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The following paper covers the topics discussed by Dr Des Gorman during this conference

THE DISTRIBUTION OF ARTERIAL GAS EMBOLI IN THE PIAL CIRCULATION

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INTRODUCTION

A. The natural history of cerebral arterial gas embolism

Once introduced into a large artery, gas emboli will distribute according to their buoyancy, such that the cerebral circulation is embolised in humans and experimental animals placed in a head-up (upright) position.[1-3] A head-down (inverted) position protects the cephalic circulations.[3] Because of their upright posture during ascent, divers and submariners with arterial gas embolism (AGE) usually present with neurological symptoms and signs consistent with cerebral arterial gas embolism (CAGE).[4-8]

Before any study of CAGE treatment can be undertaken, the natural history of gas emboli in the cerebral circulation must be documented. Although it has not been shown directly, it is assumed that the gas emboli that arise during decompression occur as a result of pulmonary over-inflation and direct embolism of the pulmonary veins.[7,9,10] Such emboli may be coated with surfactants,[11] and this may alter subsequent events in the cerebral circulation.

From available studies it would appear that regardless of the form in which gas is introduced into the arterial circulation, coalescence of small emboli will create cylindrical gas columns.[11,12] It also appears that the larger the embolus, the more likely that it will lodge in a small arteriole and block blood flow.[12-15] The conventional pathophysiological model of CAGE is based on the physical blockage of a cerebral arteriole by gas,[9,10,12-15] and assumes that the observed regional brain ischaemia,[12,17-20] platelet accumulation,[21] thrombi formation,[21-25] and increased blood-brain barrier (BBB) permeability[15,19,20,26-30] are secondary to this blockage.

However, researchers using cranial windows to observe pial gas embolism[13,14,16] have obscured the natural history of the emboli by compressing their experimental animals in a recompression chamber (RCC). The potential for the results of these studies to be misleading is demonstrated by work with several animal models not incorporating a cranial window.[3,12,18,31] In these models gas emboli have been shown to spontaneously redistribute from the cerebral arteries to the jugular veins,[3,12,18,31] to the right ventricle, and to the pulmonary arteries.[12,31] It is not known what proportion of gas emboli entering the cerebral arterioles undergo such redistribution, nor is it known what effect they may have after redistributing. It is even possible that gas emboli may only lodge in cerebral arterioles temporarily, eventually redistributing to the venous circulation. The last possibility is a plausible explanation of the large number of human patients with CAGE that experience some resolution of symptoms and signs prior to any treatment.[32,33]

Almost all of the animal models of CAGE on which the conventional model is based, have involved the direct injection of gas into a carotid artery.[13,14,16] With the single exception of carotid artery surgery,[34] these vessels are not the usual source of arterial gas emboli. Also, it is known that the carotid artery gas infusion techniques employed by these researchers can avoid embolism of the brain stem circulation.[3,12-14,18,24] Gas embolism of the brain stem causes cardiac dysrrhythmias,[3,9,18,31,35-42] respiratory depression,[3,12-14,18,31,43] and an increase in arterial blood pressure[3,9,12-14,18,31,37-39,43] that exceeds the limits of cerebrovascular autoregulation.[42,44,45] The result is a significant increase in cerebral blood flow (CBF),[42,44,45] which will have a major influence on the passage of gas emboli through the cerebral circulation. This casts further doubt on the animal model data from which the conventional pathophysiological model of CAGE is derived. It follows that the natural history of gas emboli in the cerebral circulation is yet to be described.

B. The factors that could influence the passage of gas emboli through the cerebral circulation

The arrest of a region of the cerebral circulation, as a consequence of a gas embolus lodging in a small arteriole, will only occur if the forces that oppose embolus movement exceed the local cerebral perfusion pressure (CPP).[9,13]

The forces that oppose embolus movement increase as the length of the embolus increases.[14,19,22,31] The length of a gas embolus is a function of both its volume and the diameter of the vessel it occupies.

Local CPP is an interaction of mean arterial blood pressure (MABP), the level of cerebrovascular resistance (CVR), and the intra-cranial pressure (ICP).[46-50] The interaction of these factors is made more complex by the variation of CVR with MABP, such that CBF remains constant over a range of arterial pressures.[51-53] This latter phenomenon is called cerebrovascular autoregulation.

The infusion of gas into the carotid or vertebral arteries can inhibit this autoregulation, so that increases in MABP are accompanied by increases in CBF.[42,44,45] Accordingly,

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CPP will vary with MABP, and the progress of gas emboli through the cerebral circulation will be directly influenced by the MABP.

The infusion of gas into the carotid or vertebral arteries, or into the aorta or pulmonary veins can cause a transient, but significant increase in MABP.[3,9,12-14,18,31,37-39,43] Embolism of the brain stem circulation appears necessary for the typical hypertensive response to gas emboli.[3,12-14,18,24] Because autoregulation of CBF is lost,[42,44,45] the transient hypertension that accompanies AGE will itself promote spontaneous redistribution of emboli from cerebral arterioles to the venous circulation.[3,12,18,31]

C. Aims of the studies

A series of studies were conducted with a rabbit animal model of CAGE to describe the natural history of gas emboli in the systemic circulation, and in particular in the cerebral circulation. The studies also aimed to identify the factors involved in the passage to these emboli through the cerebral vessels.

Methods

New Zealand (NZ) White Rabbits, of either sex, weighing between 4 and 6 kg were used in all experiments. This species was chosen because the behaviour of their pial arterioles has been shown to parallel that of intra-parencyhmal brain vessels of similar size[54] because the behaviour of their pial arterioles is not affected by being exposed in an open-brain preparation,[54] and because the modulation of cerebral vessel reactivity by changes in blood pressure persists in this species despite halothane anaesthesia.[55,56]

Pilot studies demonstrated that halothane was the only available anaesthetic that enabled both a steady-state of anaesthesia and prolonged survival after CAGE. The minimum alveolar concentration (MAC) for halothane in the NZ White Rabbit is well established.[55,56] The pilot studies also demonstrated that accurate measurements of pial arteriole diameter after gas embolism required exposure of the brain as an open-brain preparation.

Tracheal preparation
Following induction of anaesthesia in a perspex anaesthetic box, a tracheostomy was created. This was intubated with a size 3 or 4 cuffed endotracheal tube.

The cuff was inflated with isotonic saline. The tube was sutured into position, and connected to a respiratory circuit that included gas cylinders, pressure regulators, calibrated rotameter flow meters, and a Fluotec Mark 2 halothane vaporiser.

Fresh gas was delivered to the circuit at 4 L/minute to prevent re-breathing. The arterial and cerebral venous oxygen and carbon dioxide tensions were regularly monitored.

The halothane vaporiser was set at 1.5 % (11.62 + 0.01 (SD) mm Hg vapour pressure).

Jugular Venous Preparation
The left jugular vein draining the cranial contents was isolated by dissection, cannulated, and connected to a heparinized loop that included a graduated air trap (with gas collected over water). The loop was reintroduced into the jugular vein at its distal end with a second cannula. A 3-way tap was incorporated into the loop to permit both intravenous infusion and collection of venous blood samples. These were analysed for oxygen and carbon dioxide levels with a Radiometer ABL 30 blood-gas analyser using appropriate temperature corrections.

Body Temperature Maintenance
The rabbits' rectal temperature was maintained between 37.5°C and 37.8°C with a variable-output heat pad.

Electrocardiogram Recording
Electrodes were implanted in the rabbit's chest and limbs to provide a continuous ECG record on a Neotrace 8-channel recorder.

Femoral Artery Preparation
The right femoral artery was isolated by dissection, cannulated, and connected via a 3-way tap to a Bell & Howell pressure transducer (with pressure displayed on a chart recorder), and to an infusion line. Infusate was warmed in a heated coil bath to 37.5°C. Arterial blood samples were analysed for oxygen and carbon dioxide levels with a Radiometer ABL 30 blood gas analyser using appropriate temperature corrections. Venous drainage from the right leg was occluded by ligature.

Cranial Preparation
A parieto-occipital craniotomy of approximately 2 x 3 cm was created with a high-speed drill. Removal of the dura enabled observation of the brain and pial vessels with a Zeiss dissecting microscope. The microscope had a magnification range of 125 to 800 times, and had both video (Sony DXC150P) and still camera (Contax 35 mm) attachments. A tape dam with a central channel was built at the posterior aspect of the craniotomy to allow and control the outflow of cerebrospinal fluid (CSF).

The exposed brain was also bathed with warmed (37.5°C) and humidified gas mixtures, that were designed to replicate brain tissue partial pressures of oxygen (PO_2) and partial pressures of carbon dioxide (PCO_2) under the various experimental conditions. These mixtures were applied as a 1.5 L/minute diffuse jet into the craniotomy.

Gas Infusion Technique
Gas was introduced into the femoral artery as microbubbles of less than 200 μm diameter. This was achieved by infusing gas at a controlled rate (0.2 ml/sec) through an orifice of 0.025 ml internal diameter.[57] Three ml of normal saline were then infused at 0.1 ml/second to clear all gas from the arterial line.

Measurement of Pial Arteriole Diameter
A pial arteriole with an external diameter between 50 and

200 μm was selected for measurement. The pilot studies demonstrated that this size of arteriole trapped gas emboli.

The segment of the arteriole where the measurements were performed was fixed at the intersection of the microscope occular cross hairs. The microscope was locked in position except for the vertical focus control. Measurements were only performed at optimal focus, such that the distance from the segment being studied to the lens remained constant.

The external arteriole diameter was calculated as the mean of 6 measurements performed on 3 successive photographs and 3 successive still frames of the video sequence. All photographs and video sequences were recorded at 500 times magnification. The diameter was measured with calibrated metal calipers (measurement error <1%). Because of the large diameter range of arterioles studied (50200 N-m), changes in diameter were recorded as fractional changes referenced to the original diameter.

The type of photographic film and video tape, exposure time, and shutter speeds, were unchanged throughout the course of the experiments.

Procedure

Twenty seven rabbits were anaesthetised with either air and halothane (10 rabbits) or oxygen and halothane (17 rabbits). Throughout all of the experiments the rabbits remained within their physiological range (when breathing air and oxygen) for both the arterial PO_2 and PCO_2.

The 27 rabbits were divided into 5 groups; each of 5 rabbits, with the exception of Group Five which had 7 rabbits.

Group One was used to observe the distribution of arterial gas emboli, and the consequent cardiovascular and respiratory effects.

Group Two was used to determine the effect of posture on the distribution of arterial gas emboli.

Groups Three and Four were used to determine the effect of altered gas solubilities on AGE.

Group Five was used to determine the effect of lowered surface tension pressure on embolus distribution, both because gas foamed in detergent has been used by previous researchers to stabilise emboli,[13,14] and because gas emboli arising during decompression may become coated with pulmonary surfactants.[31]

Group One

Five rabbits breathing air were each bound in an upright posture to a tray that was fixed at 45° to the horizontal. Five ml of normal saline were infused into the femoral artery in a manner identical to that described for gas infusions. This was followed by repeated 5 ml air infusions, as microbubbles, given at 2 minute intervals until a gas embolus became trapped in a pial arteriole which was under observation on the brain surface. If the embolus was only trapped temporarily, and subsequently redistributed from the pial arteriole, further gas infusions into the femoral artery were performed. Infusions were repeated until another embolus became trapped. Only when an embolus remained trapped after MABP had returned to pre-infusion levels was local pial circulatory arrest assumed. The size (length and diameter) of emboli that became trapped was recorded, together with systolic and diastolic blood pressure, MABP, heart rate, ECG, and respiratory rate. Air was allowed to escape from the jugular venous loop into the graduated air trap. The volume of air collected was recorded.

Group Two

Five rabbits breathing air were bound in an inverted posture to a tray that was fixed at 45° to the horizontal. Saline and gas infusions were performed as in Group One. The procedure was abandoned if either pial circulatory arrest was caused by trapped gas emboli, or if the total amount of gas infused into the femoral artery exceeded 15 ml. If pial gas embolism did not occur in these animals, they were changed to an upright posture, again at 45° to the horizontal. If after 5 minutes pial embolism had not occurred, further 5 ml air infusions, as microbubbles, were made into the femoral artery in an identical manner to that in Group One. The rabbits were monitored as described for Group One.

Group Three

These 5 rabbits were subjected to an identical procedure to that described for Group One, with the single exception that they breathed oxygen throughout the experiment.

Group Four

These 5 rabbits were subjected to an identical procedure to that described for Group One, with two exceptions. First, they breathed oxygen throughout the experiment, and second, they had oxygen rather than air microbubbles infused into their femoral arteries.

Group Five

These 7 rabbits were subjected to an identical procedure to that described for Group One, with two exceptions. First, they breathed oxygen throughout the experiments, and second, they had an air foam rather than natural air infused into their femoral arteries. The air was either foamed in a 3% Teepol solution (5 rabbits) or in a homogenized lung preparation (2 rabbits). The latter was prepared by homogenizing lungs extracted from healthy rabbits, and used within 20 minutes of the death of the donor rabbit.

Results

General Observations

Gas introduced as microbubbles into the femoral artery of an upright rabbit caused pial gas embolism in the field of view, with cylindrical columns of gas entering the arterioles. The size distribution of these emboli is displayed in Figure 1 (page 104). The proximal blood-gas interface pulsed with each cardiac systole. The pulsations were damped by the gas and were not observed at the distal interface. No

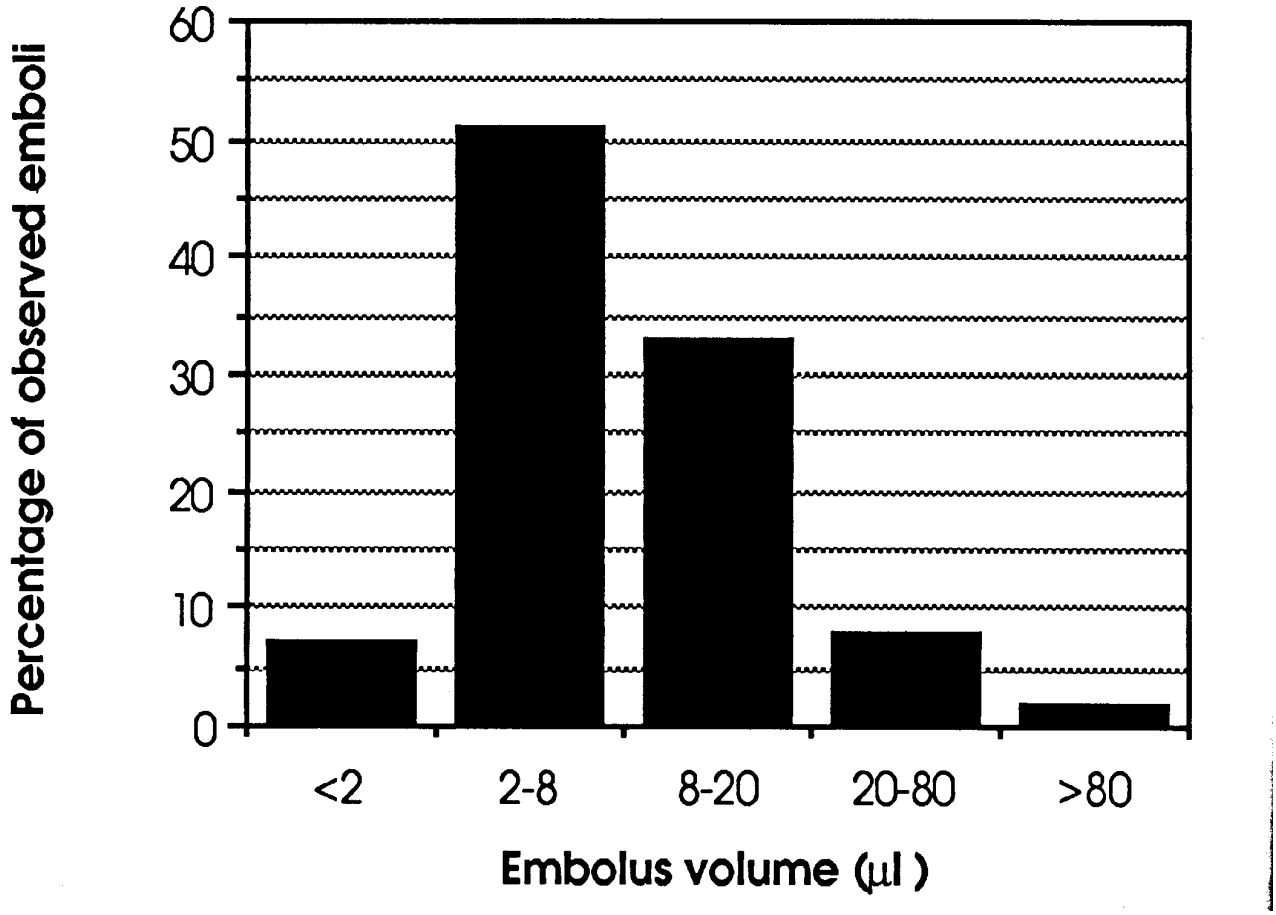

Figure 1. The size-distribution of gas emboli observed in the pial vessels of the 10 rabbits in Groups One and Two. There were 62 gas emboli.

discrete microbubbles were observed. Regardless of infusate volume, no gas entered the pial vessels of inverted rabbits.

More than 80 per cent of the gas emboli that entered the pial arterioles distributed without interruption to the veins, and gas was often seen in the large veins (>200 µm diameter). In upright rabbits, gas escaped from the jugular vein cannula within 30 seconds of gas introduction into the femoral artery. The gas was collected in the air traps as a blood foam. Gas accumulated in these air traps even when the jugular vein was ligated distal to the trap, a technique that prevented the retrograde passage of air emboli. Some gas emboli became trapped in the pial arterioles either temporarily, or permanently to cause local circulatory arrest (see Figure 2 on page 116).

The progress of a gas embolus through the pial circulation was related to the volume of the embolus (Figure 3). The larger the embolus the more likely it would lodge in a pial arteriole to block blood flow (Table 1) (Pearson ratio = 6.68; likelihood ratio — 6.73: $p < 0.01$). Emboli became trapped in arterioles of 50 to 200 µm diameter, most frequently in those vessels with external diameters of less than 100 µm (Figure 4). If an embolus entered an arteriole of this size such that the length of the embolus exceeded 5000 µm, then local circulatory arrest was inevitable. Conversely, if the length of the embolus was less than 5000 µm, it progressed to the venous circulation without interruption. Emboli of intermediate length (500-5000 µm) often became trapped, but this was usually temporary, redistributing to the veins within 3 minutes. Those intermediate length emboli that did not redistribute spontaneously were almost always trapped in arterioles with external diameters of less than 75 µm.

The spontaneous redistribution of emboli only occurred during the period of hypertension that followed gas embolism. If the embolus remained trapped in the arteriole after the blood pressure resumed normal or below normal values, then subsequent spontaneous redistribution did not occur. Redistribution always occurred, if within 10 minutes of embolus arrest, a forceful infusion of saline into the femoral artery was used to create a step increase in arterial pressure of greater than 150 mmHg. Conversely, redistribution never occurred, regardless of the increase in arterial pressure if the forceful fluid infusion occurred more than 15 minutes after embolus arrest. This inability to redistribute gas emboli from the pial arterioles was a consequence of arteriole wall collapse, and occlusion of the arteriole lumen.

Spontaneous redistribution was followed in 10 of the 27 rabbits by spontaneous re-embolism. In these rabbits, the additional gas emboli entered the pial arterioles within 5 minutes of the original emboli having redistributed. This

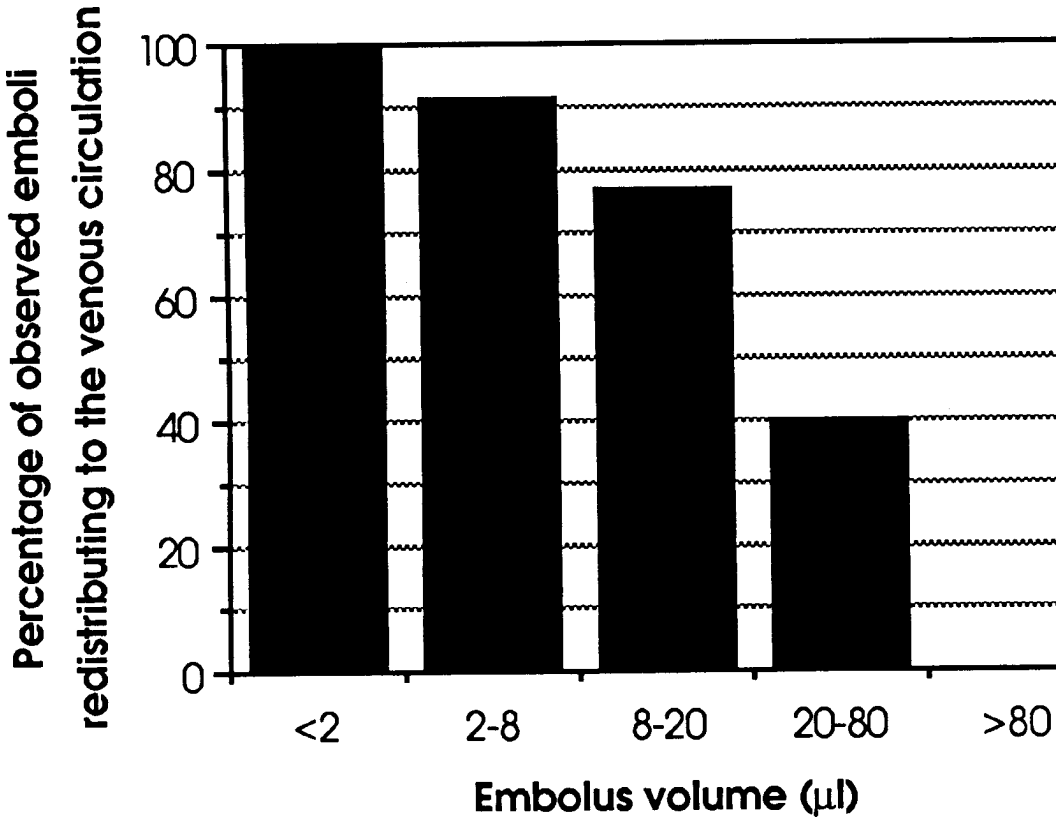

Figure 3. The relationship between the volume of gas emboli in the pial arterial circulation and the degree of redistribution of these emboli to the venous circulation in Groups One and Two (10 rabbits with 62 gas emboli).

occurred without any further gas infusion into the femoral artery, and without any other manipulation of the rabbit.

Respiration

Pial gas embolism was often accompanied by brief (< 30 seconds) periods of apnoea. If sufficient gas entered the arterioles to cause pial circulatory arrest there was invariably associated respiratory arrest. Spontaneous respiration resumed in those rabbits who became normotensive after embolism. No effect on respiration was observed if the infusion of gas into the femoral artery did not cause pial gas embolism. Regardless of infusate volume, no respiratory abnormalities were observed in inverted rabbits.

Circulation

Pial gas embolism was associated with cardiac bradyarrhythmias, and occasionally with cardiac arrest. Cardiac arrest always occurred within several minutes of respiratory arrest. A typical bradyarrhythmia is displayed in Figure 5.

If an embolis lodged in a pial arteriole, blocked blood flow, and did not redistribute to the venous circulation, then the consistent finding for all rabbits was progressive systemic arterial hypotension, and eventual death. The mean survival time for rabbits with such pial circulatory arrest was only 26 minutes ± 6.9 (SD).

TABLE 1

	EMBOLUS VOLUME µl	NUMBER OF EMBOLI	NUMBER OF EMBOLI PASSING TO VEINS	PERCENTAGE OF EMBOLI PASSING TO VEINS
	< 8	36	33	91.7
	> 8	26	17	65.4
TOTALS		62	50	80.6

The relationship between the volume of gas emboli in the pial arterial circulation and the redistribution of these emboli to the venous circulation in Groups One and Two (10 rabbits and 62 emboli).

Pearson ratio = 6.68; likelihood ratio = 6.73; $p < 0.01$; (p type 1 error = 0.009)

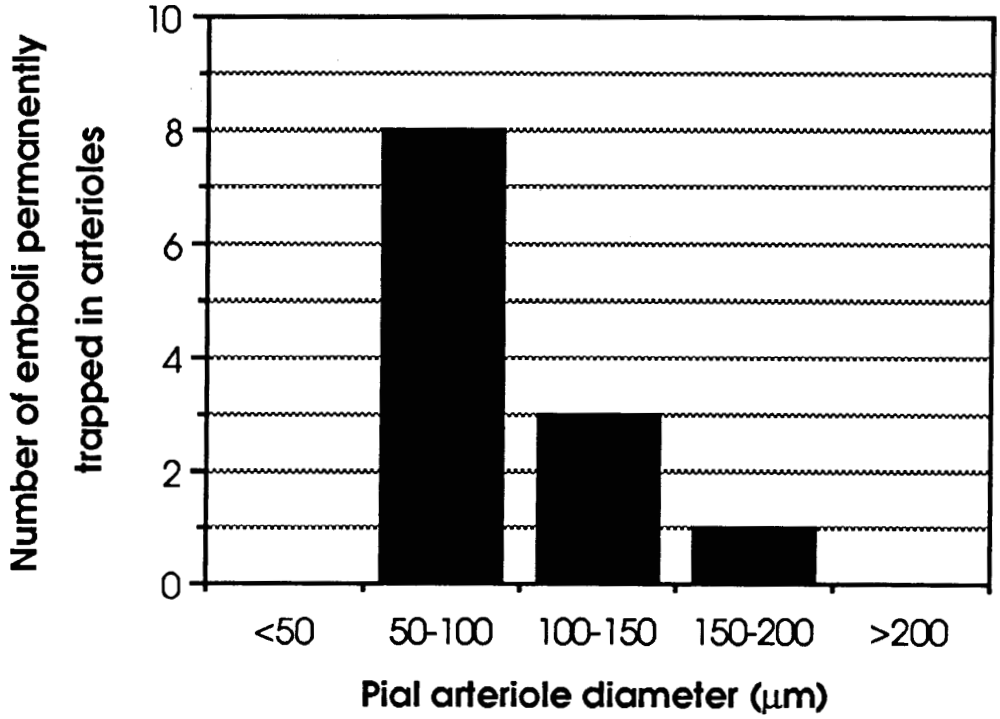

Figure 4. The relationship between the size (diameter) of pial arterioles and the number of emboli lodging in them to block blood flow in Groups One and Two (10 rabbits). n_1 = 62 gas emboli; n_2 = 12 gas emboli lodging in arterioles to block blood flow; n_1/n_2 = 0.194.

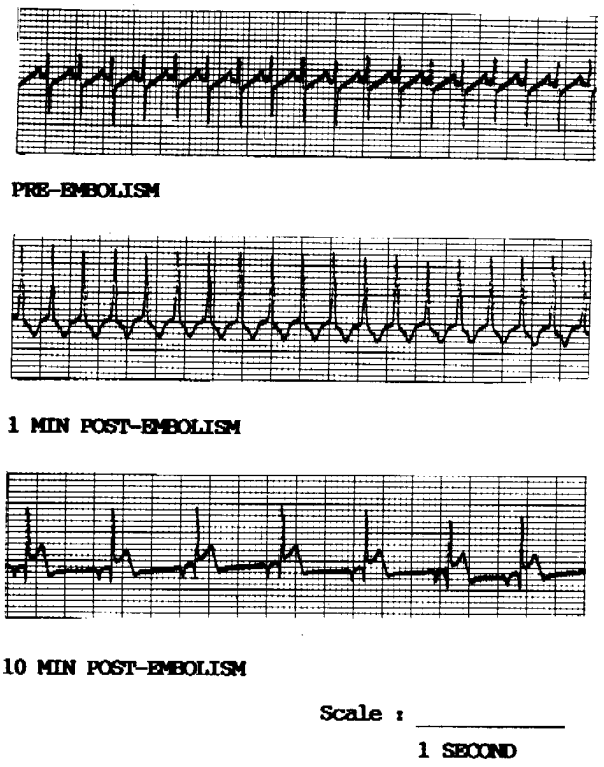

Figure 5. Cardiac bradyarrhythmia associated with pial arterial gas embolism. Scales: Vertical; 0.5 mv/major division. Horizontal; 5 major divisions/second.

The infusion of air microbubbles into an upright rabbit's femoral artery always caused a significant increase in MABP ($t_9 = 8.15, p < 0.001$). However, the accompanying increase in pulse pressure was not significant ($t_9 = 1.07$). A typical blood pressure recording with infusion of gas into a femoral artery of a rabbit is shown in Figure 6. Similar, prolonged changes in blood pressure were never demonstrated in those rabbits where saline was infused into the femoral artery using an infusion technique identical to that used for gas. A typical blood pressure recording following such a saline infusion is also shown in Figure 6.

The increase in MABP did not differ significantly between those rabbits breathing air, where air microbubbles were infused into their femoral arteries, and those rabbits breathing oxygen, where oxygen microbubbles were infused into their femoral arteries ($t_{13} = 0.6$) (Table 2). The MABP returned to pre-infusion levels within 6 minutes of embolism in those rabbits breathing air who were embolised with air microbubbles (mean: 3.15 mins+ 2.2 (SD)). The MABP returned to pre-infusion levels within 2.5 minutes of embolism in those rabbits breathing oxygen who were embolised with oxygen microbubbles (mean: 1.85 mins+ 0.46 (SD)). The difference between the recovery times in these 2 groups was not significant. ($t_{13} = 1.28$).

Gas microbubbles infusion into the femoral artery of inverted rabbits also caused a significant increase in MABP ($t_4 = 7.95, p < 0.01$). However, this increase in MABP was significantly less than that seen in upright rabbits ($t_{13} = 3.68$, $p < 0.01$; One way ANOVA $F = 8.37$, $p < 0.005$). Also, in 3 of the 5 inverted rabbits the blood pressure did

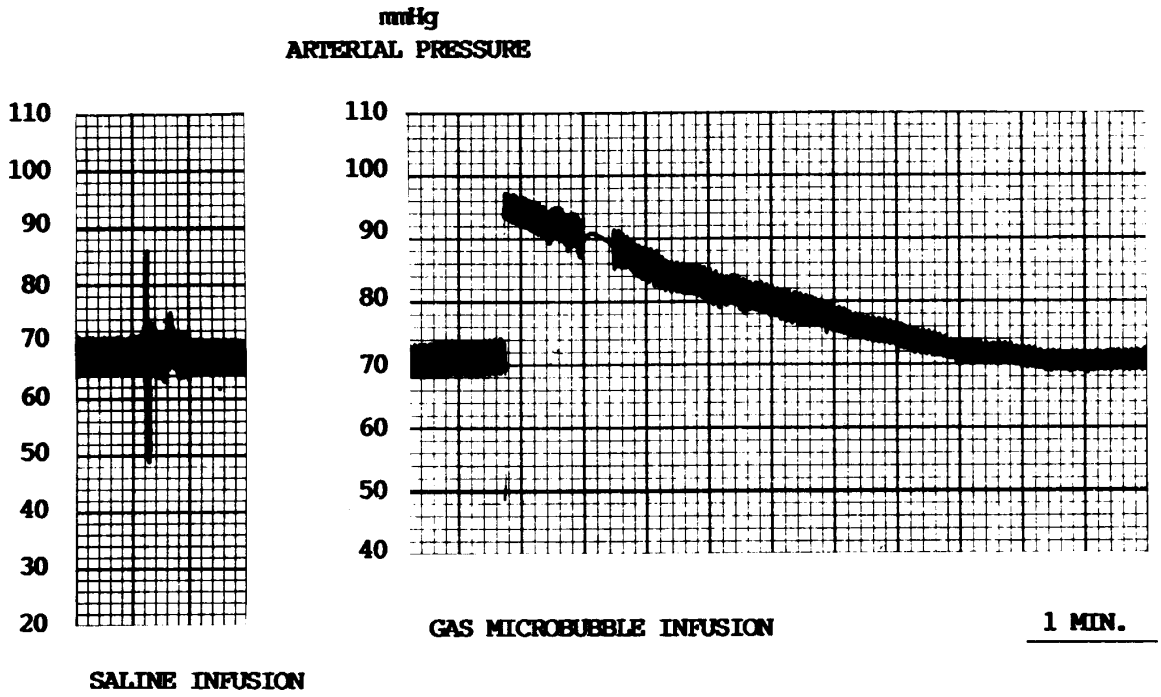

Figure 6. The effect of femoral artery gas microbubble infusion, and saline infusion on the arterial blood pressure of an anaesthetised rabbit.

TABLE 2

Increase in Mean Arterial Blood Pressure (mmHg)

	Air Emboli Head-up N=10	Air Emboli Head-down N=5	Oxygen Emboli Head-up N=5
Mean ± Standard Deviation	41.1 ± 16.0	14.0 ± 4.0	45.2 ± 13.4
Range	20 - 66	12 - 21	22 - 57

Blood pressure increases with infusion of gas microbubbles into the femoral artery of rabbits.

not return to the pre-infusion level, remaining stable at the increased level (Table 2).

The arterial hypertension that accompanied AGE was often associated with pial arterial and venous haemorrhage.

Prior to embolism, the resting MABP in upright rabbits breathing air (mean: 69.8 mmHg ± 9.1 (SD)), was the same as that recorded in upright rabbits breathing oxygen (mean: 73.6 mmHg ± 6.62 (SD)) ($t_{13} = 0.82$). However, prior to embolism, the resting MABP in inverted rabbits breathing air (mean: 84.2 mmHg ± 14.2 (SD)), was significantly greater than in upright rabbits also breathing air ($t_{13} = 2.41$, $p < 0.05$).

Pial Vessel Responses

Pial gas embolism caused an increase in pial arteriole diameter in all rabbits (mean increase: 42 % ± 28.13 (SD)). When the embolus progressed without interruption through to the venous circulation, the vessel immediately returned to its original size.

Observations on 16 of the 27 rabbits, demonstrated that the pial vasodilation that followed the infusion of gas into the femoral artery could occur without pial gas embolism (mean increase: 17 % ± 7.75 (SD)). The arteriole diameter increased concurrently with the increase in blood pressure in these 16 rabbits. Similarly, if pial gas embolism did not subsequently occur, the arteriole returned to its pre-infusion size with the fall in blood pressure.

This increase in arteriole diameter seen prior to embolism did not occur to the same extent in all the pial vessels of a given rabbit. Occasionally the arteriole wall was observed to pulse, with pulse cycle periods in a vessel segment of about 20 seconds.

Vasodilation was preceded by a transient, but measurable reduction in arteriole diameter in 7 of the 27 rabbits (mean decrease: 18.3 % + 14.5 (SD)). The reduction in arteriole diameter occurred prior to (3 animals), or without (4

animals) pial gas embolism, and was seen immediately after the infusion of gas into the femoral artery in these rabbits.

Groups One, Three, Four and Five

The gas infusion volumes necessary to cause pial circulatory arrest in rabbits in Groups One, Three, Four and Five are displayed in Table 3. A one way ANOVA ($F = 17.46$, $p < 0.005$) demonstrated that the volumes differed significantly between the groups. Further analyses with unpaired t-tests demonstrated that the gas volume necessary to cause pial circulatory arrest in Group Four (Oxygen ventilation/ Oxygen microbubbles) rabbits was significantly greater than in Group Three (Oxygen ventilation/Air microbubbles) rabbits ($t_4 = 3.96$, $p < 0.05$). In addition, the gas volume necessary to cause pial circulatory arrest in Group Three rabbits was significantly greater than in either Group One (Air ventilation/Air microbubbles) or Five (Oxygen ventilation/Air foam microbubbles) rabbits ($t_4 = 3.29$, $p < 0.05$; $t_4 = 2.88$, $p < 0.05$).

The mean volume of gas collected in the left jugular vein air-traps in upright rabbits (Group One and Two) was 24.7% $\pm$ 2.5 (SD) of the volume infused into the right femoral artery.

Group Two

Regardless of infusate volume, the infusion of air microbubbles into the femoral artery of inverted rabbits never caused pial gas embolism. Similarly, under these conditions gas was never collected in the left jugular vein air-traps. This was not due to mechanical problems with their infusion lines, because both pial gas emboli, and jugular venous gas emboli were produced in these rabbits when they were subsequently changed to an upright posture.

Discussion

Although the results of the experiments reported here deal with pial gas embolism in rabbits, the conclusions drawn can be extrapolated more generally to CAGE for two reasons. Firstly, the responses of rabbit pial arterioles to changes in blood pressure and PCO_2 are not affected by being exposed (54), nor are they abolished by a constant level of halothane anaesthesia at the MAC for this species (55,56). Secondly, in this species, pial vessel responses parallel those of intro-parenchymal vessels of similar size (54).

Respiratory and Circulatory Effects of AGE

The infusion of air, of air foamed in either detergent or a lung extract, or of microbubbles of oxygen into the femoral artery of rabbits caused respiratory depression. This varied from a brief apnoea to lethal respiratory arrest. Respiratory depression was never produced in inverted rabbits, supporting the association of respiratory depression with CAGE reported elsewhere.[3,12-14,18,31,43]

TABLE 3

	NUMBER OF RABBITS	EXPERIMENTAL CONDITION	MEAN VOLUME OF GAS TO EFFECT ARREST (ml)
GROUP ONE	5	Air/Air microbubbles	10.0 + 1.6
GROUP THREE	5	O_2/Air microbubbles	30.0 + 12.2
GROUP FOUR	5	O_2/O_2 microbubbles	60.0 + 19.0
GROUP FIVE	7	O_2/Air^2 microbubbles	9.0 + 1.6

Mean (+ Standard Deviation) volumes of gas infused into the femoral artery of rabbits to effect pial circulatory arrest under varied experimental conditions ($F = 17.46$, $p < 0.005$).

NOTE: Air foamed in 3% teepol or lung preparation.

The mean volume of gas collected in the left jugular vein air-traps in upright rabbits (Group One and Two) was 24.7% $\pm$ 2.5 (SD) of the volume infused into the right femoral artery.

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Gas microbubble infusion into the femoral artery was also associated with cardiac bradyarrhythmias and occasionally with cardiac arrest, but only if pial gas emboli were produced. The role of coronary artery embolism was not measured, but it is accepted by other authors that gas emboli can effect heart function by entering the brain stem circulation, the coronary circulation, the heart chambers, or can affect cardiac function indirectly by enhancing the release of catecholamines into the systemic circulation.3[,9,18,31,35,36,37-39,40,42]

The infusion of oxygen or air microbubbles into the femoral artery of upright rabbits caused the MABP to increase. This increase was significantly different from the increases seen either after the infusion of saline into upright rabbits, or the infusion of gas microbubbles into the femoral artery of inverted rabbits. Similar increases in MABP have been demonstrated by other researchers, with infusion of gas into either the carotid or vertebral arteries, or into the aorta or pulmonary veins.3,9,12-14,18,31,37-40 Embolism of the brain stem circulation appears necessary for the typical hypertensive response to gas emboli.3,12-14,18,24,58-62 This conclusion is based on the observation that this characteristic increase in MABP can be prevented by bypassing the brain stem by either

using a slow infusion carotid artery, or by isolation of the vertebrobasilar system. The transient nature of the hypertensive response to gas emboli demonstrated in this study has also been seen elsewhere.3,12-14,18,38,39,43

In inverted rabbits, embolism of the brain stem circulation can not explain the small, but often prolonged increase in MABP that followed gas microbubble infusion into the femoral artery. This increase in MABP was identical to that reported by another researcher who introduced gas into a pulmonary vein of inverted dogs.[3] It was also consistent with other studies where gas emboli were injected into peripheral arteries.[63,64] These increases in blood pressure may be a consequence of emboli becoming trapped and so physically causing an increase in peripheral vascular resistance.[3]

Pial gas embolism was often associated with pial arterial and venous haemorrhage. Haemorrhage concurrent with CAGE has already been reported.

The increase in MABP recorded after the infusion of oxygen microbubbles into the femoral artery of rabbits being ventilated with oxygen, was not significantly different from the increase seen after the infusion of air microbubbles into rabbits ventilated with air. It follows that blood pressure changes could not explain the greater volume of oxygen microbubbles needed to cause pial circulatory arrest.

The diameter of the affected arterioles increased after pial gas embolism. Similar diameter increases have been reported previously, and attributed to either local acidosis, or to endothelial damage causing local vasoparalysis. In this study, if the emboli did not become trapped, the vessel immediately returned to its pre-infusion size. This rapid reversal is not consistent with the time course of a vasoparalytic state resulting from either the local hydrogen ion concentration, or endothelial damage. More significantly, arteriole dilation was recorded after gas microbubble infusion when pial gas embolism was not observed, demonstrating that the blood vessel dilation was not entirely due to local, gas-induced, phenomena.

The concurrence of arteriole dilation and an increase in MABP after gas infusion demonstrated that AGE in this model was associated with a loss of cerebrovascular autoregulation. This was confirmed by the observation that if gas embolism did not occur, the arterioles returned to their pre-infusion size as the MABP returned to normal levels.

One significant observation in this study was that AGE, and not the nature of the anaesthesia or the surgical preparation of these rabbits, was responsible for the demonstrated loss of cerebrovascular autoregulation. Seven rabbits exhibited a reduction in arteriole diameter with the initial increase in blood pressure. That is, they demonstrated normal cerebrovascular autoregulation. Further increases in the blood pressure of these 7 rabbits caused the vessels to dilate, which suggests that the loss of autoregulation was a consequence of the blood pressure exceeding the upper limit at which this regulation of CBF can exist.[52,53]

Other researchers have shown that rabbit pial vessels exhibit cerebrovascular autoregulation, and that creation of an open-brain preparation does not inhibit these responses. For example, both normal cerebrovascular autoregulation to reductions in blood pressure, and cerebral vasoreactivity to changes in PCO_2, have been demonstrated in rabbit pial arterioles despite an open-brain preparation.[54] Normal cerebrovascular autoregulation to increases in blood pressure has also been demonstrated with open brain preparations; a 5 to 6% decrease in diameter of rabbit and cat pial arteries of about 120 μm diameter has been reported in response to blood pressure increases within the physiological range.[46] Importantly, in the NZ White Rabbit, it can be assumed that the behaviour of pial arterioles is similar to that of intra-parenchymal vessels of similar size.[54]

Research with other species also demonstrates that exposed pial vessels remain reactive to changes in carbon dioxide, vasoactive metabolite, and to cation and anion concentration.[66-68] Pial arterioles of 50 to 300 μm diameter contribute to overall cerebrovascular resistance, with 15 to 21% of the drop of total CPP occurring across these vessels.[69] Furthermore, cerebrovascular autoregulation is largely independent of changes in ICP, CSF pressure, and cerebral venous pressure.[47,70,71]

Although halothane has been shown to inhibit cerebrovascular autoregulation in some species,[72-74] it clearly did not in this study as the rabbits demonstrated a normal response to the initial increase in blood pressure. Other researchers have also shown that cerebral vessel reactivity, and its modulation by changes in systemic blood pressure, persists in NZ White Rabbits despite halothane anaesthesia.[55,56] As in this study, these researchers maintained anaesthesia with a constant halothane vapour pressure, equivalent to the MAC for this species.[56]

A review of the available literature also supports the argument that AGE itself can disrupt cerebrovascular autoregulation. The most important finding is that cerebrovascular autoregulation is lost in animal models of AGE not involving either halothane anaesthesia or a craniotomy, where CBF rather than vessel diameter has been measured

The mechanics of normal cerebrovascular autoregulation remains controversial.[51-53] The mechanism by which AGE disrupts autoregulation was not addressed by this study. However, the simplistic explanation that the disruption was the consequence of exceeding the upper limit of blood pressure at which autoregulation can exist, has attraction.[52,53] Because the loss of autoregulation often occurred in the absence of pial gas emboli, it can be concluded that it was not entirely due to gas-induced endothelial damage, or to local acidosis as a consequence of circulatory arrest. The disruption of the normal autoregulation of CBF will influence the outcome of patients with CAGE because both CPP and CBF will passively follow MABP, such that rises and fails in MABP will respectively promote and

inhibit embolus passage to the venous circulation.

Arterial Gas Embolus Distribution

Gas microbubbles infused into the femoral artery of upright rabbits distributed against aortic flow to embolise the pial circulation. Conversely, pial gas emboli were never observed in inverted rabbits. These observations are consistent with other reports on the relationship of posture to the distribution of arterial gas emboli,[1-3] and with the frequent neurological involvement in divers and submariners with AGE.[4-8,32,40] This study also supports the use of an inverted posture in the treatment of AGE, to restrict embolism of the cerebral circulations.[65,75,76] It is even possible that posture may influence the redistribution of gas emboli that have already entered the brain vessels.[65,77,78]

Although the gas was infused into the femoral artery as microbubbles, only coalesced columns of gas were observed in the pial vessels. Such coalescence is predictable gas behaviour,[14,36,76] and was not prevented by foaming the gas in either a detergent or a homogenised lung preparation. Only cylindrical gas emboli became trapped in the pial vessels. This is consistent with previous reports, and supports the argument that the cylinder, and not the sphere, is the appropriate gas model for CAGE

The passage of a gas embolus through the pial circulation of this animal model was determined by the MABP, the volume, and the length of the embolus, and the diameter of the vessels. The redistribution of emboli from pial arterioles to the venous circulation only occurred while the MABP remained elevated above pre-infusion levels. Movement of emboli after this time only occurred if a step increase in arterial pressure was created by forceful infusion of saline into the femoral artery. On this evidence induced hypertension could become an important component of the treatment of patients with CAGE.[80] However, any therapeutically induced hypertension needs to be controlled to avoid either increasing the permeability of the BBB, or further disturbing cerebrovascular autoregulation.[52,81,82]

While an increase in arterial pressure induced shortly after the pial circulation was arrested by gas emboli was highly effective, the universal failure of similar increases induced more than 15 minutes after embolus arrest suggests that therapeutic gas embolus redistribution is only possible for a short time after embolism; before arteriolar collapse. The time scale of arteriolar collapse found in this animal model may not be the same in humans. Nevertheless, this phenomenon may explain the difference in morbidity with CAGE between those patients compressed in a RCC immediately after the onset of symptoms and signs[4,6-8,40,83] and those with a delay prior to compression[4,6-8,32,34,40,83,84]

Large emboli (> 5000 μm length; > 20 μm volume) usually became trapped in a pial arteriole, and caused local circulatory arrest. Conversely, small emboli (< 500 μm length; < 8 μm volume) usually did not become trapped; emboli passed through without interruption, to the pial veins. Many intermediate- sized emboli (500-5000 μm length; 8-20 μm volume) were temporarily trapped. Most of these emboli (> 75%) eventually passed through to the venous circulation during the period of hypertension that followed embolism.

Less than 20 % of all the observed emboli lodged permanently in pial arterioles and blocked blood flow. This usually occurred in vessels less than 100 μm in diameter. The measured mean survival time of rabbits in whom emboli were large enough to cause pial circulatory arrest was only 26 minutes. This mortality contrasts with the observation that most humans with CAGE do not die, but rather experience some degree of improvement prior to any treatment.[32,33] When coupled with the finding that more than 80% of the emboli that were seen to enter the pial arteries in our study eventually redistributed to the venous circulation, it is clear that the conventional pathophysiological model of AGE, one depending on the blockage of arterioles by gas, is not supported by these data.

The frequent redistribution of gas emboli from pial arterioles to the venous circulation without any therapeutic manoeuvre can explain why most human patients with CAGE experience some degree of spontaneous recovery[32,33] However, even in those with complete recovery, many will subsequently relapse.[32] Our results suggest one mechanism to account for some of these relapses.

The patient's initial improvement is probably due to spontaneous redistribution of gas emboli from cerebral arteries to the venous circulation. However, in some patients, intermediate-sized emboli will remain in vessels less than 75 μm in diameter. Recovery of brain function will still be possible, because of the collateral pathways that exist at this level of the brain circulation.[85] The passage of gas emboli through the larger vessels will have disrupted the BBB[15,20,26-30,32,83] and stimulated the local accumulation of platelets.[24] As platelet thrombi form there will be a progressive fall in CBF.[21-25] The resulting reduction in flow through the collateral pathways will eventually cause a loss of function in the areas of brain tissue supplied by the embolised vessels, and the patient will relapse with similar symptoms to their original presentation. The small number of patients with CAGE that have fulminant, and occasionally lethal disease,[4,7,40,83] are well explained by the observed behaviour of large emboli.

It has already been argued[19] that the course of one group of patients with CAGE can only be adequately explained by re-embolism. In contrast, the mechanism of relapse detailed above is proposed only for those patients that relapse with similar symptoms and signs to their initial presentation .[8,86]

There is a simple explanation for the relationship between the size (length in a given vessel) of an embolus and its eventual distribution. This can be derived from the La Place Equation, and is based on the difference in arteriole diameter, and hence surface tension pressure, at the extremes of the embolus. As the embolus length increases, the difference in diameter, and hence the nett surface tension

pressure opposing embolus movement also increases.

A simplified schematic is presented in Figure 7. In this schematic, Øp and Ød are measured contact angles, and rp and rd are the proximal and distal embolus radii respectively. The driving force will be the nett CPP (Δ CPP), and will be opposed by the nett surface tension pressure. The La Place equation, Equation 1, defines the condition for movement of an embolus:

$$\Delta CPP > \frac{2\gamma \cos Ød}{rd} - \frac{2\gamma \cos Øp}{rp} \quad \text{(Equation 1)}$$

where: y is the plasma surface tension.

Figure 7 is a simplified schematic, and Equation 1 does not account for the irregular arteriole dilation associated with gas embolism. Similarly, it ignores the pulsatile nature of the proximal interface of the gas embolus. Nevertheless, the principle established above remains valid.

did not allow for spontaneous embolus redistribution, and so have probably overestimated the success of the regimens tested.

Some rabbits not only demonstrated spontaneous redistribution of gas emboli from the pial arterioles, but also spontaneous re-embolism. The subsequent emboli entered the pial circulation without further infusion of gas, and without manipulation of the rabbit. It follows that re-embolism of the brain circulation can occur whenever gas emboli exist in the arterial circulation, and does not require continued embolus production. This phenomenon can explain the progress of those patients with CAGE who, after an initial improvement, relapse with a different set of focal symptoms and signs.[4,86]

More oxygen microbubbles had to be infused into rabbits ventilated with oxygen to cause pial circulatory arrest, than either the volume of oxygen microbubbles used in rabbits ventilated with air, or the volume of air microbubbles

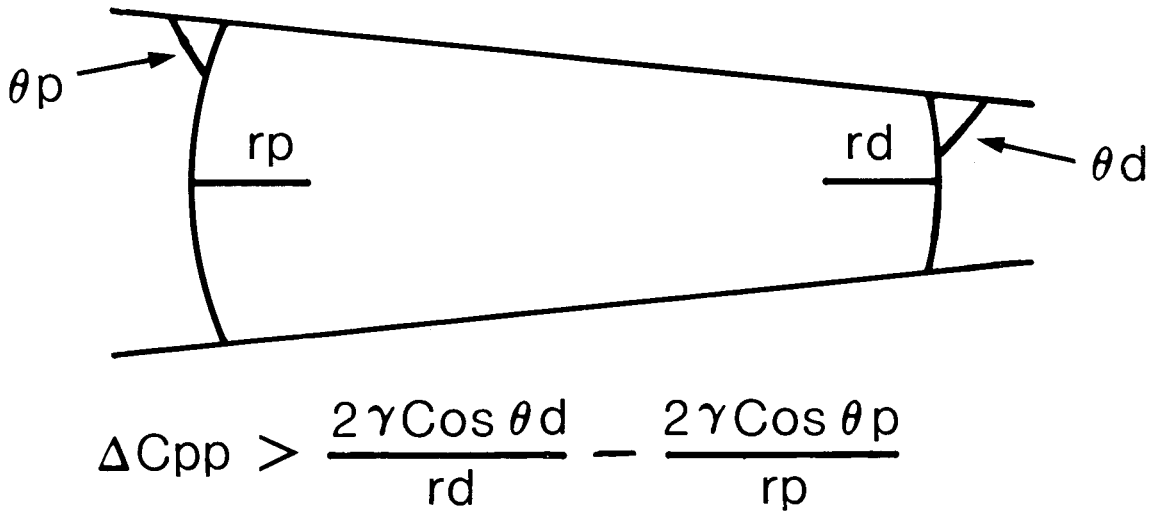

Figure 7. Simplified schematic of pial arterial gas embolism demonstrating a state of embolus progression.

The large volumes of gas collected in the jugular vein air-traps in this study, were similar to those reported by another group of researchers who also used jugular vein air traps.[3] Clearly, redistribution of gas emboli from pial arteries, and presumably other cerebral arteries, to the venous circulation can occur without compression of subjects in a RCC. Other authors have also reported the spontaneous redistribution of gas emboli from cerebral arteries to veins and to the right ventricle and pulmonary arteries.[12,31] Significantly, the earlier this redistribution occurs, the quicker animals with experimental CAGE improve.

The spontaneous redistribution of gas emboli seen in this study, and the similar observations in other animal models of CAGE, not only casts doubt on the conventional model of CAGE, but also on the validity of findings in several animal model studies of CAGE treatment.[13,14,16] These studies demonstrated clearance of gas emboli from pial arterioles during compression to 6 Bars. However, they

used in rabbits ventilated with air to achieve the same result. This difference can not be explained on the basis of desaturation, but does support previous studies of oxygen gas embolism.[12,18] It also supports the suggestion that oxygen be breathed by submariners during an escape from a stricken submarine, where the pressure exposure would be brief, and overt central nervous system oxygen toxicity unlikely.[87,88]

Multiple infusions of gas into the femoral artery, and large volumes of gas in comparison to those used in previous studies,[13,14,16,18,21-29,31,33,37-39, 58,60-62] were necessary to cause circulatory arrest in a pial arteriole in this study. The reasons for the relatively large gas volumes include how the end-point of circulatory arrest was chosen, and the site of gas infusion.

Since previous animal model studies of CAGE in which the pial circulation was observed have not allowed for any spontaneous redistribution of emboli,[13,14,16] a condition of

pial circulatory arrest may not have been created. It is also possible that the subsequent embolus redistribution seen by these researchers may have occurred regardless of the treatment they administered to their animals.

Most animal model studies of CAGE have used carotid artery gas infusions.[13,14,16,18,21-29,31,33,58,60-62] Emboli from such infusions can bypass the brain stem circulation, and so avoid triggering an increase in blood pressure.3,12-14,18,24,58-62 It is clear from this study, that the transient, but significant increases in blood pressure that accompany AGE are critical determinants of the passage of an embolus through the cerebral vessels. Carotid artery cannulation itself may alter cerebral perfusion, and so distort the balance of forces that determine embolus distribution.

Other approaches to the study of CAGE have involved either the measurement of neurophysiological parameters, or studies of subsequent cerebral histopathology.[18,58,60-62,89] Despite using gas volumes which were much smaller than those necessary to cause pial circulatory arrest in this study, these authors have reported significant brain pathology. It follows that such pathology can be associated with CAGE even though cerebral circulatory arrest, due to gas emboli, has not occurred. The likely explanation is the decrease in CBF that occurs after CAGE.[21-25] Once stimulated, the processes that account for this fall in CBF would not require the continued presence of a gas embolus, and would eventually cause the CBF to become inadequate for normal neuron function.[21-25]

Summary and Conclusions

It follows from these data and arguments that an alternative pathophysiological model of CAGE should be used. This model must be able to account for a small number of very large emboli becoming trapped in cerebral arterioles and blocking blood flow. This is the rare situation of fulminant, and sometimes lethal CAGE. The model must also attribute much of the brain pathology that results from CAGE to the effects of a transient gas-endothelial interaction (accumulation of platelets, formation of platelet thrombi, disruption of the BBB) rather than to the direct mechanical effects of gas emboli themselves. Finally, the alternative pathophysiological model must be able to explain both the improvement seen in most patients prior to any treatment, and any subsequent relapse.

The aims of treating patients with CAGE must remain the removal of gas emboli from cerebral arterioles, and the restoration of CBF. Although a study of the former is only applicable to the small number of emboli large enough to become entrapped, such emboli probably underlie fulminant disease, and contribute significantly to subsequent relapses in brain function in those patients that survive the initial episode. Because available data on this subject are very limited, and will have overestimated treatment efficacy, it is clear that such a study is needed.

The data presented here also demonstrate that any study of therapeutic embolus redistribution must be able to measure spontaneous embolus passage to the venous circulation. Furthermore, it is essential that all treatment trials begin from a point of established cerebral circulatory arrest.

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KEY WORDS

Arterial Gas Embolism, Cerebral Arterial Gas Embolism, Gas Embolism

Figure 2 appears, in colour, on page 116.

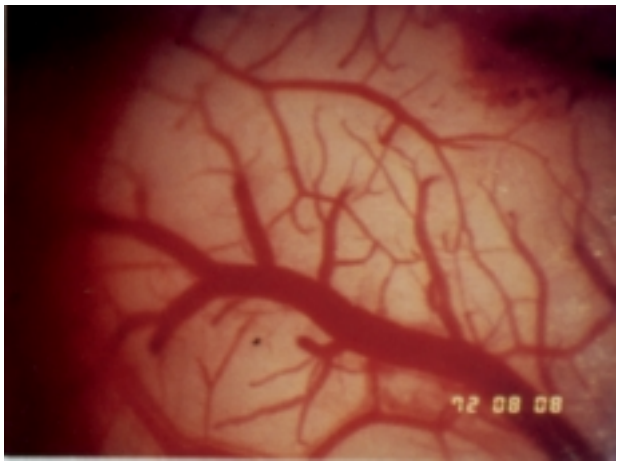

Figure 2A Photomicrograph (x500) of rabbit brain surface before arterial gas embolism.

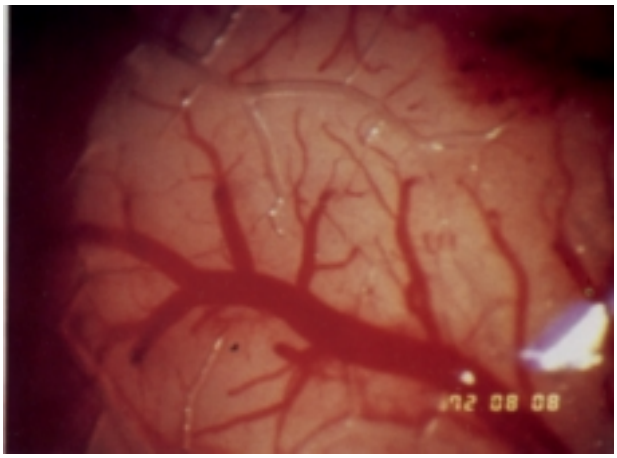

Figure 2B Photomicrograph (x500) of rabbit brain surface after arterial gas embolism.

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SCOMBROID POISONING

John Knight

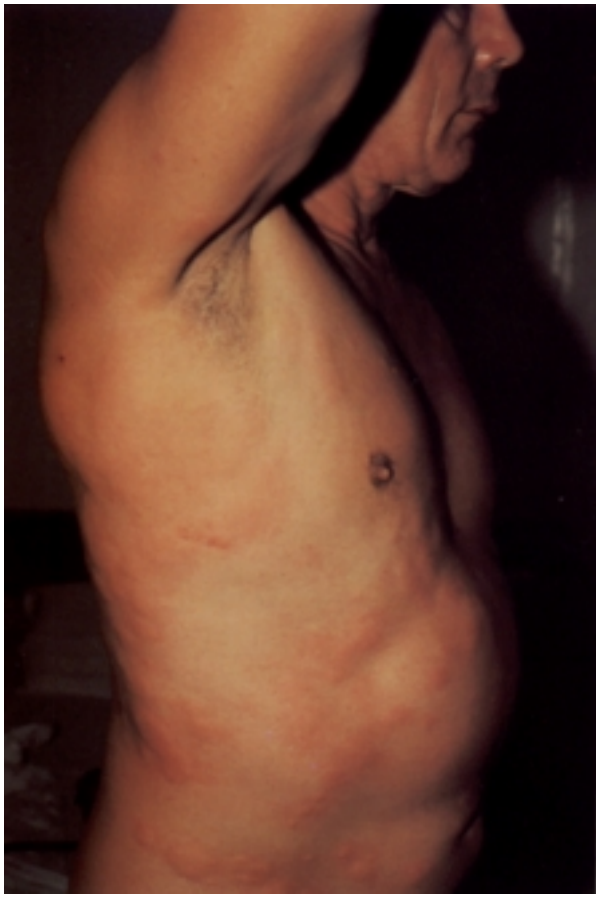

Figure 1. Side view of the author at 0100 on 25 April 1985.

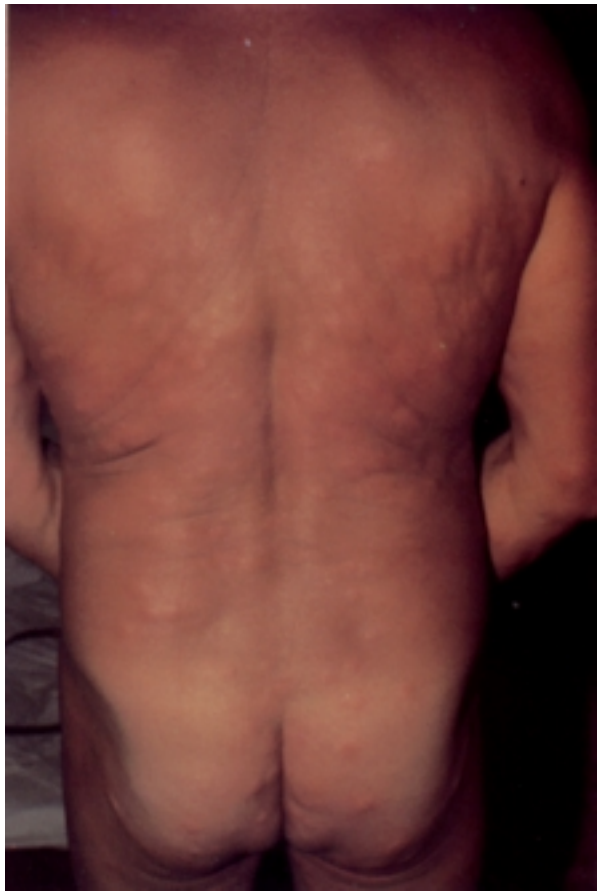

Figure 2. Back view of the author at 0100 on 27 April 1985.