
Arterial Air Embolism in the Cat Brain

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SUMMARY In cats air embolism of the brain was produced by injecting 0.6 ml blood foam into the innominate artery proximal to the origin of both common carotid arteries. Air embolism caused transient ischemia of the brain, reaching a maximum within 1 min after injection. Resolution of the air embolism began a few minutes later and was completed within 15 min in the center and within 30 min in the border zone of the main supplying arteries. During this phase tissue perfusion was inhomogenous with reduced flow rates in some areas and reactive hyperemia up to 300% in others. This resulted in venous hyperoxia and a decrease of arteriovenous oxygen difference to as low as 2 ml/100 ml blood. Reactive hyperemia was accompanied by brain swelling and an increase in intracranial pressure from 3.6 ± 1.2 to 12.3 ± 2.0 mm Hg. The reason for hyperemia was a decrease of cortical pH which fell from 7.33 ± 0.03 to 7.03 ± 0.05, and which caused a dilatation of pial arteries up to 260%.

Immediately after embolism, the EEG flattened and oxygen consumption decreased. After normalization of flow, oxygen consumption returned to normal, but EEG only partially recovered. Air embolism had little effect on the water and electrolyte content of the brain, and produced very little damage to the blood-brain barrier.

THE EFFECT of ischemia on cerebral function, metabolism and structure is a highly controversial issue which, despite extensive research during the past years, has not been satisfactorily solved. Many investigators feel that duration and intensity of ischemia are the main denominators of tissue damage, whereas others, including ourselves, are of the opinion that post-ischemic events are of equal if not greater importance. Unexpected findings, such as the observation that severe incomplete ischemia is more harmful than total cerebrovascular arrest, have added to the confusion.1 2

It is of little help when the different results are explained by differences in the experimental models as long as the pathophysiology of these models is not precisely known. We have, therefore, studied in previous investigations different forms of ischemia, and we found that, in fact, the pathomechanism of ischemia varies considerably. Besides the duration and completeness of ischemia, the site of occlusion seems to be of particular importance. For instance, following embolism of the capillary bed with microspheres, the net flow rate of the brain may remain constant because there is a redistribution of flow with hyperemia in the non-occluded vessels. The main injurious factor is the breakdown of the blood-brain barrier (BBB), leading within a few minutes to severe vasogenic brain edema and intracranial hypertension.3 4 On the other hand, ischemia produced by extracerebral interruption of blood supply (inflow occlusion), causes primarily a breakdown of the energy producing metabolism, and an inhibition of all endergetic processes. But there is no change in the permeability of the blood-brain barrier to serum proteins.5 Edema, if present, is of the cytotoxic type, and it is rapidly reversible upon restoration of blood flow.6 Finally, occlusion of the middle cerebral artery causes initially metabolic disturbances and a cytotoxic type of brain edema, but after a few hours vasogenic edema supervenes.7 8

In the present series of experiments we have studied the pathophysiology of air embolism, which is a model of intracerebral small vessel occlusion. Air bubbles are trapped in small intracerebral arteries, leading to acute interruption of blood flow in the supplying territories of the affected vessels.9 10 The site of occlusion, consequently, is proximal to the capillary bed but distal from the large supplying arteries. We were, therefore, interested to know whether the pathophysiology of air embolism resembles the inflow occlusion or the microembolism type of ischemia. Our results indicate that it combines elements of both types, and that, for this reason, it is a useful model for...
studying the response of the brain to ischemia in a more general way.

**Material and Methods**

Twenty-eight cats weighing 1.9 to 3.5 kg were anesthetized with intraperitoneal injection of pentobarbital (Nembutal®, 30 mg/kg), paralyzed with gallamine triethiodide (Flaxedil®, 10–20 mg/kg) and artificially ventilated with room air.

Blood pressure, body temperature and carbon dioxide were monitored continuously, blood gases and arterial pH monitored intermittently. All measurements were maintained in the normal range throughout the experiments.

Reversible air embolism of the brain was produced by injecting 0.6 ml blood foam into the innominate artery proximal to the origin of both common carotid arteries. Foam was used to obtain small air bubbles by shaking 1 ml of heparinized blood in a 2 ml syringe filled with room air. The catheter used for injection of blood foam was placed into the innominate artery via the right subclavian artery. The tip of the catheter was brought into its correct position as follows: first, the catheter was advanced into the aorta; this could be monitored by injecting a bolus of 133Xenon through the catheter and recording the radioactivity with a scintillation detector placed over the abdominal aorta. A second detector was then placed over the carotid artery, and the catheter was withdrawn stepwise until injection of Xenon resulted in an increased radioactivity only over the carotid artery, but not over the abdominal aorta. This occurred as soon as the tip was distal from the origin of the innominate artery at the aorta and proximal to the origin of the common carotid arteries. The correct placement was also controlled visually at the end of the experiment.

Blood foam was injected into the innominate artery over a period of 10–15 sec. The catheter subsequently was rinsed with blood and saline to remove the rest of the air. Since the catheter was distal from the origin of both carotid arteries, air embolism affected both hemispheres.

Extent and duration of embolism was followed by vital microscopy of the cortical surface. A craniotomy was made over the gyrus lateralis and gyrus suprasylvius, and microphotographs were taken before and at different times after injection of blood foam. Changes in the diameter of pial vessels were assessed on the same photographs and expressed as percent of control (14 animals). The distribution of air in the brain was also studied by injecting carbon black into the innominate artery at 30 sec, 3 min and 50 min after embolism, respectively (4 animals).

**Cerebral Blood Flow**

Cerebral blood flow was measured using the following 3 techniques: 1) A heated thermo-couple was placed on the frontal cortex, and qualitative changes of cortical blood flow were measured continuously by calculating the heat conductance (5 animals). 2) Quantitative determination of cerebral blood flow was performed using the 133Xenon clearance technique. 133Xenon was injected as a bolus into the innominate artery, and clearance was recorded using a modification of the venous sampling technique described by Meyer et al. For this purpose sagittal sinus blood was shunted into the femoral vein, and radioactivity was monitored by passing the blood through a glass coil near a scintillation detector (6 animals). 3) Xenon clearance following intra-arterial bolus injection was also monitored by an extracranial detector placed over the skull after removal of the soft tissues. The clearance curves were evaluated by biexponential curve fitting technique.

**Cerebral Metabolic Rate**

The cerebral metabolic rate of oxygen, glucose and lactate was calculated at the time of 133Xenon clearance measurements. Arterial–venous differences were determined by taking blood samples from the femoral arteries and from the sagittal sinus. The oxygen content of the blood was determined using a direct reading oxymeter (Lex-O2-Con, Lexington Instruments Corp., MA), and glucose and lactate by standard enzymatic analysis. Blood flow was determined by method (2), i.e. the sagittal sinus sampling technique, which has the advantage that blood flow was measured in exactly the same tissue compartment from which the venous samples were drawn (5 animals).

**ECoG**

The electrocorticogram (ECoG) was recorded bilaterally from the frontal regions with bipolar silver-ball electrodes. The ECoG was written on a polygraph (Dynograph RM, Beckman Instruments, Fullerton, CA), and stored on a multichannel analogue tape recorder (Ampex Corporation, Redwood City, CA). Frequency analysis of the ECoG was performed by fast Fourier transform using a laboratory computer (PDP 12, Digital Equipment, Maynard, MA). The square roots of the Fourier coefficients were calculated to obtain linearity with ECoG amplitude, and the intensity of the ECoG was then expressed as the sum of these values. An ECoG frequency index was also calculated by dividing the ECoG intensity of the beta- and alpha-bands by that of the theta- and delta-bands (5 animals).

**pH**

Subarachnoid pH was monitored in 5 animals by placing a flat surface pH combination electrode on the surface of the parietal cortex (5 animals).

**Brain Volume**

Brain volume changes were monitored using a device which has been described by Betz et al. This consisted of an induction coil implanted in the skull, and a piston placed on the cortex. The movement of the piston was recorded using the induction coil. Intracranial pressure was recorded with a transducer.
connected to the induction coil housing (5 animals).

The BBB permeability was studied at different times after embolism using 4 ml 2% Evans blue in buffer as the intravascular tracer. The dye circulated for 15 min before the animal was killed (11 animals).

At the end of the experiment, the brain was removed, one hemisphere was used for the macroscopical and fluorescence microscopical localization of extravasated Evans blue, and the other hemisphere for determination of water and electrolytes. For this purpose the brain was dissected in a moist chamber, and samples were taken from grey and white matter, dried to constant weight and subsequently digested in concentrated HNO₃ (11 animals). Statistical differences were assessed using Student's t-test.

Results

Air Distribution and Recirculation

The time course of air embolism was studied by vital microscopy of the pial vasculature. Air bubbles appeared 35 ± 4 sec (n = 14) after the beginning of injecting blood foam into the innominate artery. The maximum of embolism was reached first in the gyrus suprasylvius which is supplied by the middle cerebral artery and slightly later in the gyrus lateralis which is the border zone between the anterior and middle cerebral arteries. There was also a difference between the two gyri during recirculation: air bubbles disappeared from the gyrus suprasylvius within 15 min, whereas in the border zone some air was visible up to 30 min after embolism (fig. 1).

The distribution of air in the brain was further investigated by intra-arterial injection of carbon black. One minute after embolism, air was distributed all over the brain. After 3 min the the pial vasculature of the middle part of the lateral gyrus was still completely embolized, the middle part of the pyriform lobe partly embolized. Both regions are border zones between the arterial territories in which the perfusion pressure is lowest. The rest of the hemispheres showed no filling with air. Fifteen min after embolism the whole brain was reperfused with the exception of a few vessels in the lateral gyrus.

Changes in the Diameter of Pial Arteries

Pronounced vascular dilation occurred 3-4 min after the beginning of embolism. Dilation reached a maximum of 150-260% of control after 10-15 min. Subsequently, the pial arteries gradually constricted; in a few vessels normal vascular tone returned within
60 min, but mostly vasodilation of about 40% was still present after 2 hours (fig. 1).

Cerebral Blood Flow

Measurement of cerebral blood flow revealed quite different results depending on the technique used (fig. 2). Heat conductance fell by 2.05 ± 0.6 × 10^{-4} cal × cm^{-1} × sec^{-1} × °C^{-1} (n = 5) immediately after embolism. Subsequently, it improved with a slight overshoot of 1.24 ± 1.03 × 10^{-4} cal × cm^{-1} × sec^{-1} × °C^{-1} (n = 5) at 12 min. Normalization or a decrease below control value came after 1-2 h (fig. 2).

This time course differed from the measurements made by sampling venous blood from the sagittal sinus following intraarterial $^{133}$Xenon injection. There was considerable hyperemia with peak flow rates of 200–300% of control 5 min after embolism. Subsequently, flow gradually decreased and returned to normal after 1–2 h (fig. 2). The flow values obtained by extracranial monitoring of $^{133}$Xenon clearance, were in between. There was an average increase of 154% after 5 min, and normal flow rates during the rest of the experiment.

The reason for the differences between the 3 methods could be clarified by injecting $^{133}$Xenon immediately before embolism (fig. 3). Using the external detector, Xenon clearance slowed down in parallel with the decrease in heat conductance, but there was an acceleration of clearance when Xenon activity was measured simultaneously in blood withdrawn from the sagittal sinus. This is explained by the fact that both the external probe and the thermocouple recorded blood flow from the whole tissue whereas the sinus probe received blood only from those areas which were still perfused after embolism. Air embolism consequently leads to grossly inhomogenous perfusion with reduced blood flow in some and increased flow in other regions.

Cerebral Metabolic Rate of Oxygen, Glucose, Lactate

During the initial 30 min after embolism, the absence of steady state conditions resulted in considerable scatter of values. The tendency was a rapid increase in glucose uptake and lactate clearance and a decrease in the metabolic rate of oxygen during the initial 15 to 30 min (fig. 4). Since the metabolic rate of oxygen immediately after embolization was relatively low and blood flow increased (see above), venous hyperoxia developed, and the arteriovenous oxygen difference fell to as low as 2 ml/100 ml (fig. 4).

Cortical pH

Cortical pH following embolism decreased significantly from 7.33 ± 0.03 to 7.03 ± 0.05 (n = 5) within 4–5 min, followed by gradual normalization within one hour (fig. 1). Subsequently, it slightly decreased which, however, was a methodological error because the same shift was observed in control animals.

Electrocoricogram

Air embolism led to a flattening of the electrocoricogram (ECoG) within 15 sec (fig. 5). Frequency analysis revealed that ECoG intensity in the alpha, beta and theta bands decreased to about 20–30% of control, followed by a gradual recovery to 50–70% after 30–60 min. Intensity of the delta band returned to 80% within 5 min, but then gradually decreased to 60% after 60 min (fig. 6). The relatively higher inten-
FIGURE 4. Changes of arterio-venous difference of oxygen (A-VDO2) and cerebral metabolic rate of oxygen (CMRO2) after air embolism. Means ± SE. Closed symbols: statistically different from controls, p < 0.005.

sity in the faster frequency bands resulted in an increase of the frequency index indicating that at longer recirculation times the ECoG became faster.

In one animal the ECoG was recorded simultaneously in the gyrus suprasylvius and the gyrus lateralis, and compared with the time course of vascular embolism in both gyri (fig. 7). The gyrus suprasylvius is in the center of the supplying territory of the middle cerebral artery whereas the gyrus lateralis is the border zone between the middle and anterior cerebral arteries. Wash-out of air bubbles from the gyrus suprasylvius began 5 min after embolism and was reflected by the fast recovery of the ECoG in this area. This was in contrast to the border zone in which both air embolism and suppression of ECoG lasted considerably longer (fig. 7).

Brain Volume and Intracranial Pressure
Within 45–60 sec the brain began to swell; after 2 min a peak displacement of the cortex of 160–260 µ was reached. Brain volume then gradually decreased but was still above normal after 15–20 min. Controls did not change more than ±39 µ. Intracranial pressure rose from 3.6 ± 1.2 to 12.3 ± 2.0 mm Hg (n = 3) at 45 sec, and decreased to 6.5 ± 0.75 mm Hg after 15–20 min (fig. 8).

Brain Water and Electrolytes
Water content of the grey matter increased from 81.0 ± 0.1 to 81.7 ± 0.1 (n = 3) 15 min after embolism, followed by a normalization after 30 min and secondary increase after 2 h (81.6 ± 0.2; n = 8). Water content of the white matter changed in the opposite direction, but this decrease was not statistically significant (fig. 9). Sodium and potassium increased in both grey and white matter, reaching a maximum after 5 min. These changes were not statistically significant and presumably were due to an increase in blood volume during the phase of reactive hyperemia.

Blood-Brain Barrier
The permeability of the blood-brain barrier to Evans blue was not severely disturbed. Macroscopical examination revealed not more than a few very small faint blue spots in brain recirculated for 30 or 60 min. These spots were due to slight extravasation of the tracer around a few vessels, as detected by fluorescence microscopy (n = 4). At 15 min, or 2 h following embolism, neither macroscopic nor microscopic damage was present (n = 7).

Discussion
The most important clinical counterparts to the present experimental situation are decompression sickness and accidental air embolism in vessel...
catheterization.18, 19 During the early development of extracorporeal circulation, several such accidents stimulated experimental investigation of air embolism, and most of the knowledge about the pathological sequel has been accumulated since then.

Another clinical counterpart is transient ischemic attack (TIA).20, 21 There is good evidence that most TIA’s are due to microembolism of the cerebrovascular bed with blood constituents which, after a short period, are dissolved and washed out from the cerebral vasculature. This situation has been mimicked by producing intravascular platelet aggregates with adenosine diphosphate or arachidonic acid which, however, also cause peripheral effects resulting in severe hypotension.22-24 As demonstrated in the present series of experiments, air embolism does not have this side effect, and therefore may be a better experimental model for such attacks.

Besides its clinical aspects, air embolism is of interest for the understanding of the pathophysiology of ischemic brain damage. There is a strange relationship between ischemia and BBB lesions which seems to depend on the site of the vascular occlusion. When total blood flow to the brain is completely interrupted, barrier damage is absent even when other barrier breakers, such as hypertension, supervene.6 On the other hand, embolism in a relatively small number of capillaries with 15 micron microspheres is immediately followed by severe BBB damage, even when the total flow through the brain is not compromised.4 Air embolism apparently is between these 2 extreme situations: in some earlier experiments barrier lesions have been observed11, 25-27 but in the present investigation they were almost absent.

All 3 ischemic models — complete ischemia, microembolism, air embolism — have in common severe cerebral blood acidosis causing vasoparalysis of the vascular bed. When the brain is recirculated after complete ischemia, the vascular bed is patent, and since the vessels are dilated, considerable hyperemia ensues.28-29 As long as a no-reflow phenomenon can be avoided, this type of hyperemia is homogenous. In microembolism, part of the capillary bed is permanently occluded but there is increased flow through the non-occluded capillaries causing inhomogenous perfusion at the microcirculatory level.3 In air embolism, relatively large branches of the cerebral arteries are interrupted leading to transient complete ischemia of the peripheral capillary bed. As demonstrated in this investigation, there is also considerable inhomogeneity of blood flow and hyperemia in the non-occluded vessels, but, in contrast to microembolism, redistribution of flow is at the macro- and not at the microcirculatory level. It is therefore suggested that the barrier lesion depends on the microcirculatory redistribution of flow rather than on...
FIGURE 7. Relationship between duration of embolism and EEG changes in the gyrus suprasylvius (left) and the gyrus lateralis (right) of a representative animal. Values represent the percentage of air-occluded vessels, the percent changes of EEG-intensity (power) and the EEG frequency index.

FIGURE 8. Effect of embolism on the electroencephalogram (EEG), brain volume, intracranial pressure (ICP) and systemic arterial pressure (SAP). Note the rapid increase in brain volume.
the lactacidosis or other metabolic changes related to the degree or duration of ischemia.

Apart from the barrier lesions, the sequel of air embolism was very similar to that of other forms of reversible ischemia.22, 23, 26 During the phase of reactive hyperemia, blood flow and brain metabolism were uncoupled, causing venous hyperoxia. This phenomenon has been noted before, and it is in line with the concept of post-ischemic "luxury perfusion."19 There was also a close relationship between the duration of ischemia and the return of the EEG. In the border zone in which perfusion pressure was lowest, air was washed from the vessels at the latest stage, and this was accompanied by a delayed return of the EEG. The longer duration of ischemia in the border zone explains that morphological damage preferentially occurs in these areas, which, in fact, has been reported in earlier investigations.11, 30

An interesting observation concerns the recovery of the EEG after embolism. In agreement with earlier reports, the EEG transiently flattened and slowed down,9-11 but there was an increase of the mean frequency above normal after blood flow had been restored. It could be argued that because of posts ischemic hyperperfusion following air embolism, the anesthetic drug was cleared faster from the brain tissue than in control animals. However, the metabolic rate of oxygen did not increase which makes it unlikely that the activation of the EEG was simply due to a decrease in the depth of anesthesia. The changes, therefore, indicate that even after relatively mild ischemic impacts, such as reversible air embolism, prolonged functional changes persist.

References

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Platelet Coagulant Activities in Arterial Occlusive Disease of the Eye

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SUMMARY  Ischemic optic neuritis and retinal arterial occlusion are 2 forms of arterial occlusive disease affecting the eye. Reports in the literature suggest platelet hyperactivity in acute arterial occlusive diseases affecting other organ systems. Therefore, 14 patients with ischemic optic neuritis and 17 patients with central or branch retinal artery occlusion were studied to determine whether platelets have a role in the pathogenesis of these vascular occlusive disorders. The results of the following investigations were no different in these patients compared with those in 18 control patients with non-vascular eye diseases: prothrombin times, partial thromboplastin times, plasma fibrinogen, factor V, factor VIII, platelet counts and threshold concentrations of ADP, epinephrine and collagen resulting in secondary platelet aggregation and serotonin release. In contrast, platelet coagulant activities concerned with the early stages of intrinsic coagulation were significantly increased in patients with retinal artery occlusion without hypertension or type IV hyperlipoproteinemia, but generally normal in patients with ischemic optic neuritis and in patients with retinal artery occlusion associated with hypertension, type IV hyperlipoproteinemia, diabetes mellitus and generalized atherosclerosis. These results are consistent with a platelet contribution to retinal arterial occlusive disease in patients without other known contributing factors such as hypertension, serum lipid abnormalities, diabetes mellitus and generalized atherosclerosis and may have implications regarding prophylaxis.

ARTERIAL occlusive disease affecting the eye may present either as ischemic optic neuritis or retinal artery occlusion. Ischemic optic neuritis results from acute infarction of the optic nerve which receives its blood supply from the posterior ciliary artery.1 The etiology of idiopathic ischemic optic neuritis is unknown.2 In contrast, retinal ischemia due to retinal artery occlusion has been attributed to the occurrence of platelet-fibrin emboli,3-4 to emboli of atheromatous material,5-10 to hemodynamic factors or to circulatory obstruction proximal to the eye.11 In addition, current evidence suggests that platelets play an important part in the pathogenesis of both atherosclerosis and arterial thrombosis.11

It has been shown that platelets participate in the initiation of intrinsic coagulation and promote subsequent intrinsic coagulation reactions that result in thrombin generation.12 Platelet coagulant activities concerned with the initiation and early stages of intrinsic coagulation were previously found to be increased 2-4-fold in patients with transient cerebral ischemic attacks and normal serum lipids but not in patients with transient ischemic attacks associated with type IV hyperlipoproteinemia.13 Similar abnormalities of platelet coagulant activities were also found in patients with acute primary retinal vein thrombosis, and normal results were found in patients with retinal vein occlusion secondary to other diseases.14 These observations suggest that platelets contribute to the development of acute arterial and venous occlusive disease in certain patients, but other factors such as hypertension, atherosclerosis, serum lipid abnormalities and diabetes mellitus may be more important pathogenetic factors in other patients. To examine the possible role of platelets in the pathogenesis of arterial occlusive diseases of the eye, we have studied platelet coagulant activities, platelet...
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