Many bubbles that enter the brain circulation pass through the arterioles and capillary beds and do not obstruct blood flow. Nevertheless, such bubbles could still disrupt brain function. An open-brain model in five anesthetized rabbits used the minimum dose of air (25 μl) necessary to cause embolism of the exposed vessels, and these bubbles passed through the vessels without any trapping. Despite their rapid transit, the bubbles provoked a marked dilatation of the affected pial arterioles (mean increase after 15 minutes of 27%) that persisted for 90 minutes after the bubbles had disappeared. The changes in vessel diameter were associated with a delayed, but significant and progressive, reduction in both cerebral blood flow measured by hydrogen clearance and neural function measured by cortical somatosensory evoked response. The decrease in blood flow correlated well with the depression of neural function ($r=0.67$).

Because both cerebral blood flow and neural function temporarily returned to normal after air embolism, the subsequent changes seen in this model cannot be explained simply by the mechanical obstruction of blood flow by bubbles. (Stroke 1990;21:94–99)

To test the hypothesis that bubbles that are not trapped in cerebral arterioles may still disrupt brain function, we studied the effects of a carotid gas infusion in which all of the observed bubbles pass through the exposed pial vessels.

**Materials and Methods**

We used New Zealand White rabbits of either sex weighing 2.1–2.4 kg because the behavior of pial vessels in this species parallels that of intraparenchymal brain vessels of similar size. This study was performed in accordance with the guidelines and with the approval of the Animal Ethics Committee of the Institute of Medical and Veterinary Science (Adelaide). We anesthetized 11 rabbits with 2 g/kg i.v. urethane, which is a suitable general anesthetic for studying function in both the central and the peripheral nervous systems. All rabbits were given oxygen-enriched air to breathe and were prepared in an identical manner before being randomly assigned to either the gas/saline (embolism) or the saline only (control) infusion group.

A tracheostomy was performed in each rabbit. Femoral arterial and venous catheters (Dow-Corning silicone 602-175, Corning, New York) were introduced for blood sample collection, blood pressure recording, and fluid infusion. The left external and internal carotid arteries were isolated. A silicone cannula was introduced into the external carotid artery so that the catheter's tip was adjacent to the opening of the still-patent internal carotid artery. The rabbit was then placed in the sphinx position in
a stereotactic frame (David Kopf Instruments, Tujunga, California), connected to a ventilator (Harvard Apparatus, South Natick, Massachusetts), and paralyzed with 10 mg/hr gallamine triethiodide. The rabbit's scalp was reflected, and a craniotomy was performed over the left sensorimotor cortex. The dura was removed, and a polypropylene cylinder 1.5 cm long and 1 cm in diameter was cemented to the skull. This cylinder was filled with paraffin oil to a depth of >1 cm to maintain pial-surface pH.16 A 1-mm burr hole was also made over the right sensorimotor cortex. PaCO₂ and Pao₂ were maintained within the physiologic ranges17 by varying the ventilator stroke volume and rate and the inspired concentration of oxygen. Rectal temperature was maintained at 38° C with a heating pad.

To measure CBF, electrodes were prepared from sharpened 0.2-mm Teflon-coated platinum wire. The bare platinum tips were placed in the right and left cerebral cortices to a depth of 1 mm using an operating microscope (OPMI, Carl Zeiss, Inc., Thornwood, New York) and microelectrode carriers to avoid puncturing the exposed vessels. An indifferent silver-silver chloride electrode was placed subcutaneously in the rabbit's back. A two-channel polarographic amplifier system was used to measure the concentration of hydrogen. To measure CBF, hydrogen gas (approximately 10% by volume) was added to the ventilator inlet. After 5 minutes, the hydrogen supply was discontinued. Data from the first 30 seconds of the hydrogen clearance were ignored, and data from the next 90 seconds were log-transformed. A least-squares regression procedure was used to estimate the half-time of hydrogen clearance, and from this CBF in milliliters per minute per 100 grams brain was calculated.18 Two minutes after the beginning of each hydrogen clearance, 50 μl blood was taken for PacO₂ and PacO₂ analysis. The temperature, mean arterial blood pressure (MABP), and heart rate were also recorded.

To measure pial arteriole diameter, 2 minutes after the beginning of each hydrogen clearance the brain surface was photographed (Ilford FP4 film, Melbourne, Australia). Arterioles with an external diameter before treatment of 40–100 μm were selected and measured from the projected film. Arteriole diameter was calibrated against a 35-μm suture thread. These vessels were chosen because if bubbles do become trapped, they are trapped in arterioles of this size.2

To measure cortical somatosensory evoked response, a silver ball electrode 0.5 mm in diameter was placed on the brain surface. The rabbit's right forepaw was stimulated via needle electrodes for 0.5 msec at a frequency of 1 Hz and a voltage three times that producing a detectable response. The ball electrode was positioned to record the maximum signal from the left somatosensory area I,19 with a frequency response of 5–2,000 Hz. Two minutes after the beginning of each hydrogen clearance, 16 evoked responses were recorded and averaged. In pilot studies, the second positive wave (P₂) of such a cortical somatosensory evoked response was found to be the most sensitive to gas embolism. P₂ arises from generators in the somatosensory cortex.20 Hence, the voltage amplitude (AP₂) and the latency from the stimulus to the peak (LP₂) of this wave were measured and recorded (Figure 1).

All 11 rabbits were maintained within the physiologic ranges17 for PaO₂ and PacO₂ for at least 90 minutes. Then, either 25 μl air plus 100 μl saline (embolism group, n=5), or 100 μl saline alone (control group, n=6) was infused into the carotid artery cannula during 1 second. All rabbits were monitored for 3 hours following the infusion and the rabbits were then killed by a barbiturate overdose. All parameters were recorded every 15 minutes.

For each parameter, the mean of the preinfusion data was assigned a value of 100%. All subsequent data were recorded as a percentage of the relevant preinfusion mean and are expressed as mean±SEM. Data were tested using analyses of variance, regression analyses, and Student's t tests. A significance level of p<0.05 was chosen, and when simultaneous multiple comparisons were performed the Bonferroni method was used.21

Results

MABP, PacO₂, PacO₂, and heart rate did not change significantly at any time in either group. Similarly, there were no significant preinfusion changes in
CBF, cortical somatosensory evoked response, or arteriole diameter.

Following infusion of 25 μl (10.4–11.9 μl/kg) air into the left internal carotid artery, bubbles appeared in the pial arteries of all five embolism group rabbits within 10 seconds. These bubbles were displaced by blood; the blood–air interface advanced with each cardiac systole, and no bubbles remained in view after 30 seconds.

CBF in the left cortex 15 minutes after the infusion was not significantly changed from the preinfusion mean in either the embolism (92±9%) or the control (101±12%) group, and no significant difference existed between the groups at this time (Figure 2). Thereafter, CBF in the left cortex progressively decreased in the embolism compared with the control group, and this difference became significant 90 minutes after infusion (mean decrease in the embolism group 41±3%, p<0.05). At no time did CBF in the left cortex of the control group differ significantly from its preinfusion mean, whereas that in the embolism group significantly and progressively decreased (F=2.6, p=0.02).

There were no significant differences in CBF in the right cortex either between groups or over time (data not shown).

The control group showed no significant variation in pial arteriole diameter during the course of the experiment, whereas the embolism group showed a significant increase immediately after the infusion (F=2.03, p=0.04; mean increase after 15 minutes 27±8%, p<0.05) (Figure 3). The diameter then slowly returned to the preinfusion value so that by 90 minutes after infusion, arteriole diameters in the two groups were similar.

LP2 did not change significantly at any time in either group (data not shown). AP2 15 minutes after the infusion showed no significant changes from the preinfusion mean in either the embolism (85±6%) or the control (101±21%) group, and no significant difference existed between the groups at this time (Figure 4). Thereafter, AP2 progressively decreased in the embolism group compared with the control group, and this difference became significant 75 minutes after infusion (mean decrease in the embolism group 43±3%, p<0.05). AP2 in the control group never differed from the preinfusion mean, whereas that in the embolism group significantly and progressively decreased (F=2.49, p=0.02).

Regression analysis of left cortex CBF versus AP2 in the embolism group demonstrated a linear relation (r=0.67, F=8.9; p=0.012) over the data range, expressed by the equation AP2=0.69×CBF+17.2.

Discussion

P2 of a cortical somatosensory evoked response produced by stimulation of a rabbit's right forepaw is projected to a small area on the surface of the left cerebral hemisphere. The hydrogen clearance technique measures CBF of a small region (approximately 8 mm3) of brain. Hence, we were able to observe the changes in CBF and the cortical somatosensory evoked response in a very localized region in which we observed bubble passage. The decreases in both CBF and AP2 in this region contrasted with the data from the contralateral hemisphere in the
vascular architecture makes bubble entrapment most likely in the intraparenchymal vessels at the junction of the gray and white matter. Bubbles trapped in intraparenchymal vessels are not detected by this model. However, such bubbles by themselves probably cannot produce the changes in CBF that we saw, for two reasons. First, the mechanical effect of bubbles trapped in intraparenchymal vessels should have been apparent in the first measurement of CBF after air/saline infusion. However, 15 minutes after infusion, CBF in the left cortex of the embolism group did not differ significantly from either the preinfusion mean for this group or from CBF in the left cortex of the control group. Second, CBF after air/saline infusion showed a progressive and significant decline of >40% during 90 minutes. This progressive decrease is best explained by gas-induced changes in blood and/or blood vessels. It follows then that although clearance of bubbles from intraparenchymal vessels has not been demonstrated in this model, the CBF changes that we saw cannot be attributed simply to mechanical obstruction of the vessels by bubbles. The progressive reduction of CBF in the left cortex is probably not due to any transient cerebral vessel occlusion. Brief periods (5–30 seconds) of arrested CBF are instead followed by a reactive hyperemia. The decrease in CBF also cannot be explained by changes in MABP, PaCO₂, or PaO₂ (all of which remained stable) nor by changes in intracranial pressure (which does not increase in this open-brain model). The stable MABP in the embolism group suggests that blood supply to the brainstem was not affected and that local causes were responsible for the decline in CBF.

The infusion of air into the left internal carotid artery had no effect on CBF in the right cortex. This suggests that there was little or no embolism of the contralateral hemisphere and is consistent with other observations. The external diameters of the embolized vessels increased significantly. In this model, the dilatation cannot be ascribed to brainstem reflexes nor to changes in MABP or PaCO₂. Bubbles in the capillaries or intraparenchymal arterioles may increase transmural pressure, but the response of normal vessels should be to constrict rather than to dilate. Pial vasoreactivity is not abolished by gas embolism, but bubbles do damage endothelial cells and the normal vasoconstrictor response to increases in transmural pressure may require intact endothelium. The cerebrovascular response to hydrostatic pressure can also be overcome at very high pressures (absolute pressure [Pₚₐₜ] of >935 mm Hg), but the calculated pressure in bubbles trapped in pial vessels is lower (Pₚₐₜ of <870 mm Hg). Furthermore, the characteristic sausage-shaped or head-string dilatation caused by such elevated pressures was not seen in our rabbits. It follows that if the vasodilatation was a passive response to increased transmural pressure, then the dilatation must have been secondary to endothelial damage.

Despite stable MABP, the 27% increase in the external diameter of embolized pial arterioles was not associated with any significant change in regional CBF. Assuming newtonian flow, if the internal vessel diameter also increased by 27%, then in the absence of any other changes there should have been a 260% increase in CBF. The maintenance of CBF might be explained by an increase in resistive pressure secondary to bubbles in the capillaries or intraparenchymal arterioles, or by the effects that bubbles have on the vascular endothelium and blood constituents (such that blood vessel wall thickness will increase), or by gas-induced disruption of the blood–brain barrier (and a consequent increase in blood viscosity).

The arterioles returned to their preinfusion size by 90 minutes after infusion, and this was associated with a reduction in local CBF to 60% of preinfusion values. The concurrence of these decreases in arteriolar diameter and CBF demonstrates that the changes were not autoregulatory. Similarly, it shows that the initial dilatation was not due to bubbles in the capillaries or intraparenchymal arterioles since the return to preinfusion diameters could be explained only by the clearance of bubbles into the veins or by the recruitment of alternative vascular channels. Either process would clearly not have been associated with a progressive decrease in CBF, as was seen here.

Air embolism also diminished AP₂, indicating that sensorimotor cortex function was impaired. This impairment correlated well (r=0.67) with the reduced CBF. A coupling of neural function and blood flow has also been demonstrated in the cat brain after air embolism, and in dogs the recovery of cortical somatosensory evoked response after gas embolism correlates well with blood flow in the sensorimotor cortex.

Therefore, in this model the changes in CBF, neural function, and arteriole diameter can best be explained by the effects of air on the blood vessels and/or on the blood itself. These findings have two important consequences for the treatment of patients with cerebral arterial gas embolism. First, although treatment in a recompression chamber will reduce gas embolus volume and so help to redistribute trapped emboli into the venous circulation, treatment by compression alone could be expected to have a significant failure rate because it does not take...
into account these secondary effects. Indeed, a significant failure rate has been shown for compression treatment alone for cerebral arterial gas embolism in both animals (30–50%)45,46 and in human divers (22%).45

Second, a posttransit, gas-induced decrease in CBF to neuron-disabling levels4,12,46 may explain why many patients who appear to have recovered from cerebral arterial gas embolism subsequently relapse.50 If our model is a reasonable predictor for humans, this relapse should occur within 2 hours after embolism. Whereas the speed of endothelial damage and the response of the blood system may be different in humans, this predicted time frame is consistent with the peak occurrence of relapses in those patients with cerebral arterial gas embolism who initially respond to recompression therapy.51

If the processes that produced the progressive deteriorations of CBF and neural function after gas embolism in our model can be identified, it should be possible to optimize the treatment of patients with, or those at risk of, cerebral arterial gas embolism.

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S C Helps, D W Parsons, P L Reilly and D F Gorman

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