboratory this condition has been experimentally reproduced by expanding a supratentorial extradural balloon. Rapid decompression after a given period of brain compression can produce cortical hypoperfusion of the decompressed area, intracranial hypertension, cerebral edema, and evidence of considerable damage of the microcirculation, including hemorrhage lesions.

These abnormalities have been attributed to loss of vasomotor tone due to ischemic compression, brain-stem ischemia leading to loss of vasomotor tone with attendant intracranial hypertension and edema upon decompression, membrane phospholipid degradation, and, in turn, lipid peroxidation caused by traumatic injury to vascular endothelium upon decompression. A more logical mechanism is that the triad of hypoperfusion, edema, and vascular damage is a manifestation of reperfusion injury by oxygen radicals as a consequence of ischemic compression and mechanical injury to the microcirculation during mass expansion. This hypothesis is plausible since the superoxide anion radical is implicated in vascular injury associated with acute hypertensive episodes, concussive brain injury,
cold-induced edema, and focal brain ischemia.\textsuperscript{5,10,21,22} The direct detection of oxygen free radicals over the decompressed area, however, is both technically difficult and not easily compatible with the experimental model of balloon expansion and decompression. A more indirect yet valid method utilizes an appropriate scavenger of the oxygen free radical and thereby attenuates the free radical-induced changes.\textsuperscript{8}

The present study compared the efficacy of dehydrating modalities with the use of superoxide dismutase (SOD) alone in attenuating the postdecompression triad of cortical hypoperfusion, vascular damage, and cerebral edema. If the triad is due to a reperfusion injury it ought to be attenuated by SOD, because the superoxide anion acts as a precursor to more reactive radicals, easily escapes into the brain extracellular space,\textsuperscript{49} and appears to be implicated in vasogenic edema.\textsuperscript{4-5} For comparison, dehydration modalities (with or without barbiturate therapy) were used to achieve rapid short-term decompression and to attenuate cerebral edema, thereby also improving microvascular perfusion.\textsuperscript{31}

A unique aspect of the present investigation is the measurement of brain elastic response (BER) to monitor the progression of intracranial mass (balloon) expansion and to detect the \textit{in vivo} development of brain edema from changes in the elastic parameters of BER: the tangent modulus, \(G_t\) (mm Hg/mm), and the curvature modulus, \(G_c\) (mm Hg/sq mm). These changes are then correlated with postmortem measurement of brain water. The validity of the BER measurements in intracranial mass expansion and in cerebral edema has been documented in two previous studies.\textsuperscript{30,41} Briefly, incremental expansion of a supratentorial extradural balloon caused a progressive fall in \(G_t\) and nonsignificant changes in \(G_c\) (in nine of 10 dogs). These changes were related to both a fall in local cerebral blood flow (ICBF) and an alteration in brain elastic behavior induced by the expanding mass.\textsuperscript{30} In the other study, a cryogenic lesion caused, within 60 minutes, progressive falls in both \(G_t\) and \(G_c\) until a BER could not be measured (in eight of 11 dogs). The degree of alteration in BER and/or its partial recovery in the subsequent 48 hours correlated with the severity of cerebral edema and the amount of increase in brain water content.\textsuperscript{41}

These experiments were approved by the Institutional Animal Care and Use Committee, Medical College of Virginia and Hunter Holmes McGuire Veterans Administration Medical Center, Richmond, Virginia. Twenty conditioned mongrel dogs, each weighing 18 to 20 kg and with normal hemoglobin, electrolytes, and glucose, were chronically prepared for epidural balloon expansion. Appropriate openings were drilled in the skull to accommodate: 1) a Teflon threaded collar for the coplanar transducer; 2) a ventricular cannula; 3) four 250-\(\mu\) platinum electrodes implanted in the frontal and occipital cortex bilaterally for measuring ICBF (by the \(H_2\) clearance method); 4) bifronto-occipital electroencephalographic (EEG) and ground electrodes; and 5) a calibrated 7-ml balloon catheter. Indwelling catheters (arterial and venous) were also placed in the femoral vessels.

The left lateral ventricle was entered stereotactically using the infusion method and with the coordinates 1 cm anterior to the biauricular line and 1 cm lateral to the midsagittal line. The balloon was tested for leakage and then implanted over the left or right frontal area (seven dogs) or over the right or left occipital area (13 dogs) to relate BER to the site of balloon expansion.\textsuperscript{39} The skull defects were sealed with acrylic cement and all devices were fastened to the skull with stainless steel screws and dental acrylic. The \(H_2\) electrode housings, collar, and cannula were sealed and exteriorized through the scalp which was closed in layers. The dog was then given a broad-spectrum antibiotic course.

Four days later, after overnight fasting, each dog was anesthetized with thiopental (100 to 150 mg), intubated, and ventilated mechanically with \(N_2O:O_2\) (50:50 ratio) to a normal \(PaCO_2\) (39 \(\pm\) 2 mm Hg, mean \(\pm\) standard deviation); this was verified by monitoring end-tidal \(CO_2\) (infrared analyzer) and by frequently measuring blood gas tensions and pH. Analgesia was maintained with intermittent doses of thiopental (50 mg) and fentanyl (0.05 mg). The dog's esophageal temperature (central core) was maintained near 37\(^\circ\)C with a heating blanket. Each dog received a constant intravenous infusion (0.9\% NaCl) at 50 ml/hr.

The cisterna magna was entered with a No. 20 spinal needle. Continuous monitoring of mean arterial blood pressure (MAPB), ventricular cerebrospinal fluid pressure (PVCSF) and cisterna magna pressure (PCM), and EEG and electrocardiographic (EKG) recordings was then begun.

\textbf{Instrumentation and Measurements}

\textbf{Local CBF Measurements.} Local cerebral blood flow was measured by the \(H_2\) clearance method, and \(H_2\) gas (10\%) was administered through the endotracheal tube. Based on linear regression analysis, flow (initial slope index) was calculated from the exponential decay of the \(H_2\) from the tissues. For the on-line calculation from the four electrodes, a multiple \(H_2\) amplifier-microprocessor system was used which sampled 75 to 100 points on the \(H_2\) decay curves, discarding the first 40 seconds (arterial clearance). A storage oscilloscope was also used to monitor the saturation and the decay curve of each electrode.\textsuperscript{42} Each flow measurement was paired with blood gas measurements; auto-regulation was tested with phenylephrine-induced hy-
pertension (MABP approximately 150 mm Hg) and CO₂ responsiveness was tested with hyperventilation (PaCO₂ approximately 25 mm Hg).

Measurement of Brain Elastic Response. Brain elastic parameters (G₀ and G₂) were calculated from elastic response tests. The instrumentation, methods, and equations for characterizing BER have been described in a previous publication. Briefly, the coplanar pressure-displacement transducer was first calibrated, then sterilized with glutaraldehyde, threaded to the implanted collar, and manually advanced to the point of initial dural contact. Next, the transducer was inserted at a uniform rate (0.02 mm/sec) to a depth corresponding to a predetermined pressure (40 to 45 mm Hg) followed by immediate withdrawal at the same uniform rate. The pressure-displacement diagram of this test was used to identify the depth of substantial brain contact (δₛ) beyond which the elastic response test is carried out. The elastic response test consists of rapid insertion over 2 to 3 seconds of the transducer 0.2 to 0.6 mm beyond δₛ, and after 1 to 2 seconds it is quickly withdrawn to the point of initial dural contact. Four data points of pressure (P) and displacement (δ), over the range from δₛ to δₛ + 0.3 mm are obtained from each elastic response test and used in the solution of the equation, δ - δₛ = k ln (P/Pₛ). From this, it can be established that G₀ = dP/dδ, which (when evaluated at the initial δₛ position) represents the slope of the pressure-depth response at δₛ, and G₂ = d²P/dδ² (again evaluated at δₛ) represents the initial curvature or nonlinearity of the response. These calculations take the forms:

\[ G₀ = \frac{P_r}{k}, \quad G₂ = \frac{P_r}{k²}. \]

For the control measurements, three elastic response tests are usually performed at 10-minute intervals to allow recovery of the compression-induced deformation (0.1 to 0.2 mm; viscoelastic recovery). The data were recorded using an oscillographic recorder and a x-y plotter for in vivo analysis of the elastic response, and on a frequency modulation tape recorder for subsequent retrieval and in-depth analysis of the data.

The EEG recordings were made from bifronto-occipital screw electrodes and a midline reference electrode on an EEG amplifier.* The recorder was calibrated at 50 μV/cm, with a recording sensitivity of 10 to 20 μV, and a low- and high-frequency filter at 0.1 Hz and 60 Hz, respectively. After baseline measurements, sample tracings were taken with each increment of balloon inflation every 10 minutes for 4 hours after balloon deflation, and were continuously recorded at low speed (5 mm/sec) thereafter.

Experimental Design

After control measurements were obtained, the balloon was inflated with normal saline in 0.5-ml increments (0.07 ml/sec) at 15-minute intervals, during which measurements of ICBF, G₀, G₂, blood gas tensions, and pH were made. The end-point of balloon expansion was the onset of electrical cortical silence and an ICBF (compression hemisphere) of less than 10 ml/100 gm/min, which was held constant for exactly 15 minutes and then deflated. Balloon expansion lasted about 225 minutes with a total volume of 5.5 ml.

Three dogs were excluded from the study: one with frontal and two with occipital balloon expansion that deviated from the expected response to extradural balloon expansion by exhibiting the early onset (that is, a change in volume (ΔV) = 3.0 ml vs. 4.5 to 5.0 ml) of a total distortion of BER and a large increasing intracranial pressure (ICP) gradient (that is, 30 mm Hg at ΔV = 3.0 ml). These findings indicated early advanced transtentorial herniation with brain-stem distortion and displacement, thereby introducing a mechanical factor (vascular tear) in addition to compressive ischemia. A fourth dog was excluded, when, on decompression, the amount of saline withdrawn from the balloon did not match the amount injected (5.0 ml vs. 5.5 ml).

After decompression of the balloon over 1 minute the dogs were randomly assigned to one of four treatment groups (five dogs each). Group I was hyperventilated (room air/O₂) to a PaCO₂ of 28 ± 1 mm Hg; Group II received furosemide (2.4 mg/kg) and pentobarbital (10 mg/kg) every 8 hours; Group III received 20% mannitol (1.4 gm/kg) as an intravenous bolus plus furosemide (0.5 mg/kg); and Group IV received only SOD (pathogen-free) as an intravenous bolus of 15,000 U/kg every 15 minutes for 3 hours, beginning immediately after decompression. Evans blue dye (EB 2%, 2 ml/kg) was given intravenously during the first 60 minutes of decompression. Measurements of ICBF and elastic parameters were repeated every 15 minutes for the first 4 hours of decompression. The dogs were then ventilated overnight (room air/O₂), sedated with a fentanyl infusion (2 μg/kg/hr), and MABP, end-tidal CO₂, PVCSF, PCM, EKG, and EEG monitoring was performed. At 24 hours the survivors were restudied and then sacrificed with a barbiturate injection.

Blood-Brain Barrier Permeability and Brain Water Content

The brain was quickly removed, immersed in kerosene, and sectioned into the decompressed and contralateral hemisphere and infratentorial structures (cerebellum, brain stem, pons, and medulla oblongata). Cross sections from each hemisphere (frontal, parietal, temporal, and occipital) and infratentorial structures were macroscopically examined for hemorrhages and EB extravasation. The degree of EB extravasation in each section was rated on a grading scale of 1 to 3: Grade 1, light staining; Grade 2, moderate staining; and Grade 3, marked staining.

Next, five 2-cm samples from each cross section were suspended in a kerosene-bromobenzene column

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for specific gravity measurements. Brain water content was calculated from the specific gravity measurement and expressed in gm H2O/(%)/gm tissue. In dogs with progressive cardiovascular collapse, brain specific gravity was measured within 30 minutes of circulatory collapse.

Statistical Analysis

Statistical significance among groups at each observation period was tested by analysis of variance, using the General Linear Models of the Statistical Analysis System. A comparison of the means at each observation period was performed with the Tukey-Kramer test with level of significance at p < 0.05. Statistical significance among groups for degree of EB extravasation was tested by the Fisher’s exact test with level of significance at p < 0.05 and p < 0.01.

Results

Physiological Findings

The major physiological data are summarized in Figs. 1 and 2. The site of balloon implant had no influence on BER, severity of intracranial hypertension, or degree of brain herniation.

At the end-point of balloon expansion all four groups showed isoelectric EEG recordings, dilated fixed pupils, marked intracranial hypertension (60 to 80 mm Hg), and a supra-infratentorial ICP gradient of (means ± standard deviations): 26 ± 16 mm Hg for Group I, 15 ± 5 mm Hg for Group II, 20 ± 13 mm Hg for Group III, and 18 ± 12 mm Hg for Group IV.

The reduction in cerebral perfusion pressure (CPP = MABP – PVCSF) was modest, probably because of arterial hypertension (MABP > 180 mm Hg), even though ICBF had fallen to 10% or less of baseline value for the compressed hemisphere and to 30% or less of baseline for the contralateral hemisphere. The CPP tended to be higher in Group IV, but was statistically significant (p < 0.05) only at 60 minutes of decompression. Of the two elastic parameters, the nonlinear elastic modulus (G_n) was reduced to 20% or less of baseline, while the tangent modulus (G_t: a direct measure of brain tissue elasticity) was better preserved, probably because of concomitant cerebral venous hypertension. Differences among groups for each parameter were statistically nonsignificant (Fig. 1).

With balloon decompression, ICP progressively rose; this increase was greater in Groups I and II than in III and IV. These changes, however, were statistically nonsignificant, even though the increase was lowest (19.2 ± 6.2 mm Hg) in Group IV and the highest (40 ± 3.2 mm Hg) in Group I at 3 hours of decompression. The ICP gradient either did not change or increased in Groups I and II, transiently decreased in Group III, and consistently decreased in Group IV.

Cerebral blood flow in the decompressed hemisphere was significantly higher in Group IV than in the other groups at 60 and 240 minutes of reperfusion (p < 0.05).

Beyond 240 minutes the data were skewed due to different survival rates for Group I (20%), Group II (60%), Group III (80%), and Group IV (100%) (Fig. 1). Recovery in contralateral ICBF was more uniform in the four groups, although it was significantly higher in Group IV than in Groups I and II at 240 minutes of decompression (p < 0.05) (Fig. 1).

Recovery in brain elastic parameters reflected both the development of cerebral edema and the influence of the therapeutic modalities (Fig. 2). In Group I, both G_n and G_t showed initial increases at 15 minutes of 140% and 128%, respectively, which probably reflected an initial postischemic hyperemia. After that, G_n progressively decreased by 50% and G_t fell to zero at 60
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FIG. 2. Recovery rate (%) of brain elastic parameters following decompression of an expanded extradural balloon in four treatment groups of dogs. Values are means ± standard error of the means. $G_0 =$ initial tangent pressure-depth ratio, a measure of brain tissue elasticity; $G_o =$ initial curvature pressure-depth ratio, a measure of the nonlinearity of the elastic response. For group identification see Fig. 1.

minutes of decompression. This pattern of fall in $G_0$ and $G_o$ suggested cerebral edema. Groups II and III followed a nearly identical pattern, although it was more gradual, since it developed over a 4-hour period (Fig. 2). In contrast, in Group IV $G_0$ and $G_o$ showed a gradual rise without any decrease in the first 60 minutes of decompression. Beyond 60 minutes the recovery in $G_0$ and $G_o$ was significantly higher ($p < 0.05$) than in the other groups at each observation period, with 100% recovery at 3 hours, decreasing to 67% at 24 hours (Fig. 2).

Causes of Failure to Survive

Four of the five dogs in Group I (PaCO$_2$ 28 ± 1 mm Hg) developed progressive intracranial hypertension (ICP > 50 mm Hg), an increasing ICP gradient, and arterial hypertension (MABP > 180 mm Hg). Thereafter, sinus tachycardia (180 to 250/min) and progressive decline in MABP and CPP to zero followed at 6 to 8 hours of decompression. In Group II (furosemide treatment), cardiovascular collapse in two dogs was more gradual and was not preceded by systemic and cerebral hypertensive crises. In Group III, osmotic loop diuresis blunted intracranial hypertensive crisis. In one dog, however, it failed to prevent the early onset (< 60 minutes) of progressive intracranial hypertension with peaks in ICP exceeding 80 mm Hg, an increasing ICP gradient (15 to 56 mm Hg), and a progressive fall in CPP to zero, which was followed by rapid circulatory collapse at 6 hours of decompression.

Pathological Findings, Blood-Brain Barrier Permeability, and Brain Water Content

In Group I, II, and III dogs, the entire brain was swollen (swollen gyri and obliterated sulci) and stained with EB (Fig. 3 upper left and lower). Transtentorial herniation was present in all, but was more marked (embedded cerebral peduncle) in those with circulatory collapse. In the brain cross sections, areas with Grade 2 and 3 EB extravasation were seen in the gray and white matter of the decompressed hemisphere and Grade 1 to 2 areas were observed in the contralateral hemisphere and infratentorial structures (Table 1). In all three groups, intraparenchymal perivascular hemorrhages were found throughout the brain, including brain stem. Brain water was increased in both hemispheres (Fig. 4). Differences in the extent and severity of EB extravasation and in brain water content among the three groups were not statistically significant (Table 1 and Fig. 4).

In four of the five Group IV dogs, the brain appeared normal (demarcated gyri and sulci), with EB staining predominantly limited to the site of balloon compression (Fig. 3 upper right). In cross sections, Grade 1 areas of EB extravasation in the gray and white matter of the decompressed and in the contralateral hemisphere (calcarine cortex) were seen in one dog. No EB extravasation was seen in the infratentorial structures (Table 1). Intraparenchymal hemorrhages were not seen beyond the balloon site (Fig. 5).

Differences in the extent and severity of EB extravasation between Group IV and the remaining groups...
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were statistically significant at p < 0.05 for the decompressed hemisphere and at p < 0.01 for the infratentorial structures (Table 1). The increase in brain water content over the decompressed hemisphere was significantly less than in Groups I and II (p < 0.05), but not from Group III except at 5 mm from the lesion. In the contralateral hemisphere Group IV had significantly less edema than Groups I, II, and III (p < 0.05) (Fig. 4).

**Discussion**

In these decompression experiments, SOD treatment resulted in significantly higher recovery in elastic curvature modulus (\(G_0\)) and cortical CBF (p < 0.05), less cerebral edema (p < 0.05), marked reduction in dye extravasation (p < 0.05) and vascular damage, and a 100% survival. Although our results are based upon a limited number of dogs (five in each group), this paucity is more than offset by the multifactorial end-points, three quantitative (CBF, brain elastic parameters, and brain water content) and one semiquantitative (EB extravasation), all of which converge in one direction with statistical significance. These findings provide compelling evidence that SOD therapy provided this protection by blunting an oxidative reaction initiated by the superoxide anion radical with rapid decompression (> 1 minute) of an expanded extradural balloon. As SOD is a relatively large molecular weight compound and therefore likely excluded by the blood-brain barrier, the efficacy of SOD treatment implies that the blood-brain barrier was disrupted by decompression and that the superoxide anion radical was available.

### Table 1

**Extent and severity of Evans blue dye extravasation following decompression of a supratentorial extradural balloon in the dog**

<table>
<thead>
<tr>
<th>Experimental Groups</th>
<th>Lesion</th>
<th>5 mm</th>
<th>10 mm</th>
<th>15 mm</th>
<th>30 mm</th>
<th>Contralateral</th>
<th>Cerebellum</th>
<th>Brain Stem</th>
<th>Pons &amp; Medulla/Oblongata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (hyperventilation)</td>
<td>3.0 ± 0</td>
<td>3.0 ± 0</td>
<td>2.8 ± 0.45</td>
<td>2.4 ± 0.55</td>
<td>1.4 ± 0.90</td>
<td>1.2 ± 0.84</td>
<td>1 ± 0</td>
<td>1 ± 0</td>
<td>1 ± 0</td>
</tr>
<tr>
<td>Group II (furosemide &amp; pentobarbital)</td>
<td>2.6 ± 0.90</td>
<td>2.4 ± 0.89</td>
<td>2.0 ± 0.71</td>
<td>1.8 ± 0.84</td>
<td>0.4 ± 0.55</td>
<td>1.4 ± 0.55</td>
<td>0.8 ± 0.45</td>
<td>0.4 ± 0.55</td>
<td>0.4 ± 0.55</td>
</tr>
<tr>
<td>Group III (osmotic-loop)</td>
<td>3.0 ± 0.0</td>
<td>2.6 ± 0.55</td>
<td>2.4 ± 0.55</td>
<td>2.4 ± 0.55</td>
<td>0.6 ± 0.89</td>
<td>2.0 ± 0</td>
<td>0.4 ± 0.89</td>
<td>1.2 ± 0.84</td>
<td>1.2 ± 0.84</td>
</tr>
<tr>
<td>Group IV (superoxide dismutase)</td>
<td>1.8 ± 0.84</td>
<td>0.6 ± 0.54</td>
<td>0.2 ± 0.45</td>
<td>0.2 ± 0.45</td>
<td>0.2 ± 0.45</td>
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<td>0.2 ± 0.45</td>
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</table>

* Values are grades of Evans blue dye extravasation expressed as means ± standard deviations. Grade 1 = light staining; Grade 2 = moderate staining; Grade 3 = deep staining. Statistical significance by Fisher's exact test: a = p < 0.05, Group IV vs. III; b = p < 0.01, Group IV vs. I.
extracellularly. This is, as predicted, the common mechanism for brain injury induced by oxygen free radicals. 22 Oxygen free radicals are implicated as mediators of ischemia-reperfusion injury of various tissues, including brain and spinal cord. 8,10,19,25,33 This injury may also occur with rapid decompression of a supratentorial mass. The superoxide anion may have originated from two main sources. The first is as a by-product of the xanthine oxidase reaction during reperfusion, which may have occurred in cerebral microvessels damaged by hypertension crises and mechanical injury (tethering) during balloon expansion and decompression. 2,4,23,33 A second source for superoxide anion production is from the degradation of membrane phospholipid and arachidonic acid accumulation during ischemic compression, 11,36,51 and accelerated metabolism of arachidonic acid with formation of superoxide anion during reperfusion. 14,22,26,34

Although oxidative reactions start as intracellular processes, the superoxide anion can escape through an anion channel into the extracellular space, 24 where, in the presence of reduced iron (Fe++) as a catalyst, it rapidly converts in the hydroxyl radical. 15,33,35 The hydroxyl radical is highly reactive and is responsible for cerebrovascular injury associated with acute sustained arterial hypertension, concussive brain injury, and vasogenic edema following a freeze-induced lesion. 5,32,23,47

In our experiments, SOD might have been effective by two mechanisms. It might have acted by reducing capillary vascular permeability, as evidenced by the striking difference in EB extravasation between SOD-treated and the remaining dogs. Altered capillary vascular permeability is a major component of decompression edema. 6,52 With intracranial and systemic hypertension increased, vascular permeability can proceed to frank bleeding; hemoglobin is a good source of superoxide formation. 6,52 In the second possible mechanism, SOD might have mitigated the initial (15-minute) postischemic hyperemia and facilitated (perhaps indirectly) the return in cerebrovascular tone, as reflected in the recovery pattern of brain elastic parameters. In Groups I and II both elastic parameters rose by approximately 40% above the baseline in the first 30 minutes of reperfusion, but then progressively fell
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(Fig. 2). This initial rise could only be due to cerebrovascular volume expansion and increased transmural pressure of cerebral resistance vessels; however, this facilitated fluid extravasation through the vessels unable to constrict (loss in autoregulation). As a result, the elastic parameters (in particular $G_e$) and the ICBF progressively decreased. In contrast, in the SOD-treated dogs the elastic parameters (in particular $G_e$) exhibited a gradual and progressive increase without any decline. Thus, at 60 minutes of reperfusion $G_e$, $G_o$, and ICBF (ipsilateral) recovered 100%, 80%, and 60% of their baseline values, respectively. Since $G_o$ is a function of vascular wall tension and transmural pressure of cerebral resistance vessels, its recovery means a partial recovery in cerebrovascular tone. This, however, is indirect evidence since we did not test autoregulation during decompression. Perhaps the postischemic initial hyperemia and increased transmural pressure may also be responsible for hemorrhages in those vessels (arteries, arterioles, and capillaries) already prone to rupture as a result of increased tensile stress induced by the mass (balloon) and/or localized vascular damage induced by the hydroxyl radical.

Our protocol of high SOD dosage was influenced by three major considerations: 1) the short half-life (6 minutes) of free SOD; 2) the observation that, following a cortical freezing lesion, superoxide anion production on brain cortical surface peaked (fivefold) at 60 minutes after the lesion, slowly decreased (twofold) at 150 minutes, and then gradually rebounded (threefold) at 24 hours; and 3) our effort to achieve a sustained recovery in $G_e$, since a marked fall in $G_e$ coupled with a moderate reduction in $G_o$ indicated the presence of cerebral edema. In fact, in an initial pilot study, when SOD was given as one single intravenous bolus injection (15,000 U/hr) brain elastic parameters ($G_e$ and $G_o$) failed to recover (unpublished observation). Since the curvature modulus ($G_o$) is influenced by both transmural pressure and wall tension of cerebral resistance vessels, a full recovery in $G_e$ at 3 and 4 hours of decompression indicated the absence of cerebral edema (Fig. 2). The subsequent deterioration in $G_o$ recovery (65% of baseline) suggests that some edema must have developed at between 5 and 24 hours of decompression. These data underscore the significance of measuring brain elastic parameters in the detection and treatment of cerebral edema.

Undoubtedly, the use of long-acting SOD, such as liposome-entrapped SOD or polyethylene glycol-conjugated SOD would have been more effective. These agents can penetrate intracellularly where oxidative reactions initiate, and because of their much longer half-life.

A reperfusion injury, however, may not be the only mechanism for producing decompression intracranial hypertension, cerebral edema, and cerebrovascular injury. As the brain exhibits viscoelastic behavior, an expanding supratentorial mass (balloon) will cause a shift in brain tissue mass along its horizontal (outward and midline) and vertical (transientorial) planes. When the vertical shift becomes predominant, it is directly transmitted to the brain stem and causes its progressive caudal displacement and distortion and a concomitantly increasing tensile stress (stretching) of its relatively fixed (anchored) vascular supply. This initiates brain-stem ischemia and, in turn, loss in cerebral vasomotor tone, intracranial and systemic hypertension, brain swelling, and coma following decompression. This second mechanism might account, at least in part, for the death of dogs after decompression, but could not alone explain the 24-hour survival of the SOD-treated dogs.

Rapid decompression of supratentorial mass (balloon) has also been associated with secondary brain-stem hemorrhages, a third mechanism for intracranial hypertension, edema, and coma. Although such hemorrhages have been attributed to arterial wall necrosis, venous stasis, or trauma to the brain stem and its vascular structures by the expanded supratentorial mass, the exact pathogenesis remains controversial. Klintworth demonstrated in dogs that these hemorrhages are a function of the supratentorial mass volume ($> 5$ ml), its rapidity of expansion, downward displacement and distortion of the brain stem, and a viable (“active”) systemic circulation at the time of decompression. However, the hemorrhages were of variable degrees (arteries, arterioles, capillaries, and veins) and occurred in both the supratentorial brain parenchyma and in the brain stem. This has been confirmed by other investigators. With our experimental conditions (that is, limited volume of supratentorial mass and rapid decompression), the mechanical effect of rostrocaudal displacement and distortion of the brain stem was minimized. Yet, dogs in Groups I, II, and III all exhibited moderate degrees of supra- and infratentorial hemorrhages, which were not seen in the SOD-treated dogs.

It is possible that oxidative reactions, superimposed on the mechanical stress (tethering) of cerebral and vascular structures produced by the expanding mass, weaken vessels and make them more prone to rupture with restoration of circulation and postischemic hyperemia. It remains to be proved whether our present results are reproducible at a larger intracranial volume mass.

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