

# Perspective on Cerebral Microemboli in Cardiac Surgery: Significant Problem or Much Ado About Nothing?

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**Abstract:** From the time an association was perceived between cardiac surgery and post-operative cognitive dysfunction (POCD), there has been interest in arterial microemboli as one explanation. A succession of studies in the mid-1990s reported a correlation between microemboli exposure and POCD and there followed a focus on microemboli reduction (along with other strategies) in pursuit of peri-operative neuroprotection. There is some evidence that the initiatives developed during this period were successful in reducing neurologic morbidity in cardiac surgery. More recently, however, there is increasing awareness of similar rates of POCD following on and off pump cardiac operations, and following many other types of surgery in elderly patients. This has led some to suggest that cardiopulmonary bypass (CPB) and microemboli exposure by implication are non-contributory. Although the risk

factors for POCD may be more patient-centered and multifactorial than previously appreciated, it would be unwise to assume that CPB and exposure to microemboli are unimportant. Improvements in CPB safety (including emboli reduction) achieved over the last 20 years may be partly responsible for difficulty demonstrating higher rates of POCD after cardiac surgery involving CPB in contemporary comparisons with other operations. Moreover, microemboli (including bubbles) have been proven harmful in experimental and clinical situations uncontaminated by other confounding factors. It remains important to continue to minimize patient exposure to microemboli as far as is practicable. **Keywords:** cardiopulmonary bypass, CPB, embolism, cerebral complications, cerebral protection, gaseous microemboli. *JECT. 2015;47:10–15*

The issue of cerebral exposure to emboli during cardiac surgery has been of great interest to the perfusion community over many decades. It is appropriate on the 10th anniversary of the Perfusion Down Under meeting to review this problem and to ask whether it should still be regarded as a matter warranting concern.

Few would argue with the notion that arterial macroemboli of solid composition (such as atheroma fragments) are potential causes of significant ischemic brain injury. Indeed, there is compelling evidence of an association between mobile atheromatous plaque and post-operative stroke (1,2). In contrast, the significance of microembolism is less certain. Even in the modern setting it is possible to detect many “microemboli” of variable composition (but

most are probably bubbles) in the arterial circulation during and after cardiopulmonary bypass (CPB) (3,4). There has been much debate around the role of these emboli in causation of post-operative cognitive dysfunction (POCD). Our aim in this article is to appraise that debate.

## HISTORICAL PERSPECTIVE

During the early-mid 1990s the Green Lane perfusion group (Green Lane Hospital, Auckland, New Zealand) developed a research interest in exposure of cardiac surgery patients to emboli in the cerebral circulation. At that time much attention was being given to neurological outcomes and, based on a series of studies published over the previous decade (Table 1), there was a widespread perception that cardiac surgery was associated with a greater risk of POCD and peri-operative stroke than other types of operation (5–12). In fact, Table 1 suggests that even in that era there was evidence that any particular disadvantage of cardiac surgery in causation of POCD was largely limited to the immediate post-operative period. Differences between cardiac and other forms of surgery had usually resolved by

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**Table 1.** Studies from the early period of high interest in neurocognitive outcomes after cardiac surgery where outcomes for cardiac patients were compared with those for patients undergoing other types of surgery.

Study	Comparator Group	Outcomes	Follow-up	Cardiac Worse?
Aberg and Kihlgren (5)	Thoracic	Cognitive	1 w, 2 m	Yes, yes
Smith et al. (6)	Thoracic and vascular	New signs	1 d, 1 w, 2 m	Yes, no, no
		Cognitive	1 w, 2 m	No, no
Smith (7)	Thoracic and vascular	Cognitive	1 w, 2 m	Yes, no
Shaw et al. (8)	Vascular	Stroke	Any time	Yes
		New signs	1 w	Yes
		Cognitive	1 w	Yes
Williams-Russo et al. (9)	TKJR	Cognitive	1 w, 6 m	Yes, no
Heyer et al. (10)	Misc. non-cardiac	Cognitive	1 w, 6 m	Yes, no
Murkin et al. (11)	Thoracic and vascular	Cognitive	1 w, 2 m	Yes, no
Vingerhoets et al. (12)	Thoracic and vascular	Cognitive	1 w, 6 m	No, no

d, day; m, month; misc., miscellaneous; TKJR, total knee joint replacement; w, week.

the time medium-term follow-up was undertaken (typically around 3 months), although POCD per se was subsequently shown to persist in a significant proportion of patients (13).

Notwithstanding the frequently evanescent nature of the short-term “cardiac disadvantage,” there was considerable interest in the underlying mechanism(s). Three etiologic hypotheses gained prominence: cerebral hypoperfusion, cerebral arterial embolization, and a systemic inflammatory response following CPB and surgery (14). There was evidence to support all mechanisms, but cerebral perfusion and embolization were the focus of most early attention. Hypoperfusion and the inflammatory response are not discussed further here.

Many potential sources of emboli were recognized. Relatively large and dangerous solid emboli could arise if atheroma was dislodged during aortic manipulation (1,2). But while important in causation of stroke, these emboli were not the focus of interest in etiology of POCD. Smaller particulate emboli could arise from silicone or polyvinyl chloride released from CPB circuit tubing (15), from platelet–fibrin aggregates (16), and from the surgical field in various forms such as fat, bone fragments, cotton fibers, talc bone wax, and others (17). One intriguing discovery which emerged during the period of peak interest was the postmortem finding of thousands of small lipid emboli in the brain microcirculation following CPB (18). These were thought most likely to have entered the circulation from the surgical field via the cardiomy suction and CPB machine. Many sources of gaseous microemboli were identified including bubble oxygenators, the venous reservoir (19), air in the CPB venous line (20), inadequate surgical de-airing in open chamber procedures (21), introduction by perfusionist interventions (22), and entrainment of air into the blood in the cardiomy suction (4).

The result of this intense interest in neuroprotection in general (and emboli reduction in particular) was the development of an extensive suite of putatively neuropro-

tective initiatives advocated over a period of years in an attempt to ameliorate the perceived problem. These included better design of venous reservoirs, increased uptake of CPB arterial line filters, increased awareness among surgeons about the dangers of venous air, sequestration and/or cell saver processing of cardiomy blood, care with perfusionist interventions, increased uptake of epiaortic scanning prior to aortic cannulation, CO<sub>2</sub> flooding of the surgical field, and better attention to surgical de-airing of the cardiac chambers. Significant non-emboli-related initiatives that occurred around the same time included increased avoidance of cerebral hyperthermia during rewarming; tighter glycemic control; the use of heparin-bonded circuits, leukocyte filters, and other anti-inflammatory strategies; a trend toward increasing mean arterial pressure targets during CPB in selected patients; and widespread adoption of the alpha-stat acid–base management regimen. These strategies have collectively formed the basis for multiple contemporary reviews and best practice guidelines (23–26).

Not only is there evidence for progressive uptake of some of the relevant recommendations (27), there is also evidence (albeit somewhat circumstantial) that progress on risk reduction has been achieved over the period of interest. For example, we used similar measurement methodology and definitions of POCD in two separate neuroprotection studies almost 10 years apart in the same cardiac surgical suite (28,29) and found that the incidence of early deficits in the control group fell from 75% to 41%. Similarly, several recent studies have reported a progressive reduction in the incidence in stroke and other major morbidity following CABG. This has occurred despite a concomitant worsening of the risk profile of the typical patient (30,31). It is clearly not possible to draw definitive conclusions about trends in risk or to identify which strategies have been most effective in reducing it, but there is a general sense within the field that genuine progress was made in the “golden era” of interest in neurological outcomes through the 1990s and early 2000s.

## MICROEMBOLI AND POCD

Returning specifically to emboli, an obvious question raised many times over the years was the extent to which POCD could be correlated against intra-operative exposure to microemboli. Many studies have addressed this question, and these were incompletely summarized by Kruis et al. (32) who described five studies that found such a correlation and ten that did not. Their article omitted five studies (albeit including several published only as abstracts) from the early period of high interest, which all demonstrated a correlation between emboli exposure and outcome (33–37). Since publication of that review the issue has continued to appear in the literature with several studies indicating a role for emboli in POCD (38,39), and another not (40). One could argue that the literature is in a state of approximate equipoise in respect of this matter.

Given uncertainty about the significance of emboli and about causation of POCD, it is not surprising that present-day investigations have become more “outward looking.” It has become increasingly clear that POCD occurs in many types of surgery. Evered et al. (41) recently revisited the issue of whether cardiac surgery (CABG only) represented a higher risk for POCD than two other surgical interventions: coronary angiogram (performed under sedation) and total hip joint replacement (often performed under regional anesthesia). This study was notable in incorporating a non-operative control group, and for using the same investigators to administer a standard test neurocognitive test battery across all groups of patients investigated. Consistent with the findings of many of the studies listed in Table 1, they reported a higher incidence of POCD in CABG patients early after surgery (Day 7), but by 3 months there was no difference in the incidence of POCD between the three operative groups. Thus, there was a homogenous incidence of medium-term POCD despite the heterogenous nature of the surgical procedures and anesthetic techniques, and the authors argued that “these results shift the focus from a procedural cause to a patient susceptibility and beckon us to identify why some patients exhibit POCD even after simple coronary angiography with sedation and no general anaesthesia.”

Although their study included three procedures all known to be potentially associated with arterial emboli exposure and although CABG surgery presents a substantially lower risk of emboli exposure than open chamber cardiac surgery (21), the clear implication that patient factors are important, perhaps pre-eminently so, seems valid. The same authors have subsequently written on the potential role of pre-existing mild cognitive impairment/Alzheimers pathology and factors that might exacerbate it in the peri-operative period (42–44). The existence of complex, poorly elucidated multifactorial causes of POCD is supported by a recent contemporary expert review (26). How-

ever, while the list of “contributory suspects” is growing, we cannot not agree with the recent suggestion that CPB (and emboli by implication) have been “exonerated” in causation of POCD (43). Our particular reasons for suggesting this are outlined below.

First, as implied earlier, there has been considerable effort spanning two decades to improve the safety of CPB practice in general and exposure of patients to emboli in particular. Difficulty in demonstrating a medium- to long-term difference in POCD between patients undergoing CPB vs. non-CPB procedures in the modern setting may, in part, reflect improvements in the safety of CPB (45). In addition, although the significance of early POCD can be debated, there is evidence in both older (Table 1) (5–12) and contemporary studies (41) comparing cardiac and non-cardiac procedures suggesting that cardiac surgery involving CPB carries greater risk of early POCD which remains unexplained.

Second, approximately 50% of relevant studies have demonstrated a positive correlation between emboli exposure and cognitive outcome. This finding of an inconsistent (but unidirectional) correlation is unlikely to be due to random “noise,” which would be expected to result in some studies reporting a benefit from emboli exposure. In appraising these inconsistent data, the implicit assumption that serial administration of neurocognitive tests will detect harm specifically caused by what we now believe to be just one of many potential contributors to POCD also deserves scrutiny. In fact, such tests may lack the precision (and some studies the power) required for the task (45).

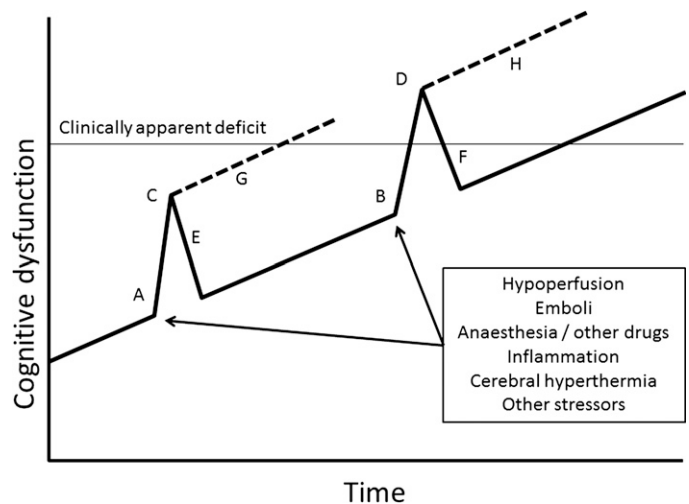
Third, there is abundant experimental evidence that small circulating bubbles can cause harm. The mere presence of bubbles in blood can incite a variety of inflammatory processes such as platelet activation, coagulation, and the complement pathway (46). Bubbles in the cerebral vasculature have been shown to disrupt the blood–brain barrier (47–49), including very small bubbles in the size range  $15 \pm 5 \mu\text{m}$  (SD) (50), and patients undergoing CPB are exposed to many arterial bubbles of this size (3). Similarly, despite rapid redistribution into the venous circulation, small aliquots of intra-carotid gas cause a subsequent reduction in cerebral blood flow and neuro-electrical function (51,52) through leukocyte-mediated inflammatory changes in the cerebral vasculature (53,54). Reduction of gaseous microemboli was shown to reduce evidence of cerebral microvascular damage in perfused swine (55). Thus, there is a sound pathophysiological basis for anticipating possible harm, even by small bubbles (56). This perception is supported by the finding of magnetic resonance imaging–detected cerebral infarction in 4 of 7 rats exposed to 1800 microbubbles of carefully controlled size ( $45 \mu\text{m}$  diameter) delivered over 2 minutes (57). Although not an invariable finding (58), it is notable that some

deleterious effects of bubbles on the brain seem somewhat independent of gas dose or its mode of delivery. For example, markedly different volumes of intra-carotid air produced a similar vascular inflammatory response (and decline in blood flow) in rabbits (52), and a standard volume of air has been found to produce the same degree of harm whether delivered as many small bubbles or a smaller number of bigger bubbles (57). Such findings may help explain inconsistent results when attempts are made to correlate bubble counts against cerebral outcomes.

Fourth, there is human evidence of harm to the brain by arterial microbubbles in settings that are not recently contaminated by any effects of anesthesia or surgery. For example, patients with mechanical heart valves chronically producing microemboli (most likely bubbles) exhibit memory deficits when compared to matched patients with tissue valves (and no emboli) and matched controls (59). There are other relevant scenarios where there is demonstrably no effect of anesthesia, surgery, or the comorbidities of advanced age. For example, positive bubble contrast tests for right-to-left shunts sometimes produce symptoms of cerebral dysfunction (60,61). When positive, these tests expose the patient to arterial microbubbles of similar size (62) to those detected in the arterial line of a CPB machine (3). Another example from a parallel field is the association between right-to-left shunts (that allow the passage of venous microbubbles into the arterial circulation) and cerebral decompression sickness (63), which may cause dysexecutive symptoms (64). These bubbles are similar in size (65) to those measured in the CPB arterial line (3). Similarly, divers have a greater incidence of ocular fundus lesions consistent with embolic injury than non-divers (66) thus implicating small arterial bubbles in causation. There is no reason such bubbles should be more harmful in divers. Although bubbles entering tissues after surfacing from a dive may grow as local dissolved inert gas diffuses into them, this is unlikely in the brain or retina, which wash inert gas out extremely quickly (67).

### MICROEMBOLI AND PATIENT-CENTERED RISK

None of the above discussion should be interpreted as an attempt to over-emphasize the role of emboli in POCD. Indeed, we agree with contemporary commentators who suggest the previous focus on emboli was almost certainly too narrow and that other patient-centered factors should be considered. For example, Silbert et al. (43) advance the hypothesis that POCD measured in studies of post-operative outcomes may in some (or even all) cases be a manifestation of accelerated pre-existing neurodegenerative processes, such as Alzheimer's disease. They identified anesthesia as a potential promoter of such processes, particularly in at-risk patients such as those with pre-



**Figure 1.** Conceptual paradigm for the development of POCD, which embraces the modern notion of patient-centered (pre-existing) risk, but within which emboli and other peri-operative stressors may cause exacerbations. See text for explanation.

existing mild cognitive impairment. We believe there is sufficient evidence to suggest emboli remain a potential contributor to a complex multifactorial process like this, and that they should not be ignored. In Figure 1, we propose a conceptual paradigm for POCD (similar to one for radiation tissue injury [68]), which embraces the modern notion of patient-centered risk, but within which emboli may play a role. Thus, a patient with underlying risk factors (such as mild cognitive impairment/underlying Alzheimer's pathology) progresses closer to clinically apparent cognitive impairment as they age. During this progression, exposure to one or more peri-operative stressors such as anesthesia, microemboli, or other pro-inflammatory events (Points A or B) may precipitate a subclinical deterioration (Point C) or clinical POCD (Point D). The patient may recover from the effects of these stressors (Points E and F) that may result in apparent resolution of a transient clinical deficit (Point F). But recovery may not occur (dashed lines and Points G and H) thus bringing the patient prematurely closer to the clinical threshold (Point G) or causing permanent POCD (Point H).

In summary, while there is growing evidence pointing to a multifactorial cause for POCD in the modern setting, we do not believe it is either possible or appropriate to confidently exclude a contributory role for arterial microemboli. In their recent review, Kruijs et al. (32) concluded "it remains prudent to minimise the microembolic load in clinical practice." A related perspective was provided by Martin et al. (69) who opined that "given a choice between a microembolism and no microembolism, we postulate that most patients would prefer no microembolism." We agree with these sentiments and consider that pragmatic and successful strategies to minimize patient exposure

to arterial microemboli should continue to be identified and implemented in perfusion and cardiac surgical practice.

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