Increase in regional cerebral blood flow following experimental arterial air embolism

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If acute intracranial hemodynamic alterations consequent to arterial air embolism were studied in the dog using the radioxenon clearance technique. In eight dogs, the mean pre-embolic (control) hemispheric flow was 28.3 ml/100 gm/min. Following the injection of varying amounts of air into the right vertebral artery, there was an augmentation in the measured cerebral blood flow in all animals. Statistical analysis revealed the flow response to be independent of the amounts of air used in these experiments. The mean post-embolic cerebral blood flow was 39.3 ml/100 gm/min, representing a statistically significant increase of 11.0 ml/100 gm/min. Although the post-embolic supernormal flow may be due to the interaction of multiple pathophysiologic factors, air-induced traumatic vasodilatation is advocated as the most important pathogenetic mechanism. Prolonged vasodilatation with loss of autoregulation results in physiological shunting of blood through the affected capillary beds. Alterations in the intracerebral vasculature due to arterial air embolism are compared with studies by other investigators who have observed the effects in extracerebral vessels.

Key Words: arterial air embolism, cerebral blood flow, traumatic vasodilatation

Cerebral air embolism occurs in a number of clinical situations, and a compilation of the diverse predisposing factors has been presented elsewhere. However, a few of the more common causes bear mentioning. Air may enter the pulmonary veins as a result of direct surgical trauma, and during the ascent phase of underwater diving maneuvers. Air may enter the arterial system during the performance of cerebral arteriography, and during open heart surgery. Paradoxical air embolism occurs when venous air passes into the arterial circulation via an atrial septal defect. Venous air has also reached the arterial side of the circulation by traversing the barrier of the pulmonary capillaries. Thus, venous air embolism occurring during neurosurgical procedures performed in the sitting position could conceivably produce cerebral symptomatology.

Clinical manifestations of cerebral vascular air embolism are protean and include alterations in the sensorium, convulsions, hemiplegia, monoplegia, hemianesthesia, hemianopsia, nystagmus, and strabismus. Respiratory disturbances such as bradypnea and Cheyne-Stokes breathing are common. Manifestations of peripheral vascular collapse may eventually supervene. Similar
symptoms have been reported in experimental animals.\textsuperscript{7,13}

Scant attention has been paid to the intracranial flow alterations induced by gaseous embolism. The pathophysiology of blood flow dynamics associated with this entity is incompletely understood. Our preliminary observations have concurred with those of Waltz\textsuperscript{8} who, by means of the operating microscope, has observed “red venous blood” in feline and primate cerebral cortices following air embolization. Canine experiments in our laboratories\textsuperscript{2} have consistently shown an increase in the pO\textsubscript{2} of sagittal sinus venous blood after the introduction of intravascular air. This step-up in oxygen tension suggested the mechanism of arteriovenous shunting and/or an increased blood flow through cerebral capillaries (physiological shunting). This report concerns our studies to investigate this observation.

Materials and Methods

Eight healthy mongrel dogs weighing 10 to 21 kg were used for the regional cerebral blood flow (rCBF) study group. In addition, two dogs that did not receive air emboli were used to assess the variability of the blood flow response with repeated radioisotopic injections. The dogs were anesthetized with the intravenous administration of pentobarbital (30 mg/kg) and atropine (0.2 mg), intubated with cuffed tubes, and paralyzed with intravenous gallamine triethiodide (1 mg/kg). They were ventilated with room air, and the minute respiratory volume was carefully controlled with a Harvard constant volume ventilator to maintain a constant arterial pCO\textsubscript{2} (PaCO\textsubscript{2}). Supplemental 100% oxygen was supplied to the ventilator to maintain the eupoxic state. Polyethylene cannulas were placed in the femoral artery to monitor blood pressure and to acquire specimens for serial pCO\textsubscript{2} determinations, and in the femoral vein for the administration of medications and maintenance of fluids. The extraspinal portion of the right vertebral artery was exposed at the base of the neck, and a polyethylene tube was threaded cephalad through the intraspinal part of the artery toward the foramen magnum. In three animals, the cisterna magna was punctured percutaneously with an 18-gauge spinal needle to monitor CSF pressure. All animals in the study group had Lead II electrocardiographic monitoring. To eliminate or minimize contamination of results by the blood flow in the soft tissues external to the skull, a midline scalp incision was performed and the large temporalis muscles on each side dissected subperiosteally from the surface of the skull. The scalp and temporalis muscles were then reflected laterally and sutured in place, because angiographic and anatomic studies in the dog have demonstrated potential extracranial-intracranial anastomoses.\textsuperscript{8}

A solution of 6 to 8 millicuries (mCi) of \textsuperscript{133}Xe dissolved in 5 ml saline was injected rapidly into the vertebral artery to determine the pre-embolic (control) rCBF. An animal lying either supine or in the left lateral recumbent position received intravertebral artery air (measured in ml/kg of body weight) injected within a 30-sec interval in the following amounts: 1.0, 0.5, 0.25, or 0.05 ml/kg. Immediately after air embolization, a second similar dose of radioxenon was given to determine the post-embolic rCBF. In this manner each animal served as its own control. With the surface of the exposed skull in juxtaposition to an Anger scintillation camera, pre- and post-embolic clearance curves were obtained over a 10-min period of radioisotopic washout. The data were accumulated on a 1600 channel memory system and stored on magnetic tape for computer analysis. The average blood flow of 16 to 22 regions of interest covering both cerebral hemispheres was calculated from the equation of Høødt-Rasmussen:\textsuperscript{17}

\[
\text{CBF} = \frac{100 \cdot \lambda \cdot \Delta H}{\Delta A}\text{ ml/100 gm/min,}
\]

where 100 is the constant that converts the flow value into unit of flow per min for 100 gm of tissue; \( \lambda \) (lambda) is the partition coefficient of \textsuperscript{133}Xe between brain tissue and blood; \( \Delta H \) is the difference between the peak height of the curve (in counts per min) at the beginning and after 10 min of isotopic washout; and \( \Delta A \) is the total area under the clearance curve between peak time and 10 min later.

The rCBF values were calculated according to the equation above, on a Control Data Corporation 3300 digital computer. The use of the Anger scintillation camera,
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a relatively new tool for the assessment of the cerebral circulation, deserves further elaboration. The characteristics of the equipment used for data acquisition and analysis have been fully described elsewhere. The technique in this institution has been successful and reproducible in renal studies and in the evaluation of regional pulmonary function. With respect to cerebral blood flow, the technique compares favorably with a dual probe scintillation detector system with a 2 x 2 in. sodium iodide crystal. The method is currently undergoing further refinements and continues to receive critical analysis.

In this study the criterion used for determining a significant change in CBF between the pre-embolic and post-embolic flows was a value which exceeds 16%. This was the coefficient of variation that was found with repeated 133Xe injections in the non-embolized animals and includes a 5% variability across the surface of the sodium iodide crystal. Criteria differ in other studies as to what constitutes a significant change in CBF between control and experimental values. Uniform criteria for flows that exceed control values (supernormal flow) are certainly lacking at the present time.

Results

Symptoms and Signs

The symptoms and signs evident in this group of animals are similar to those in canine air embolism studies reported by other investigators. Mydriasis, loss of blink and corneal reflexes, and cardiac arrhythmias occurred within 30 sec of gaseous embolization. Cardiac arrhythmias included varying combinations of bradycardia, electrical alternans, bigeminy, and ST-T wave changes; these disturbances were most prominent during the first 5 min after embolization in the animals receiving 0.25 ml air/kg or more, and were associated with macroscopic subarachnoid hemorrhage. In a separate group of nonparalyzed animals not included in the present study, respiratory abnormalities (apnea, hypopnea, or “ataxic” pattern), extensor hypertonia, and opisthotonus were also prominent findings.

Intracranial Hypertension

Others have reported that arterial air embolism causes intracranial hypertension. Figure 1 illustrates studies on three animals receiving either 0.05, 0.10, or 0.5 ml air/kg. Cisternal CSF pressure, femoral arterial

![Fig. 1. Simultaneous recording of cisternal CSF pressure, femoral arterial pressure, and pulse rate in three dogs receiving varying amounts of air. Air-induced intracranial hypertension was associated with systemic hypertension and bradycardia in each animal (Cushing reflex).](image)
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and bradycardia. Similar results were observed in the animals receiving smaller dosages, although the magnitude of the responses was correspondingly lessened. The hemodynamic data indicate that the classical Cushing reflex occurs as a sequel of air-induced intracranial hypertension.

Cerebral Blood Flow Data Analysis

The record of a representative animal that received 0.25 ml air/kg (4.2 ml total) is shown in Fig. 2. Regional cerebral blood flows were calculated over 21 areas covering both hemispheres. The figure indicates that flow was augmented in all areas studied consequent to arterial air embolism.

Table 1 summarizes the flow data for the entire group of animals. To simplify data presentation, blood flows have been calculated for hemispheric areas to the left and right of the midline, the midline itself, and the composite for all regions counted (mean hemispheric flow) which for simplicity we term the "total CBF."

An analysis of variance was performed on the differences between the blood flow before (pre-embolic flow) and after (post-embolic flow) injection of the predetermined dose of air. This analysis was performed for measurements in the areas to the left and right of the midline, as well as for the midline regions. Tests for possible differences in means among dosages, positions, and areas

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<td><strong>Summary of regional cerebral blood flow data in eight dogs (ml/100 gm/min)</strong></td>
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* Odd-numbered animals were placed in the supine position. Even-numbered animals were placed in the left lateral recumbent position.
Cerebral blood flow following arterial air embolism showed no statistically significant results for any of these factors (Table 2). Since dose and position did not have a significant influence on CBF, the data on total CBF were pooled. The mean pre-embolic total CBF was 28.3 ml/100 gm/min, whereas the mean post-embolic flow was 39.3 ml/100 gm/min. The mean difference (post-embolic flow minus pre-embolic flow) was 11.0 ml /100 gm/min (S.E. ± 1.4 ml/100 gm/min). This mean difference, an increase of 11.0 ml /100 gm/min, is statistically significant at p < 0.001.

**Discussion**

Air introduced into arteries in various anatomical sites leads to a biphasic vascular response. The primary phase is characterized by transient arteriolar blockade lasting 2 to 3 min. Some investigators have also described an accompanying vascular constriction (vasospasm) during this initial obstructive phase. The secondary phase is characterized by a prolonged period of vasodilatation. Quantitative flow studies in dog extremity arteries have demonstrated increased vascular resistance with decreased flow during the primary phase, and decreased resistance with increased flow during the secondary dilatation phase. Plethysmographic blood flow studies in the human forearm have revealed similar results; there is a small decrease in hand and forearm flow which lasts 1 or 2 min followed by a sustained three- to fourfold increase in flow. To our knowledge, no quantitative flow studies on the response of the cerebral arteries to intravascular air have been reported.

The data derived from our canine CBF studies indicate that flow is augmented or becomes "supernormal" following gaseous embolization. This knowledge, coupled with the finding that sagittal sinus venous PO₂ tensions rise consequent to air embolism, leads to interesting speculations concerning the pathophysiological mechanisms. First, during the primary obstructive phase, the vessels with small resistance (the arterioles) are mechanically occluded, and blood may be diverted at an increased rate through patent, unobstructed neighboring channels. Second, the impacted bubbles may induce arteriovenous shunting. Hasegawa, et al., have demonstrated precapillary arteriovenous anastomoses ("thoroughfare channels") in the brains of dogs and man. Possibly, entrapment of air bubbles just beyond the origin of these communications would provide a stimulus for their becoming patent and functional. The degree to which these possible compensating factors could counterbalance the decreased flow present during the primary obstructive phase is not known, and they may indeed be insignificant.

Hemodynamic alterations extant during the prolonged dilatation period would seem to offer the most feasible explanation for the observed supernormal flow. Studies in extracerebral arteries have revealed that the protracted diminution in vascular resistance is not due to any of the following mechanisms: a release in sympathetic tone, increased tissue metabolism, cellular anoxia, alterations in systemic pH, or reactive hyperemia. With respect to reactive hyperemia, Lewis and Grant have shown that the increased flow that follows temporary arrest of the circulation approximately repays the oxygen debt and, if overpayment occurs, this does not amount to more than 1 1/2 times the original debt. With gaseous embolization, however, the resultant enhancement in flow repays the oxygen debt some 15 to 30 times. Because of these observations, the suggestion remains that the response is primarily

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<td><strong>Mean differences in cerebral blood flow (post-injection minus pre-injection) for the factors of air dosage, position, and brain area</strong></td>
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due to direct mechanical vascular injury resulting in loss of vasomotor tone. With respect to the duration of the response, the vasodilating action of air introduced into extracerebral vessels may last 30 min to 1 hr, or longer. That a similar duration exists in the canine brain is suggested by our observation that the elevated sagittal sinus venous oxygen tensions are diminishing and approximating the pre-embolic values at 1 hr.

Irrespective of the pathogenetic mechanism, the profound vasodilatation could be expected to interfere with the ability of the cerebral vasculature to maintain constancy of flow (autoregulation). It is known that cortical vessels near an ischemic lesion lose autoregulatory function and that the blood flow of the affected region passively follows the blood pressure in a near linear relation. Diminution in cerebrovascular resistance with constant arterial pressure would then lead to an augmented flow response through the affected capillary beds; the systemic hypertension occurring reflexly to the raised intracranial pressure in these animals could be expected to enhance the already augmented blood flow even more. Thus, impaired autoregulation during the prolonged vasodilatation phase with physiological shunting through cerebral capillaries appears to be the single most attractive explanation for the post-embolic supernormal regional cerebral blood flow.

Hypercapnia is known to alter autoregulation by dilating cerebral arteries, thus producing an increase in cerebral blood flow. We do not feel that the minimal rises in PaCO₂ that occurred under the conditions of our experiments contributed significantly to the reported results. The highest PaCO₂ values in a separate group of animals studied under identical experimental circumstances occurred 15 min post-embolism and averaged only 7.2 mm Hg. Since ischemic lesions of the cerebral cortex are known to abolish or seriously interfere with the reactivity of the cerebral vessels to CO₂, we would not expect this degree of arterial CO₂ elevation to be important. The multifocal arteriolar obstructions from gaseous emboli produce severe ischemia and vasodilatation on their own accord, and the small rises in PaCO₂ therefore, are likely to be inconsequential.

The flow enhancement in this group of animals averaged 39% above pre-embolic values. In each animal, with one exception (Dog 3, 13%), the increase in flow exceeded the level of 16%, which was felt to be the upper limit of variability of the experimental method. Increases averaging 165% in dog extremity arteries and a sustained three- to fourfold increase in human forearm flow have been reported. This suggests that the response of the cerebral vessels to intravascular air is somehow inherently different than that in extracerebral sites or, more likely, that their location in an unyielding cranial vault modifies the flow response. In this regard, the most important factor may be the air-induced intracranial hypertension. Raised intracranial pressure under these circumstances could be expected to exert a damping effect on the circulation of blood through cerebral vessels. The degree of raised pressure was consistently greater with the larger doses of air. This may provide a partial explanation for the observed fact that the flows were independent of the amounts of air employed. A second potentially important factor is subarachnoid hemorrhage, which not only raises intracranial pressure but may also cause vasospasm in those vessels not obstructed by air bubbles. Subarachnoid hemorrhage was more severe with the more massive amounts of air, and for the stated reasons this phenomenon may also exert a restraining effect on the cerebral blood flow response to gaseous emboli.

Conclusions

A greater than normal (supernormal) regional cerebral blood flow with physiological shunting through capillaries is one of the pathophysiologic sequelae of arterial air embolism. The enhancement in blood flow appears to be non-nutritive and does not appear to provide a protective or compensatory mechanism for the brain in which it occurs. During increased flow, functional capillary perfusion obviously must be impaired, for the animals exhibited profound and lasting neurological deficits. A somewhat analogous situation has been described in humans in which hyperemia is evident around an area of cerebral infarction, the so-called “luxury perfusion syndrome.”

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