

# The Pathophysiology of Cerebral Arterial Gas Embolism

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**Abstract:** Bubbles are introduced to the arterial circulation in many patients undergoing cardiac surgical procedures, and some of these distribute to the cerebral vessels. Larger bubbles may arrest in cerebral arterioles, causing ischemia and neuronal injury in the downstream territory. Smaller bubbles may redistribute through the cerebral circulation, but this is not a benign event. Their passage may cause transient ischemia and cause damage to endothelium. Margination and activation of leukocytes follows, and may cause a secondary ischemia. Although the potential of large bubbles to cause cerebral injury is not disputed, there is controversy over the significance of exposure to

small bubbles in cardiac surgery. It is known that postsurgical neuropsychological deficits do correlate positively with numbers of emboli to which patients are exposed, but to date, the technology to distinguish between gaseous and particulate emboli or to size emboli accurately is not readily available. Until this technology becomes available and is applied in large studies designed to determine the importance of small bubbles, it seems prudent to take all practical steps to prevent introduction of arterial bubbles in cardiac surgery. **Keywords:** gas embolism, cardiac surgery, cardiopulmonary bypass. *JECT. 2002; 34:18–23*

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Cerebral arterial gas embolism (CAGE) may follow many accidental or iatrogenic events (1). There is a particularly high risk of CAGE during cardiac surgery. Many potential mechanisms for introduction of gas to the arterial circulation during cardiac surgical procedures have been identified. These include: the ejection of residual air from the heart chambers or pulmonary veins after aortic declamping (2); aortic cannulation (3); bubble generation by cardiopulmonary bypass (CPB) venous reservoirs (4); entrainment of air into the CPB venous line (5); and a variety of perfusion accidents. Most patients undergoing cardiac surgery are exposed to bubbles from one or more of these sources (6). Although there is evidence that exposure to “emboli” (whose composition is usually not determined) causes neuropsychological (NP) deficits (7), many patients with Doppler proved emboli exposure exhibit no obvious adverse consequences (8). This has led to the perception that cerebral embolism by bubbles, particularly small bubbles, may be a relatively benign event (9).

This brief review discusses the factors that influence the distribution of arterial bubbles to the brain, the patho-

physiological consequences of CAGE, and the argument that CAGE by small bubbles may be relatively harmless.

## DISTRIBUTION OF BUBBLES TO THE CEREBRAL CIRCULATION

When a bubble is introduced to the arterial circulation, both blood flow and its buoyancy influence its distribution. Because the brain receives 20% of the arterial blood flow at rest, it could be expected that 20% of neutrally buoyant particles would distribute to the brain. However, distribution of bubbles is also influenced by their buoyancy; minimally so in the horizontal patient, but to a greater degree if there is any deviation from the horizontal posture. In an upright patient, the buoyancy of bubbles will favor distribution to the cerebral circulation; whereas, a patient in the head down position may suffer less CAGE. These concepts were validated in vivo by van Allen et al. (10), who introduced air to the pulmonary artery of dogs and demonstrated reduced CAGE in those placed in a head-down position. However, a strong argument has also been made for a predominance of flow effects over buoyancy (11). In fact, the influence of buoyancy is likely related to bubble size. Smaller bubbles displace less fluid and are, therefore, less buoyant. Very small bubbles can, therefore, be expected to behave more like

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neutrally buoyant particles whose distribution is determined largely by blood flow. It follows that head-down positioning to prevent CAGE may reduce exposure to large (buoyant) bubbles, but may have little influence on cephalad distribution of small bubbles. In addition, the head-down position increases intracranial pressure and if prolonged, may precipitate or exacerbate cerebral edema (12).

## BEHAVIOR OF BUBBLES IN BLOOD

Gas introduced into blood forms a spherical bubble (13) unless it enters a blood vessel of lesser diameter, in which case the bubble forms a cylinder (14). Bubbles may coalesce to form larger bubbles if trapped in immediate proximity to one another (15). Alternatively, larger bubbles may break up in areas of turbulent blood movement, such as the heart chambers.

From the moment a bubble is introduced into blood, there is a natural tendency for its component gases to dissolve into solution, provided there is not a relative tissue and blood gas "supersaturation" such as exists after decompression from a compressed gas dive. Many factors influence the rate of dissolution; in particular, the nature of the component gas. For example, a bubble containing nitrogen dissipates much more slowly than bubbles composed of the metabolic gases oxygen or carbon dioxide (16). In addition, the "survival" time for an arterial bubble is highly dependent on its initial size. Dexter and Hindman (16) mathematically modeled survival times for 50 and 200  $\mu\text{m}$  arterial air bubbles during 50:50 oxygen:nitrogen breathing at normothermia. Survival times were 2.3 and 32 minutes, respectively, although it was notable that both times could be more than halved by changing the breathing gas from 50 to 100% oxygen. Conversely, the model predicted that administration of a rapidly diffusing gas such as nitrous oxide would result in rapid growth of any bubbles principally composed of nitrogen. Thus, depending on bubble size, bubble gas composition, and the nature of the breathing gas, bubbles may have a lifespan in blood that varies from seconds to many minutes.

Bubbles are known to interact with formed elements of blood and plasma proteins. Platelets have been observed to adhere to the surface of bubbles (17). Both leukocytes (18) and the complement system (19) are activated in the presence of bubbles, and the blood-bubble interface has been shown to precipitate denaturation of lipoproteins (20). These hematological events have received considerable attention from those whose primary interest is the study of decompression sickness in divers, a condition in which bubble formation occurs primarily in the veins. However, a bubble introduced to the arterial circulation may have an impact in the cerebral circulation within seconds, giving little time for these processes to become es-

tablished. Other injurious mechanisms (see below) are likely to predominate, and specific interactions with blood are of uncertain early relevance.

## TRAPPING OR REDISTRIBUTION?

A bubble entering the cerebral circulation may either trap or redistribute to the veins. The processes that promote trapping or redistribution have been extensively investigated by Gorman and his colleagues (14,21–23). Redistribution is encouraged by the cerebral perfusion pressure, which promotes the bubble forward. Redistribution of a bubble that forms into a cylinder is also promoted by surface tension forces at the trailing end. Trapping is promoted by surface tension forces at the leading end of the bubble. Surface tension forces are inversely proportional to the radius of the hemispherical ends of the bubble. Thus, if both ends of the bubble exist in vessel segments of equal diameter, surface tension forces effectively cancel each other out. However, if a bubble is large enough to occupy several generations of branching arterioles, its leading end may exist in vessels of considerably smaller diameter than the trailing end. Under these circumstances, surface tension forces opposing forward movement at the leading end may exceed both mean arterial blood pressure and surface tension forces at the trailing end, causing the bubble to trap. In contrast, if a bubble is small enough to enter the capillary bed, the greater mean diameter at the venous end will promote redistribution.

These observations suggest that the size of bubbles entering the cerebral circulation is an important determinant of trapping or redistribution, and this is supported by experimental observations. Feinstein et al. (13) showed that small bubbles (<15 microns) pass through the microvasculature with little or no immediate interruption of flow; whereas, bubbles 15 microns and greater interrupt flow in capillaries for short periods. Gorman and Browning (14) reported that bubbles larger than 200 microns often trap in arterioles for variable periods. Trapping is most likely in small arterioles (20–50 microns) (24), and the boundary between gray and white matter is particularly rich in vessels of this size (25). Not surprisingly, this region seems particularly susceptible to ischemia during experimental gas embolism (26).

Most bubbles that initially trap do eventually redistribute, because they continue to shrink despite interruption of blood flow (16). This continued shrinkage, coupled with the reflex cerebral vasodilation (27) and systemic hypertension (28) that may follow CAGE, promotes their redistribution.

## CONSEQUENCES OF BUBBLE TRAPPING

Trapping of large bubbles may cause sudden and critical ischemia in the downstream territory. At a cellular level,

the critical early event in neuronal ischemia is energy failure at the cell membrane and consequent dissipative ion fluxes. If ischemia is prolonged, this may result in depolarization of the cell membrane (29). There follows a sequence of events that initially includes: release of "excitotoxin" neurotransmitters such as glutamate; influx of calcium through excitotoxin and voltage gated ion channels; release of calcium from intracellular calcisomes, endoplasmic reticulum, and mitochondria; and activation of intracellular second messenger systems by excitotoxin operated "metabotropic" receptors. Through a variety of complicated and interconnected pathways, these events initiate processes that progress the cell toward necrosis or apoptosis (30). However, up to some undefined point that is perhaps linked to a threshold intracellular calcium level (31) the processes do seem reversible if ischemia is not severe and/or prolonged. This is of considerable significance in CAGE, because obstructing bubbles do eventually redistribute, and flow is consequently restored. If this occurs within a critical period, irreversible neuronal damage may be avoided.

In the clinical setting CAGE may manifest as sudden death (32), and *in vivo* experiments suggest this may be secondary to cardiac arrhythmia following embolism of the brainstem (33). More commonly, there is rapid onset of unconsciousness and/or focal neurological symptoms (34). The early loss of neuroelectrical function underpinning such symptoms has been demonstrated *in vivo* (27,28,35,36). Ischemia associated with CAGE may be of such magnitude and duration that no functional recovery is seen, even after bubbles redistribute (27). Indeed, CAGE can cause radiological evidence of cerebral infarctions (37), although these are often small and multifocal in contrast to those produced by thromboembolic events. Despite these potentially serious manifestations, spontaneous functional recovery is frequently seen after CAGE both clinically (34) and *in vivo* (27,35,36), and this is thought to follow redistribution of bubbles and restoration of flow before irreversible damage occurs (24).

### CONSEQUENCES OF BUBBLE REDISTRIBUTION

The redistribution of bubbles ameliorates ischemia, but secondary damage to the cerebral endothelium may accompany the passage of bubbles, even those too small to trap and significantly interrupt flow. Bubbles have been shown to be capable of stripping endothelium from its basement membrane (38) and disrupting the oligomellar luminal surfactant lining that is considered to contribute to the integrity of the blood-brain barrier (39).

This direct physical damage seems to precipitate several secondary processes. First, the competence of the blood-brain barrier is compromised by bubbles (40,41), even at sizes of 10–20 microns (39), although this finding is not

invariable (42). The resultant perivascular edema may increase resistance to flow through microvessels (24). Second, bubble damage to endothelium seems to incite injurious responses from leukocytes. Using rabbits, Helps et al. (43) showed that both cerebral blood flow (CBF) and neuroelectrical function progressively declined after CAGE (25 $\mu$ L air), despite the fact that this volume was insufficient to cause any initial bubble trapping. In a subsequent study, Helps and Gorman (44) showed that these changes did not occur in rabbits that had been rendered leukopenic by pretreatment with mechlorethamine, implying that leukocyte accumulation at sites of endothelial damage was responsible. Similar findings in a canine model of CAGE were reported by Dutka et al. (45). In addition to causing these rheological changes, marginated leukocytes may release cytotoxic proteases and oxygen-derived free radicals known to cause cellular damage in surrounding tissues (46). Such other formed elements as platelets may also be involved in the response to endothelial damage (47). These events may explain the frequent clinical observation of relapse in divers who suffer CAGE, recover spontaneously, but subsequently deteriorate (48).

In addition to the rheological and inflammatory changes described above, there may also be perturbation of physiological function after endothelial damage by bubbles. Disturbance of cerebral autoregulation has been reported following CAGE (21,23,27,49–51), and this is not surprising, because endothelium is considered to be both the transducer and effector of autoregulation. Dysfunctional autoregulation could be particularly dangerous if a period of relative hypotension was to supervene after the hypertensive spike that often follows CAGE.

In summary, two distinct mechanisms for injury by CAGE have been identified by *in vivo* experiments. Both may have ischemia as a final common pathway. First, bubbles reduce blood flow when they lodge in or transit the cerebral vasculature. The magnitude and duration of the consequent ischemia determines the likelihood of functional damage and is related to the volume of embolizing gas (27). Second, although relatively small bubbles redistribute quickly (13,43), with immediate restoration of CBF and function (43), their passage can incite a secondary inflammatory process that may progressively reduce CBF, impair function (44,45), and perhaps cause neurons to die.

### PATHOPHYSIOLOGICAL SIGNIFICANCE OF CAGE IN CARDIAC SURGERY

It is well understood and beyond debate that "massive" perioperative gas embolism of the cerebral circulation may result in death or stroke. There are case reports describing CAGE after perfusion and surgical accidents leaving the patients with permanent brain injury. Some

cases have been successfully treated with compression and hyperbaric oxygen. It is less clear whether the smaller bubbles to which most patients are exposed during cardiac surgery are of significance (9).

It is widely accepted that the neuropsychological (NP) deficits that are frequently detected following cardiac surgery are most likely to result from a diffuse microembolic injury (3). Indeed, there are now many studies that have linked perioperative embolism to adverse neurocognitive outcome (51–57). In addition, a relationship between emboli exposure, decline in CBF velocity, and the appearance of cerebral complications has been reported (58). Many, if not most of these emboli are likely to be bubbles. However, none of these studies distinguished gaseous from particulate emboli, and skeptics might argue that it was the particulate component of the embolic load that was responsible for any neurological injury. Advocates of a pathogenic role for bubbles might counter that the in vivo experiments cited earlier do make a convincing case for the pathogenicity of even small volumes of arterial air. However, extrapolation of the in vivo data to clinical cardiac surgery must be made cautiously. For example, as discussed previously, the size of arterial bubbles influences their potential to cause cerebral injury; however, most of the in vivo studies introduced known “volumes” of air rather than bubbles of known diameter. As illustrated by Tovar et al. (59) 500  $\mu\text{L}$  of air may generate anything from one bubble of 1-cm diameter to 1,000,000 bubbles of 100  $\mu\text{M}$  diameter. Thus, there is uncertainty over the size of bubbles that have produced pathogenic effects in vivo, and given the even greater uncertainty over the size of bubbles or volumes of gas entrained to the arterial circulation during clinical cardiac surgery, interpolations between the in vivo and clinical cardiac surgery are somewhat tenuous.

Some researchers have tried to circumvent this problem by studying the consequences of exposing animals to bubbles generated by known cardiac surgical sources. Brennan et al. (60) demonstrated a fall in CBF by 25% from baseline over a 3-hour period, beginning with an hour on unfiltered CPB using a bubble oxygenator. This fall was abolished in filtered CPB, and Doppler counting confirmed the efficacy of the filter in reducing bubble exposure. Patterson et al. (61) subjected dogs to 2 hours of CPB using a bubble oxygenator operated in such a way as to produce numerous microbubbles. Groups of dogs were sacrificed after progressively longer periods of recovery. Just before sacrifice, lamblack was injected to delineate the cerebral microvasculature. More than 50% of the vascular bed was abnormal in dogs sacrificed at day 1, with the incidence of filling defects steadily declining thereafter. The authors questioned the mechanism of this recovery without drawing conclusions, but the resolution of a bubble-induced inflammatory state (44,45) would be a plausible explanation. One study failed to find any reduc-

tion in global or regional brain perfusion in dogs during or after CPB with exposure to bubbles generated by a bubble oxygenator (62). However, the protocol specified maintenance of a relatively high mean arterial blood pressure of 78 mmHg throughout CPB. This would have promoted rapid redistribution of any small bubbles impacting in the cerebral circulation. In addition, the bubbles generated from the oxygenator were probably of a uniform (perhaps very small) size, and composed of either 100 or 50% oxygen. They cannot be considered entirely representative of the range of bubble sizes and gas compositions that might be encountered in clinical surgery.

Regardless of any such methodological issues and any conflict in the data, such in vivo studies are unlikely to resolve questions about the significance of arterial gas embolism in humans, because the outcome measures used cannot be equated with clinical cognitive function impairment.

## CONCLUSIONS

Both particulate emboli and large bubbles may cause perioperative stroke. The data suggesting that cerebral microembolism is responsible for subtle postoperative brain injury does not distinguish the relative contribution of bubbles and particulates. The debate over the effects of microemboli on the cerebral circulation in cardiac surgery is current and continues (63,64). However, this debate, and particularly the uncertainty over the true pathogenicity of small bubbles, will persist until such time that Doppler technology allows both accurate sizing of bubbles and reliable distinction between bubbles and particulate emboli in the clinical setting.

There is a significant body of in vivo data that demonstrate cerebral damage by small volumes of arterial gas. The direct relevance of these data to clinical cardiac surgery is not established. However, rejection of the hypothesis that small bubbles may inflict perioperative brain injury cannot be supported by currently available data. Indeed, any such rejection would seem highly imprudent, especially because many sources of arterial bubbles are easily resolved at little or no cost. It is recommended that all practical steps be taken to minimize perioperative exposure to arterial bubbles of all sizes.

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