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Treatment of experimental cerebral air embolism with lidocaine and hyperbaric oxygen

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McDermott JJ, Dutka AJ, Evans DE, Flynn ET. Treatment of experimental cerebral air embolism with lidocaine and hyperbaric oxygen. Undersea Biomed Res 1990; 17(6):525–534.—Experiments were performed to assess the combined therapeutic effects of hyperbaric oxygen (HBO) and i.v. lidocaine on neural function after ischemia induced by cerebral air embolism in anesthetized cats. Neural function was determined by measuring the somatosensory evoked potential (SEP) amplitude. Air was infused into the carotid artery in increments of 0.08 ml to maintain the SEP amplitude at 10% or less of baseline values for 15 min. Three groups were studied. A control group (n = 9) received no further treatment after SEP suppression. An HBO group (n = 8) was treated with oxygen at 2.8 atm abs for 130 min. A third group (n = 8) received an i.v. lidocaine infusion in addition to HBO. Air infusion suppressed the SEP amplitude to the same level in all groups. The control group recovered 27.4 ± 5.5% (mean ± SEM) of the baseline SEP amplitude, whereas the HBO group recovered 62.0% ± 7.2%, and the HBO plus lidocaine group recovered 75.3 ± 5.7%. The results show that both HBO and the combination of HBO and lidocaine promote a significant recovery of the SEP amplitude compared to no treatment. However, lidocaine therapy adds no benefit to HBO therapy alone.

lidocaine
air embolism
cerebral ischemia
hyperbaric oxygen
somatosensory evoked potentials

Cerebral air embolism can occur in a number of situations. Air embolism is a complication of pulmonary barotrauma in divers (1–3). Inadvertent air embolism can also happen as a result of surgical and invasive diagnostic procedures (4). Experimentally, air embolism has been used as a model of acute cerebral ischemia and stroke (5–7). Fritz and Hossman (6) reported that the pathophysiology of cerebral air embolism combines elements of both inflow occlusion and microembolism-induced ischemia. Currently, the recommended treatment for air embolism is rapid application of pressure and hyperbaric oxygen (HBO) (8). Increased atmospheric pressure mechanically reduces the size of air bubbles and promotes clearing of capillary networks. HBO administration increases the outward diffusion gradient for nitrogen, resulting

in a greater washout of nitrogen in the air bubbles and a further reduction in embolic size. HBO has also been reported to decrease the intracranial pressure and cerebral edema associated with cerebral air embolism (9).

Previous experiments in this laboratory reported that pretreatment of animals with i.v. lidocaine greatly attenuated the acute hypertension, cardiac arrhythmias, increase in circulating catecholamines, and intracranial hypertension (10) associated with air embolism to the posterior cerebral circulation. Subsequent studies, using the somatosensory evoked potential (SEP) as an indicator of neuronal function, found that animals pretreated with i.v. lidocaine recovered more SEP amplitude following cerebral air embolism than did untreated controls (7). Lidocaine was also shown to significantly improve neural recovery when administered therapeutically after the embolic episode (11). The present study was conducted to determine whether the therapeutic combination of i.v. lidocaine and HBO would lead to more recovery than either treatment alone.

MATERIALS AND METHODS

The institutional animal care and use committee reviewed the protocol and certified that the experiments described here were conducted according to the principles set forth in the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH publ. no. 86–23, 1985). Twenty-five adult male and female cats, weighing between 2.0 and 5.0 kg, were used in these experiments. Anesthesia was induced by an i.m. injection of ketamine HCl (15 mg $\cdot kg^{-1}$) and was maintained by an i.v. injection of alpha-chloralose (80–100 mg $\cdot kg^{-1}$) dissolved in warm saline. The alpha-chloralose was initially administered as one dose of 80 mg $\cdot kg^{-1}$ and, if required, an additional dose of 20 mg $\cdot kg^{-1}$ was administered during the surgical preparation to maintain a proper level of anesthesia. The animals were intubated and ventilation was mechanically controlled by a small-animal respirator. Throughout the experiment arterial blood gases were monitored and kept within physiologic limits through ventilator adjustment. Esophageal temperature was maintained between 37.5° and 38.5°C by use of a heating pad.

Catheters (PE-160) were inserted into the right femoral artery and vein for recording blood pressure and administering drugs, respectively. A catheter was also inserted into the left femoral vein for lidocaine infusion.

To infuse air into the cerebral circulation, the left lingual artery was cannulated as described in a previous report (11). In brief, a PE-50 catheter was inserted into the lingual artery in a retrograde direction. The tip of the catheter was advanced into the left common carotid artery. The external maxillary artery was ligated so that air would be directed into the internal maxillary and ascending pharyngeal arteries. In the adult cat these two arteries are responsible for the blood supply to the anterior portion of the brain (12).

After catheterization, the animals were placed in a stereotaxic apparatus so that the head was above the heart (sphinx position). The right sciatic nerve was exposed for electrical stimulation. The left side of the scalp was incised and retracted to allow placement of small, stainless steel screws over the frontal and temporal areas. SEPs were obtained by applying a stimulus (8 V for 0.5 ms at 1 Hz) to the right sciatic nerve and recording responses from the left temporal and indifferent (frontal) screw

electrodes. The cortical responses to 32 stimuli were averaged to yield the SEPs. Cortical responses to each stimulus were first amplified by a Grass differential preamplifier, further amplified and displayed by a Tektronix oscilloscope, and then averaged by a Nicolet model 527 signal averager. Averaged responses were plotted on an X-Y recorder. Pancuronium bromide (0.1 mg · kg^{-1}) was administered i.v. at intervals to prevent muscle movement during stimulation of the sciatic nerve.

The amplitude of the observed SEP was expressed as a percentage of the baseline control value. After the SEPs were plotted on the X-Y plotter, the waveforms were digitized with a computer program to determine the distance from the major positive peak to the major negative peak of each waveform. This amplitude is referred to as the P2-MN amplitude. The baseline control amplitude was determined as follows. First, the stability of the SEP was established by monitoring the averaged waveforms during the 1–2-h period preceding the air embolism. Then, just before the first bolus of air, four SEPs were recorded. The P2-MN amplitude of each SEP was measured and the four values averaged to establish the baseline value.

Cerebral ischemia was induced by infusion of 0.08-ml increments of air into the carotid artery until the SEP amplitude (P2-MN amplitude) was reduced to 10% or less of original baseline value. The SEP amplitude was kept below 10% over a 15-min period, with additional air infusions as needed.

After ischemia, each animal was placed inside a small animal hyperbaric chamber (Bethlehem Corp., model 18365) and randomly allocated to one of 3 groups. Group 1 served as a control ($n = 9$) and remained at the surface breathing air for the duration of the experiment. The second group ($n = 8$) received HBO therapy. These animals were compressed to 2.8 atm abs at a rate of 0.76 atm abs · min^{-1} (25 fsw · min^{-1}), breathing 100% oxygen. After 130 min of oxygen breathing at 2.8 atm abs, the animals were decompressed to the surface at a rate of 1.8 atm abs · min^{-1} (60 fsw · min^{-1}). After reaching the surface, the animals continued breathing 100% oxygen and were monitored for an additional 15 min. Group 3 ($n = 8$) received HBO therapy identical to that in Group 2, while simultaneously receiving an i.v. lidocaine infusion (*see* below). Treatment for both groups began 20 min after the initial air injection.

For the lidocaine infusion, lidocaine HCl (Xylocaine, Astra Pharmaceutical Products Inc., 40 mg · ml^{-1}, without preservatives) was diluted in saline and administered continuously by an infusion pump located inside the hyperbaric chamber. The lidocaine infusion was started in conjunction with the HBO therapy. The infusion profile for administration was 1.5 mg · kg^{-1} over the first 5 min, which served as a loading dose, followed by 3.0 mg · kg^{-1} over the next 25 min, and then 1.0 mg · kg^{-1} every 30 min for the duration of the experiment.

Results are reported as mean ± SEM. A two-way analysis of variance (ANOVA), with repeated measurements (13), was used for statistical analysis of the SEP measurements over the entire observation period. A one-way ANOVA was used to compare the SEP amplitudes after 15 min of ischemia and upon final recovery between the 3 groups. A one-way ANOVA was also used to compare all other physical and physiologic measurements. A modified t test with the Bonferroni correction was used when comparing individual groups to keep the overall alpha level less than $P = 0.05$.

RESULTS

The 3 groups were identical with regard to weight, blood gas measurements, body temperature, and amount of air infused. Table 1 shows the mean and SEM of each of

TABLE 1

COMPARISON OF PHYSICAL AND PHYSIOLOGIC PARAMETERS BETWEEN THE 3 GROUPS USING ONE-WAY ANALYSIS OF VARIANCE[a]

	Weight, kg	pH	P_{O_2}, mmHg	P_{CO_2}, mmHg	Temperature, C	Vol Air, ml	MABP: 0–20 min, mmHg	MABP: 21–165 min, mmHg
Control, $n = 9$								
Mean	3.32	7.36	92.64	32.34	38.16	0.26	92.0	99.6
SEM	0.16	0.006	1.84	0.48	0.27	0.04	2.9	1.4
HBO, $n = 8$								
Mean	3.24	7.34	92.87	34.25	38.02	0.40	99.6	107.7
SEM	0.23	0.01	3.07	1.46	0.11	0.06	3.3	1.5
HBO and lidocaine, $n = 8$								
Mean	3.67	7.35	91.05	31.72	37.75	0.41	92.6	102.4
SEM	0.19	0.06	0.85	0.90	0.18	0.04	4.1	1.5
F-ratio	1.30	3.40	0.21	1.68	1.04	2.89	1.47	7.92[b]

Critical F-value for weight, pH, P_{O_2}, P_{CO_2}, Temp, Vol. for $P = 0.05$ is 3.44.
Critical F-value for MABP for $P = 0.001$ is 6.91.

[a] pH, P_{O_2}, P_{CO_2} values are those obtained just before the air embolism. Temperature is the average of measurements taken at 5-min intervals throughout the 165-min experimental period. MABP values are the average mean blood pressure from values obtained each minute for the time periods of 0–20 min and 21–165 min; [b]significant difference $P<0.001$.

these measurements along with the average mean arterial blood pressure (MABP) for the first 20 min and the subsequent 145 min of the treatment period. The results of the one-way ANOVA comparing these groups is also shown. No significant difference in MABP existed between the 3 groups during the first 20 min. There was a statistically significant but physiologically unimportant difference between the groups for the remaining 145 min.

Table 2 shows the mean SEP amplitude obtained at the end of 15 min of ischemia and after completion of treatment, along with the corresponding *F*-values for the one-way ANOVAs comparing the 3 groups at each time point. There was no significant difference between the 3 groups with regard to severity of suppression of SEP amplitude. Figure 1 shows the final SEP values for each animal in the 3 groups along with the respective mean and standard deviation for each group. By one-way ANOVA (Table 2), a statistically significant difference in recovery among the 3 groups was observed at this final time point. A modified *t* test with Bonferroni correction for three comparisons shows that both treatment groups recovered better than control but were not different from each other at 165 min of recovery. The power of the modified *t* test based on the results obtained is 0.4. That is, there are only 4 chances out of 10 that this *t* test would have declared the observed difference significant. Given the estimated standard deviation, we had a 90% probability of detecting an improvement of 45% between the 2 groups (i.e., if the lidocaine plus HBO group recovered to at least 90% of baseline).

TABLE 2

COMPARISON OF THE SEP VALUES (PERCENT OF BASELINE AMPLITUDE) AFTER 15 MIN OF ISCHEMIA AND UPON FINAL RECOVERY BETWEEN THE 3 GROUPS USING ONE-WAY ANOVA[a]

	SEP, % 15 min	SEP, % 165 min
Control, $n = 9$		
Mean	1.4	27.4
SEM	0.7	5.5
HBO, $n = 8$		
Mean	1.5	62.0
SEM	0.5	7.2
HBO and lidocaine, $n = 8$		
Mean	3.8	75.3
SEM	1.2	5.7
F-ratio	0.6	16.7[b]
Critical *F*-values for $P = 0.05$ is 3.4 for $P = 0.001$ is 9.6		

[a]SEP values are percents of original baseline amplitudes; [b]significant difference with $P < 0.001$.

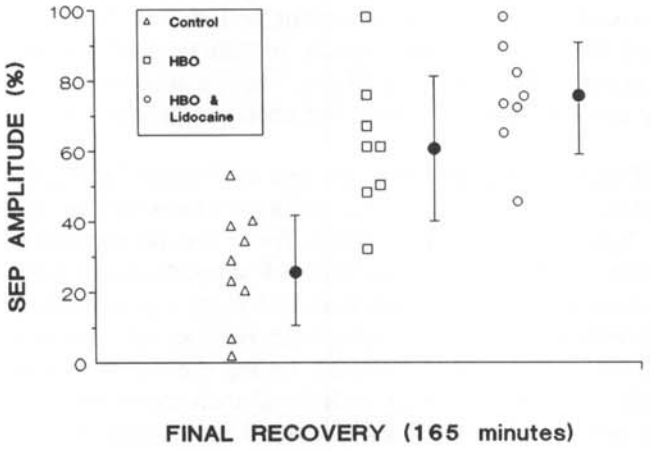

Fig. 1. Final recovery of the SEP amplitude for each animal in the control, HBO, and HBO plus lidocaine groups. Amplitude is given in percent of original baseline value for each animal. *Closed circles* to the *right* of each group represents the mean for the respective group. *Error bars* represent the standard deviation for each group.

The average change in the SEP amplitude for the 3 groups over the entire observation period is illustrated in Fig. 2. A two-way ANOVA with repeated measures revealed a statistically significant difference between the 3 groups with regard to treatment over time with a statistically significant interaction effect (Table 3). This interaction effect can be explained by the initial similarity of the 3 groups followed by the diverging trends of each group over the course of treatment, as seen in Fig. 2. No significant difference was observed with regard to the recovery in the SEP amplitude over the experimental period between the HBO group and the HBO plus lidocaine group. For these comparisons, an alpha significance level of $P < 0.025$ was chosen to maintain the experimental significance level at $P < 0.05$.

DISCUSSION

Lidocaine administered therapeutically to anesthetized cats after incremental air embolism has been shown to be of significant benefit. In an experiment reported from

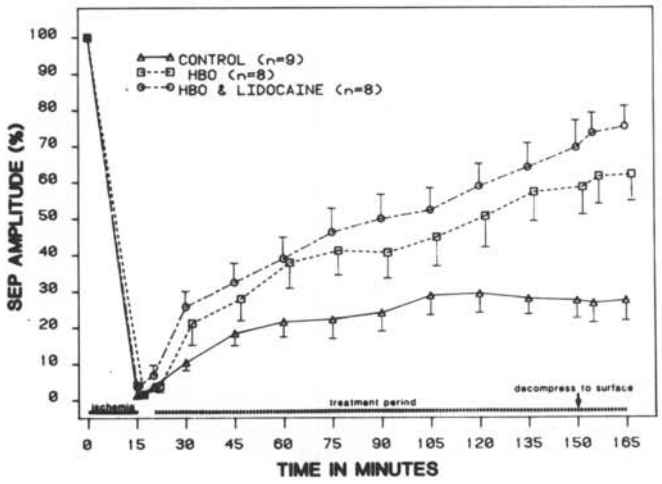

Fig. 2. Decrement and recovery of SEP amplitude in the control, HBO, and HBO plus lidocaine groups after 15 min of ischemia induced by air embolism. Amplitude is given in mean percent of original baseline values. *Error bars* represent standard error of mean values. Periods of ischemia and treatment are indicated at the *bottom of the plot*. Amplitude values for the HBO group are *offset* slightly to the *right* to allow visualization of overlapping values.

TABLE 3
ANOVA TABLE, TWO-WAY REPEATED MEASURES

	All Experimental Groups				
Source of Variation	*Df*	Sum of Squares	Mean Square	*F*-Ratio	*P* Value
Effect of treatment	2	38,169	19,084	8.3	0.002
Effect of time	12	93,426	7,785	86.0	< 0.001
Interaction	24	12,994	541	6.0	< 0.001
Error	264	23,875	90		

this laboratory, recovery of the SEP amplitude following air embolism was twice as great in animals receiving a continuous lidocaine infusion as in animals receiving no treatment (11). We elected to continue using this model for the present study for three reasons: a) the demonstrated therapeutic benefit of lidocaine in the model, b) the uniform suppression of neural responses possible with incremental infusion of air, and c) the fact that the SEP amplitude has been shown to correlate well with critical levels of cerebral blood flow in middle cerebral artery (MCA) occlusion and cerebral air embolism models (5, 14).

Recompression is the accepted therapy for cerebral arterial gas embolism. Some debate exists, however, over the ideal depth and gas mixture necessary to obtain maximum benefit (2, 3, 15). The U.S. Navy Diving Manual (8) recommends a recompression profile that involves an initial compression to 6 atm abs on air for 30 min followed by oxygen breathing at 2.8 atm abs. We chose to omit the deep portion of the treatment to simplify the experiment. Recent work indicates that this choice should have little influence on outcome. Leitch et al. (16) performed experimental studies measuring the recovery of SEPs following cerebral air embolism in dogs, and reported no additional benefit was obtained from beginning HBO therapy at 6 atm abs on air. We came to the same conclusion in cats (17). Clinically favorable results have been documented with the use of oxygen at low pressures alone (18). In a review of case records, Leitch and Green (19) compared the success rate of the two recompression profiles and concluded that arterial gas embolism patients receiving immediate HBO therapy at 2.8 atm abs will do equally well as those compressed to 6 atm abs on air before HBO therapy.

The results of this study demonstrate that HBO and the combination of HBO plus lidocaine therapy will both significantly improve neural recovery after cerebral ischemia induced by incremental air embolism. A significant benefit of adding lidocaine to recompression could not be demonstrated, however. Although Fig. 2 shows a divergence between the curves of the 2 treatment groups late in the treatment period, suggesting a greater return in the HBO plus lidocaine group, this difference was not statistically significant.

Results with lidocaine in the treatment of cerebral ischemia have not been uniformly successful. Shokunbi et al. (20), using a 4- and 6-h MCA occlusion model without reperfusion, found that lidocaine failed to protect neurons from ischemic injury. These authors used a dose of lidocaine that resulted in burst suppression on the EEG (50 mg loading dose followed by 50 mg $\cdot\cdot kg^{-1} \cdot\cdot h^{-1}$). In a 10-min global ischemia model with reperfusion, Warner et al. (21) concluded that pretreatment of rats with

lidocaine provided no protection from postischemic cerebral edema or delayed (7 day) neuronal necrosis. This group also used a dose of lidocaine that was based on EEG suppression (< 23 mg $\cdot$ kg^{-1}), a dose the authors refer to as "clinically tolerable" (21).

In contrast to these negative findings, Shokunbi et al. (22), using a 3-h MCA model with reperfusion, found that a continuous infusion of lidocaine started before occlusion and maintained throughout the experiment resulted in a significant preservation of the SEP amplitude and greatly reduced infarct size in cerebral tissue. The authors also reported that lidocaine improved cerebral blood flow in the ischemic tissue compared to control animals, and concluded that this enhancement in cerebral perfusion is responsible for cerebral preservation and the reduction of infarct size (22). Nagao et al. (23) found that a continuous lidocaine infusion, in doses similar to those in the present study, significantly decreased cerebral edema and preserved both electrocortical activity and cerebral blood flow in cortex exposed to air for 12 h.

The success or failure of lidocaine as a therapy thus seems to depend on a variety of factors. Prominent among these are the degree of ischemia, whether it is complete or partial; the duration of the ischemia; and the dose of lidocaine used. High doses are associated with activation of hippocampal neurons, resulting in increased metabolic stress (24). This factor may account for some of the negative findings in high-dose studies.

The cause of our failure to find a significant additional benefit of lidocaine administration during recompression therapy is not clear. Previous work at the surface indicates that a clear therapeutic effect of lidocaine may be discerned in this model. Since recompression therapy did not produce complete recovery, there was adequate room for additional improvement to be seen.

We do not believe the treatment failure was related to the dose of lidocaine used. The infusion profile we used was based on findings by Salzer et al. (25), who reported that a three-step administration regimen could rapidly achieve and maintain therapeutic blood levels (2–4 μg $\cdot$ ml^{-1}) in humans. We found the particular infusion profile used in this experiment to produce a mean blood concentration of 4.13 ± 0.23 μg $\cdot$ ml^{-1} of lidocaine over a 2-h period in cats (unpublished observations). This concentration is at the upper end of the normal therapeutic range and below the concentration required to activate hippocampal neurons. It is possible that pressure or HBO may have altered lidocaine kinetics or binding, but we know of no evidence to support such a hypothesis.

The control and HBO groups did not receive an equivalent volume of fluid to match the lidocaine infusion in the HBO plus lidocaine group. The difference in fluid volume received by the animals in the HBO plus lidocaine group was 7.3 ml over a 145-min period (0.8 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}). The amount of fluid needed to maintain blood volume in the resting animal is estimated at 4 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}; therefore, we believe that the extra amount of fluid given in the HBO plus lidocaine group is physiologically insignificant and did not contribute to the failure to observe a lidocaine response.

One possible explanation for the failure to observe a lidocaine response may relate to the severity of the model. In all of our previous studies of various interventions in this model, we have not seen mean recoveries greater than 60–70%. Some neurons may be irreversibly damaged during the 15 min of ischemia and will not recover regardless of treatment. The pool of neurons not irreversibly damaged may respond to lidocaine or HBO. If the response to either of these agents is nearly 100%, no effect of the additional treatment could be seen.

There is some reason to believe that HBO and lidocaine could have similar therapeutic benefits. When lidocaine is administered to embolized cats on the surface, the magnitude of the recovery of SEP is nearly the same as in the HBO group in this study (11). Although the mechanism of this beneficial action of lidocaine is unknown, speculation on possible modes of action have been previously described (7, 10, 11, 26). As a local anesthetic, lidocaine is capable of blocking nerve conduction by inhibiting sodium flux across voltage-gated sodium channels, thus inhibiting depolarization. It has been suggested that local anesthetics block neural conduction by competing with calcium for a site on the membrane that is responsible for the regulation of sodium permeability across the membrane (27). During ischemia, neurons are depolarized, resulting in an uncontrolled efflux of potassium ions and influx of sodium ions. Membrane depolarization will also activate voltage-dependent calcium channels, causing an increase in intracellular calcium concentrations (28). An increase in intracellular calcium concentration has been suggested to play a major role in ischemic cell death (28). The ability of lidocaine to block voltage-gated sodium channels would inhibit depolarization during ischemia and therefore limit intracellular accumulation of sodium and calcium and the loss of potassium. HBO therapy may have a similar end result. By rapidly relieving vascular obstruction and increasing the available supply of oxygen, normal intracellular metabolism may be restored and membrane depolarization avoided. These mechanisms remain to be proved, however.

As Fig. 1 demonstrates, there was significant individual variability in the response to both HBO and HBO plus lidocaine therapy. This large variability precluded detection of a possible small benefit of adding lidocaine to HBO therapy. The power of our test was only 40%. We decided to end the study at this point because the number of animals required to demonstrate a small difference with 95% confidence is excessively large. We feel that lidocaine addition to HBO therapy still has promise, and should be explored in an alternative, less severe model.

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