Protective effect of lidocaine in acute cerebral ischemia induced by air embolism

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To investigate possible approaches to the prevention and treatment of neural damage induced by air embolism and other forms of acute cerebral ischemia, a model was used in which cerebral air embolism was produced by infusion of air (0.4 ml) into a vertebral artery of chloralose-anesthetized cats. Neurological function was assessed by measuring cortical somatosensory evoked responses in a group of 10 untreated animals and in a group of eight animals pretreated with intravenous lidocaine (5 mg/kg). In the untreated group, the primary somatosensory amplitude was reduced to 28% ± 9% (mean ± standard error) of the value before air embolism, with a return to 60% ± 8% 1 hour and 73% ± 12% 2 hours after embolism. In the group pretreated with lidocaine, the primary somatosensory amplitude was reduced to 68% ± 9% of the value before air embolism, with a return to 92% ± 3% 1 hour and 97 ± 2% 2 hours after embolism. Pretreatment with lidocaine also greatly attenuated the acute hypertension and the increase in intracranial pressure following air embolism. These results demonstrate that pretreatment with intravenous lidocaine significantly reduces the neural decrement and increases the recovery of neural function after acute cerebral ischemia induced by air embolism.

Key Words: lidocaine • air embolism • somatosensory evoked potentials • cerebral ischemia • cerebral embolism • thrombosis

Cerebral air embolism represents a form of cerebral ischemia which can occur as a result of a large variety of primary causes in persons of all ages. It can occur in diving accidents when rupture of the lung leads to infusion of air into the left heart, which is subsequently distributed to the cerebral circulation.17,24,33 Cerebral air embolism can also occur in various clinical situations when, as a result of diagnostic or surgical procedures, air is accidentally trapped or infused into the systemic circulation.21,34,35 Regardless of the underlying cause, the ischemia resulting from cerebral air embolism has certain similarities to other forms of acute cerebral ischemia and stroke.18 Cerebral air embolism has been used experimentally in animals as a model of acute stroke. For example, Fritz and Hossmann15 demonstrated that the pathophysiology of cerebral air embolism resembles certain aspects of both inflow occlusion and microembolism-induced ischemia, and concluded that it is therefore a useful model for the study of cerebral ischemia.

Our interest in cerebral air embolism stems from its association with injury and death in diving personnel and its broader application to the study of acute cerebral ischemia. In previous studies performed to elucidate the mechanisms responsible for sudden death in dysbaric air embolism, we found that severe cardiac arrhythmias and acute hypertension resulted from the infusion of air into the cerebral circulation.12 These results suggested that, in cases of arterial air embolism, death could occur from neural effects on the heart initiated by air in the cerebral circulation alone. In further studies, we found that pretreatment of animals with lidocaine, an anti-arrhythmic drug with neurodepressant properties, eliminated the cardiac arrhythmias and greatly attenuated the acute hypertension resulting from cerebral air embolism. We also observed that lidocaine greatly attenuated the severe increase in intracranial pressure (ICP) and the large increase in plasma catecholamines following cerebral air embolism.11 These observations led us to consider whether lidocaine could protect the brain against the decrement in neurological function caused by acute cerebral ischemia. This paper describes the results of these studies in which somatosensory evoked responses (SER's) were used to
assess the effect of lidocaine on brain function after acute ischemia induced by cerebral air embolism. Measurement of the SER's was used because this index of neuronal function has been shown to correlate well with critical levels of cerebral blood flow in cerebral air embolism as well as in other models of cerebral ischemia. A preliminary abstract of this work has been published previously.

**Materials and Methods**

Male and female adult cats ranging in weight from 2.5 to 4.0 kg each were used for these experiments. Anesthesia was induced by an intramuscular injection of ketamine HCl (0.15 mg/kg). Anesthesia was maintained for the duration of the experiment by an intravenous injection of alpha-chloralose (80 to 100 mg/kg) dissolved in warm saline. After tracheal intubation, ventilation was controlled by a small-animal respirator. At frequent intervals throughout the experiment, arterial blood pressure and pH were determined and maintained within normal physiological limits by adjusting the rate and tidal volume of the respirator. Esophageal temperature was monitored and kept at 37° to 38°C by intermittent use of a heating pad.

A right femoral cutdown was performed, and catheters were inserted into the femoral artery for recording blood pressure and into the femoral vein for administering drugs. A No. 5 French catheter-tip transducer was introduced via the left carotid artery into the left ventricle for recording left ventricular pressure and left ventricular contractile force (dp/dt max). A left lateral thoracotomy was performed in which the upper three ribs were removed, and the left vertebral artery was isolated at its origin from the subclavian artery. The vertebral artery was cannulated with a PE-50 catheter filled with heparinized saline.

After the above preparation, the cat was positioned in a stereotaxic apparatus so that the head was above the level of the heart. After insuring that the animal was at a surgical level of anesthesia, pancuronium bromide (0.1 mg/kg) was administered intravenously at intervals necessary to control ventilation and to prevent muscle movement during stimulation of the sciatic nerve. The left sciatic nerve was exposed for stimulation, and the right side of the scalp was incised and retracted to allow placement of small stainless steel screws over the frontal and temporal areas. For recording ICP, a hole was drilled in the occipital area of the skull and the dura was opened. A saline-filled stopcock was fitted tightly into the hole and connected via a saline-filled catheter to a pressure transducer.

Sensory evoked responses were obtained by applying a stimulus (8 volts for 1 msec at 1 Hz) to the right sciatic nerve and recording from the temporal and indifferent (frontal) screw electrodes. Evoked cortical responses were amplified by a Grass differential preamplifier, further amplified and displayed by a Tektronix oscilloscope, and averaged by a Nicolet Model 527 signal averager. Averaged SER's were plotted on an X-Y recorder. After all surgical preparation was completed, we waited 1 to 2 hours to insure that the preparation was stable with regard to temperature, respiratory balance, cardiovascular parameters, and SER's.

The infusion into the vertebral artery consisted of 0.4 ml of air followed by 0.6 ml of saline. Both air and saline were contained in a single vertically held 1-ml syringe and administered by an infusion pump over 25 seconds. In the group of animals pretreated with lidocaine (5 mg/kg), the drug was administered constantly in the femoral vein by an infusion pump at a rate of 1.25 mg (0.25 ml)/min. In these animals, vertebral air embolism was produced within 5 minutes after the infusion of lidocaine was completed. The baseline SER's were measured after the infusion of lidocaine was completed in this group of animals.

Continuous recordings were made of the electrocardiogram, arterial blood pressure, heart rate, left ventricular pressure, left ventricular contractile force (dp/dt max), and ICP using a Gould Brush Model 481 amplification and recording system. Analog signals from the Gould system were also transmitted to a laboratory computer for on-line measurement and storage of cardiovascular, thermal, and respiratory parameters. These measurements were made at 20-second intervals throughout the experiment.

The protocol for recording SER's was as follows. First, the stability of the SER was established by monitoring the averaged waveforms during the 1- to 2-hour period preceding air embolism. Immediately before the onset of air embolism, two averaged SER's were recorded. The average of these two measurements was established as the baseline value against which succeeding SER's were compared. In the group of animals pretreated with lidocaine, SER's were recorded before and after the administration of lidocaine. However, only the two responses recorded after administration of lidocaine were used as baseline measurements against which succeeding measurements were compared. In

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*The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council, DHEW, Publ. No. (NIH) 78-23.

† No. 5 French catheter-tip transducer manufactured by Millar Instruments, Inc., Houston, Texas.


§ X-Y recorder, Model 7045 A, manufactured by Hewlett-Packard, Palo Alto, California.

¶ Gould Brush Model 481 amplification and recording system manufactured by Gould, Inc., Cleveland, Ohio.

* Laboratory computer, PDP 11/34, manufactured by Digital Equipment Corp., Maynard, Massachusetts.
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both groups of animals, SER's were recorded before the onset of air embolism and at 2, 5, 10, 15, 20, 30, 45, and 60 minutes following air embolism. Additional measurements were made every 15 minutes during the 2nd hour after the onset of air embolism. After the SER's were plotted on an X-Y recorder, the waveforms were digitized,† after which amplitude and latency measurements were made by computer. Amplitudes of SER's were measured in two ways. First, the amplitude of the primary response was measured from the baseline to the first positive peak. Next, the peak-to-trough or secondary amplitude (amplitude from the most positive peak to the most negative peak) was measured. Both measurements were made because earlier components of the SER are thought to reflect changes in subcortical activity whereas later components are thought to reflect changes in primary afferent regions of the cortex.9,23

The statistical analysis of the SER's was performed in the following manner. First, the mean and standard error (SE) of SER amplitudes at each measurement point were determined for both groups. These values were used to construct the illustrative figures. Second, an analysis of variance was performed to determine whether the values over the entire observation period were different for the control and lidocaine groups. This method, which utilized a general least-squares fitting routine, calculated the sum of squared error values that were then subjected to an F-test.5,30 These statistical methods, which are appropriate for comparing many mean values, accounted not only for the differences between group means, but also for differences among individuals within each group.

Results

The effects of cerebral air embolism on the SER in 10 control (untreated) and eight animals pretreated with lidocaine are summarized in Fig. 1. In both groups, air embolism reduced the primary and secondary amplitudes of the SER's. In the control group, the average primary SER amplitude was reduced to 28% ± 9% of the pre-air embolism value, with a return to 60% ± 8% after 1 hour and 73% ± 12% after 2 hours (Fig. 1 left). In the group pretreated with lidocaine, the primary SER amplitude was reduced to 68% ± 9% of the pre-air embolism value with a return to 89% ± 3% after 1 hour and 95 ± 2% after 2 hours (Fig. 1 left). Similar changes were observed in the secondary SER amplitudes of the control and lidocaine groups (Fig. 1 right). For both the primary and secondary SER measurements, there were statistically significant differences between the control and lidocaine-treated groups. The F-value for comparisons between the control and treated groups for the primary response was 114.72 and for the secondary response was 68.97. The critical F-value for p = 0.01 is 6.85.

Because small changes in amplitude of SER's probably have little clinical significance, we examined the SER data in another way by determining the number of animals in each group that demonstrated at least 90% recovery of SER amplitude during the 2 hours following cerebral air embolism. This examination revealed that, whereas two out of 10 control animals recovered to this degree, eight out of eight animals treated with lidocaine recovered at least 90% of SER amplitude. These data are illustrated in Fig. 2.

Latency measurements were also made on the SER wave forms, but showed only small transient changes with the onset of cerebral ischemia induced by air embolism. The mean changes in latency from the time of the stimulus to the time of peak primary response for both control and lidocaine-treated animals are shown in Fig. 3.

Because lidocaine is metabolized rapidly after administration of a single dose, it was thought that little lidocaine remained available in the treated animals after

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† Data not shown.
the 2-hour observation period. For this reason, a second infusion of air was given approximately 2 hours after the first to both control and lidocaine animals. The effect of this second infusion of air on the primary SER's in both groups is shown in Fig. 4. Statistical analysis of these data revealed no significant difference in this measurement between the two groups (the F-value for this comparison was 1.75). This information suggested that there were no differences between the two groups' response to cerebral air embolism, and that the differences observed after the first infusion of air were due only to the presence of lidocaine.

There were also differences in the cardiovascular and ICP responses to cerebral air embolism in the control versus the lidocaine-pretreated groups. Lidocaine greatly attenuated the increase in systemic blood pressure, the decrease in heart rate, and the increase in ICP induced by cerebral air embolism. The changes in these parameters for both control and lidocaine-treated animals are illustrated in Fig. 5.

Discussion

Cerebral air embolism induced via the vertebral artery was found to cause an immediate reduction in SER amplitudes, with only a small and transient change in latency. This pattern of decrement is a common finding in models of cerebral ischemia. We have found a similar pattern of decrement in ischemia induced by hypotension, in hypoxia induced by decreased inspired oxygen concentration, and in spinal cord compression. Our use of the SER amplitude as a quantifiable index of neuronal function is based on these studies and on studies that have shown a strong correlation of this measurement with critical levels of cerebral blood flow in models using occlusion of the middle cerebral artery and models using cerebral air embolism. Likewise, chloralose anesthesia was chosen because of its use in all of the studies cited above and because we have found it produces a very stable level of anesthesia with regard to cardiovascular and neural measurements in both subhuman primates and cats. Furthermore, we believe that chloralose is preferable to other alternatives such as barbiturates, which in themselves have been shown to protect the brain against cerebral ischemia.

Air embolism was used in the present study to produce cerebral ischemia because our initial interest was to find therapeutic approaches to deal with clinical cases of cerebral air embolism. We believe that the results obtained have possible implications for cerebral ischemia occurring as a result of other causes because of the similar pathophysiology of air embolism and other forms of acute cerebral ischemia.

These experiments demonstrate that pretreatment of animals with lidocaine significantly reduces the neural decrement and increases the recovery of neural function after cerebral air embolism. Measurement of both primary and secondary SER's revealed a striking difference in the degree of decrement and the recovery over a 2-hour period. The fact that eight out of eight animals (100%) pretreated with lidocaine recovered SER's to at
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FIG. 5. The effect of cerebral air embolism on heart rate and mean blood pressure (left), and intracranial pressure (right) in untreated and lidocaine-pretreated animals. All measurements were made at 20-second intervals.

least 90% of pre-embolism values, whereas only two of 10 untreated animals (20%) recovered to this degree, further demonstrates the significant effect of lidocaine in protecting the brain from acute ischemic insult in this model.

Lidocaine also attenuated the changes in heart rate, blood pressure, and ICP that follow the infusion of air into the cerebral circulation. Previously, we found that cerebral air embolism causes large increases in the levels of circulating catecholamines.

More recently, we have found that lidocaine administration greatly attenuates the elevation in plasma epinephrine and norepinephrine following air embolism.

This effect of lidocaine may be responsible for the attenuation of heart rate, blood pressure, and ICP changes seen in the present study.

The mechanisms by which lidocaine protected the brain against acute cerebral ischemia in this study are not known. A number of recent studies, however, suggest that this action may be related to the ability of lidocaine to stabilize neural membranes and reduce cerebral metabolism. In a recent review in this journal, Astrup cited his own and other work, which has shown that high doses of lidocaine, like hypothermia, reduce cerebral metabolism by several mechanisms. First, lidocaine decreases cerebral metabolism by inhibiting electrocortical activity, with a consequent decrease in oxygen and glucose consumption.

This action has been described by Astrup as a "barbiturate-like effect." Second, lidocaine has a specific membrane-sealing or stabilizing effect that restricts the movement of sodium and potassium across the membrane and thus reduces the metabolic demand of the active transport systems for these ions. This latter effect has further been shown to reduce the extracellular accumulation of potassium in the ischemic brain.

In his review, Astrup suggested that membrane failure induced by ischemia may be a key step in the irreversible damage to neural cells. Therefore, the effect of lidocaine in inhibiting or delaying membrane failure may be involved in protection of neurological function. Although Astrup used high doses of lidocaine to demonstrate these effects, other studies have suggested that, even at low doses, lidocaine has both of these effects. For example, Sakabe et al. found in dogs that intravenous lidocaine (3 and 15 mg/kg) decreased cerebral metabolic rate by 10% and 27%, respectively. In addition, lidocaine has been found to decrease oxygen consumption of rat cortex, and to decrease brain mitochondrial metabolism in vitro.

With regard to the membrane-stabilizing effect of lidocaine, Fink recently demonstrated that lidocaine in low concentrations preserved neural conduction in isolated nerves subjected to glucose-free solutions. Evidence was further obtained that lidocaine reduced the leak of potassium out of and sodium into the isolated nerves. This study provides evidence that neural conduction was preserved by the ability of lidocaine to inhibit the leak of cations across the axonal membrane. Together, the above studies indicate possible mechanisms for the protection of neurological function in ischemia demonstrated in the present study. Astrup stated that while the available evidence indi-
icates that lidocaine may have a protective effect in cerebral ischemia, the literature contains no information regarding this possibility. We believe that the present study provides such evidence.

With regard to possible clinical implications of the present findings, several points may be considered. First, it is significant that so far we have demonstrated protection of cerebral function only when lidocaine is given prior to acute cerebral ischemia induced by air embolism. Before lidocaine can be suggested as a possible therapeutic agent in the treatment of stroke, studies must be performed to demonstrate: 1) the efficacy of lidocaine in other models of acute cerebral ischemia, and 2) the efficacy of lidocaine when given after acute cerebral ischemia has occurred. With these reservations in mind, however, it is possible to speculate about the possible uses of lidocaine should the present findings be further confirmed. For example, if lidocaine administration offered protection only when given before the ischemic event, it might be useful in the management of progressing or impending stroke, or transient ischemic attack (TIA). A protective agent might also be potentially useful during endarterectomy or neurosurgical procedures such as aneurysm repair when surgical manipulation or lowered blood pressure may precipitate cerebral ischemia. Since the present study suggests that lidocaine specifically protects the brain from ischemia induced by air embolism, it may offer protection in clinical situations where air embolism can occur, such as cardiopulmonary bypass or neurosurgical procedures performed in the sitting position. In cases of air embolism resulting from diving accidents, the protective effect of a drug would be of little practical value. However, since patients suffering air embolism often exhibit a secondary deterioration after an initial improvement brought on by recompression therapy,18 lidocaine may be of benefit if administered promptly. The results of the present and other studies cited also raise the possibility that lidocaine may be effective therapeutically when given after acute cerebral ischemia. Since there is currently no specific treatment available to protect the brain from ischemia,31 intensive testing of intravenous lidocaine appears to be warranted. The fact that lidocaine is already a widely used and relatively safe drug heightens its clinical potential for the treatment of acute cerebral ischemia, should the results of the present study be further confirmed.

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