Fixing Hearts and Protecting Minds
A Review of the Multiple, Interacting Factors Influencing Cognitive Function After Coronary Artery Bypass Graft Surgery

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Ischemic heart disease is a significant cause of mortality and morbidity in Western populations. Consistent with this, coronary artery bypass graft (CABG) surgery remains one of the most frequently performed major surgeries. Improved survival rates mean that our research focus now extends beyond surgical technique to include quality of postoperative outcome. Postoperative cognitive dysfunction (POCD) has emerged as one of the most challenging and hotly debated issues, with increasing impetus to answer the unresolved question: does fixing the heart come at a cost to the brain?

CABG surgery is associated with neurological events including stroke in 1.6% and delirium in 5.8% of patients. Beyond these severe and marked alterations to neurological function, there has been a widely held belief that CABG surgery is associated with POCD, which may presage a decline toward dementia. Research has been influenced by the 1995 Consensus Statement into the study of POCD in patients undergoing CABG surgery. Although the methods of investigation set forth by the Consensus Statement achieved widespread acknowledgment, its specific recommendations have not always been followed.

Despite significant methodological issues, it seems that the balance of interpretation has historically been in favor of CABG surgery as a cause of significant POCD. More recently, however, a review of a series of publications from a well-controlled longitudinal cohort study conducted at Johns Hopkins suggested that cognition is in fact stable or may even show some improvement after CABG surgery in the majority of patients, at least within the first year (Figures 1 and 2). There is little doubt that POCD affects some patients in the short term, but the pathophysiological mechanisms underlying this and the influence on longer-term cognitive function remain uncertain. For research to progress, we require a paradigmatic shift in our focus from the somewhat limited presence of POCD or not toward understanding the profile of cognitive change within the context of acute and chronic influences on neurological function. In this review, we offer a step toward achieving this aim by describing some of the main interacting factors impacting the brain and, thus, the cognitive function in patients undergoing CABG surgery.

Intraoperative Factors – Acute Challenges to Brain Function

The brain has a high metabolic demand and must have a constant supply of blood rich in oxygen and glucose to function. However, for successful CABG surgery to occur, it is necessary to manipulate normal physiology, including that of the brain. In this case, maintaining blood supply to the brain becomes dependent on the combined skills of the surgeon, anesthetist, and perfusionist to maintain mean arterial pressure, as well as on the individual’s capacity for autoregulating cerebral perfusion. There are a number of potential ways in which the process of surgery itself may disrupt the maintenance of adequate cerebral perfusion.

Although the brain is only 2% of body mass, it requires 15% of cardiac output to maintain its metabolic demands. Under usual circumstances, blood supply to the brain is autoregulated to constantly meet this demand. This is facilitated by a dynamic relationship between systemic mean arterial pressure, cerebral blood flow, and oxygenation. However, during cardiopulmonary bypass, mean arterial pressure can vary widely, which may push the limits of cerebral autoregulation. Impairment of autoregulation occurs in 20% of patients undergoing cardiopulmonary bypass for CABG surgery and is associated with increased perioperative stroke risk (a rate of 12.8% compared with 2.7% in those with preserved autoregulation).

Those patients with preexisting or vascular disease are particularly vulnerable, because their lower limit for autoregulation may be set higher.

With regard to cognitive function, higher (80–100 mm Hg) in comparison with lower (50–60 mm Hg) mean arterial pressure in relation to cardiopulmonary bypass resulted in a trend toward reduced stroke rate (2.4% versus 7.2%, respectively, \( p=0.076 \)), but with an equivalent incidence of POCD at 6 months (11% versus 12%). Conversely, other investigators found a greater decline in Mini-Mental State Examination score at 2 days following CABG surgery in those patients who are...
maintained at lower (60–70 mmHg: 3.9±6.5 point decline) in comparison with higher (80–90 mmHg: 1.1±1.9 point decline) mean arterial pressure. The extent to which this decline persisted in the longer term is not known. Interestingly, cerebral oxygen saturation, a marker of brain autoregulatory function, was similar in both groups, possibly because mean arterial pressure ranges did not differ markedly between high and low groups. More recently, however, a study of lung recruitment and cerebral oximetry immediately following CABG surgery with cardiopulmonary bypass showed that a decrease in mean arterial pressure of only 15 mmHg was associated with a 10% decrease in brain frontal lobe oxygenation. Moreover, prolonged oxygen desaturations during CABG surgery are associated with POCD in the early weeks, but not at 3 months postsurgery. In general, these data suggest that lower mean arterial pressures and derangement in cerebral oxygenation increase vulnerability to neurological insult in the context of CABG surgery, but they do not confirm a lower limit of effective autoregulation across all patients, nor do they suggest a robust association with POCD. Ultimately, the maintenance of mean arterial pressure during CABG surgery is a balance between ensuring end-organ perfusion and yet having an arterial pressure that is not too high for the surgical procedure, and this range may vary among individuals. This suggests that a correlational approach to POCD analysis is important, taking into account intraindividual variability in cerebral autoregulatory function. In the meantime, it is disheartening to note that interventions intended to respond to cerebral oxygen desaturation intraoperatively have had little effect on the incidence of POCD postoperatively.

Another approach to neuroprotection is to reduce the metabolic demand of the brain during surgery, usually by inducing hypothermia. A number of relevant studies have been published. For example, hypothermia (cooling to 32°C with maintenance at 34°C) has been associated with reduced POCD early after CABG surgery. Others have reported no observable benefit of mild hypothermia (34°C) in comparison with normothermia, in terms of either the mean number of cerebral emboli detected by transcranial Doppler (182 in hypothermia group versus 188 in controls) or POCD incidence at both discharge (49% versus 45%) and 3 months later (4% versus 8%); nor was there any correlation between embolus rate and a composite cognitive score (r = -0.01). Consistent with this, a recent meta-analysis found no difference in the rate of stroke, focal neurological deficit, or POCD between normothermic (>34°C) and hypothermic patient subgroups. Some investigators highlight the possibility that the brain is particularly vulnerable to insult during rewarming from hypothermia. This could occur if cerebral perfusion capacity is unable to match the acute increase in metabolic activity caused by the abrupt rise in temperature. Of course, studies of hypothermia reflect only part of a complex physiological relationship between temperature, metabolism, cerebral autoregulation, and oxygenation in the context of CABG surgery. Indeed, a range of techniques, such as jugular bulb oxygen desaturation and transcranial Doppler measures of cerebral blood flow velocity have been used at the point of rewarming, with implications for our understanding of cerebral autoregulation and brain function. Nevertheless, a trial of slowed in comparison with conventional rewarming rate revealed an inconsistent effect on POCD. In summary, meta-analytic evidence suggests that hypothermia has a negligible influence on POCD incidence after CABG surgery.

Cardiopulmonary bypass enables the surgeon to perform delicate surgery on a nonbeating heart. Although this technique
has undergone numerous improvements in oxygenator design, cannulae, and perfusion pumps since its inception in the early 1960s, it remains a nonphysiological method for maintaining cardiac output during heart surgery and thus a potential source of brain insult. During cardiopulmonary bypass, blood passes through an extracorporeal circuit, where the anticoagulant factors that normally prevent clotting are absent. Heparin-coated circuits / heparinization reduced the degree of POCD in one early study, but not the incidence of brain lesions, reflecting the lack of a clear relation between these variables at least in the early postoperative period. Nevertheless, reduced (minimal) cardiopulmonary bypass circuits that limit the time blood is exposed to a foreign surface can generate fewer microemboli, which may explain the reportedly lower incidence of both intraoperative cerebral desaturation (38% minimal versus 55% conventional circuit) and POCD (41% minimal versus 65% conventional circuit at discharge and at 3 months: 21% versus 61%, respectively) associated with its use. More specific mechanical elements of the cardiopulmonary bypass circuit have also been investigated as a potential cause of POCD. For example, roller-head pumps compress blood within the tubing and thus may damage the fragile oxygen-carrying blood cells. The alternative method uses centrifugation and results in improved neurological outcome but with a nonsignificant decrease in POCD incidence.

Perhaps the most frequently described mechanism of brain injury in CABG surgery is based on the recognition that microemboli are generated by the surgeon manipulating the heart and aorta, through cardiomyotomy suctioning, and by the cardiopulmonary bypass circuit itself. Microemboli can be detected intraoperatively as high-intensity transient signals by transcranial Doppler sonography. They have the potential to lodge in cerebral microvasculature, impairing blood supply to the brain and thus cerebral oxygenation. Several phases during cardiac surgery have been associated with increased risk of embolic showers. Aortic cannulation and clamping (during application of cardiopulmonary bypass) increase the high-intensity transient signal rate, particularly if there is extensive atheroma in the ascending aorta. It is not surprising, therefore, that most (81%) microemboli are generated at the point of aortic cross-clamp release. Retaining the shed mediastinal blood with cardiomyotomy suckers provides an additional source of lipid emboli and other fragments, which can be returned into the circuit and onto the brain. Furthermore, a variety of particulate matter and air emboli are generated within the cardiopulmonary bypass circuit itself. These can be filtered before blood is returned to the patient with the assumption that fewer microemboli then travel to the brain. The use of cell salvage techniques by which red blood cells are filtered and washed before being returned to the circulation may help, but this has shown no specific neurological benefit or reduction in POCD, and, indeed, that it may disrupt coagulation. Whatever the mechanism, there is apparently no straightforward association between the number of microemboli released and postoperative pathological changes found on brain imaging or incidence of POCD.

Systemic inflammation is a feature of all types of surgery, but the use of cardiopulmonary bypass provides an additional source of proinflammatory response by exposing blood to a foreign surface. Inflammation can lead to vessel endothelial dysfunction with significant leak across the blood–brain barrier and tissue edema. Specifically, cytokines have been implicated in neuropathology, particularly that involving the hippocampi and hippocampally dependent memory dysfunction in mice models of noncardiac interventions. Such changes might affect the brain irrespective of microembolic load, and perhaps provide a better explanation for early postoperative POCD than evolving structural brain lesions per se. However, it should be borne in mind that there is no evidence of a specific deficit in hippocampally dependent memory in humans following CABG surgery, suggesting that functionally relevant pathology extends beyond this structure and involves other mechanisms. More general markers of inflammation such as C-reactive protein have been investigated in relation to POCD in humans undergoing CABG surgery, as well as markers of brain vulnerability to ischemia (S-100β). There may also be an important longer-term role for inflammation in our understanding of cognitive function. Inflammatory markers have been found in the cerebrospinal fluid of patients at 24 hours postsurgery, but also at up to 6 months after surgery, and, intriguingly, an increase in brain inflammatory markers after aortic valve surgery was noted to occur in tandem with an increase in biomarkers associated with Alzheimer disease (amyloid β peptide).

These findings should be interpreted in the knowledge that such biomarkers may also be increased in patients with more general cardiovascular disease. In general, the functional consequences of neuroinflammation are currently unclear, particularly in relation to CABG surgery and POCD.

The relation between cardiopulmonary bypass and coagulopathy, inflammation, and microemboli was one of the driving forces behind the development of off-pump surgical techniques. It was hoped that this approach would have a significant benefit in reducing the morbidity associated with CABG surgery. Indeed, stroke incidence has been described as higher in patients having cardiopulmonary bypass than in those undergoing CABG surgery off-pump, but perhaps only within the first 24 hours following surgery. Others report that, in general, there is no increased nonfatal stroke risk in on-pump in comparison with off-pump CABG surgery. There is also little support for a group difference in POCD incidence according to a systematic review and a recent meta-analysis. However, another meta-analysis found that on-pump surgery increased the incidence of POCD at early (1–2 weeks and 3 months) but not later (6 months and 12 months) stages in recovery following CABG surgery; moreover there is evidence that this lack of a ‘late’ effect persists at 5 years. The effect of cardiopulmonary bypass on POCD incidence is particularly well represented in the literature, and, on balance, the evidence suggests that this technique does not exert a major negative influence. It is possible that by avoiding cardiopulmonary bypass one simply shifts the balance from 1 set of potential neuronal insults (microemboli) to another (intermittent severe hypotension; prolonged low cardiac output state).

Anesthetic and sedative agents with γ-aminobutyric acid–mediated and N-methyl-D-aspartate–receptor antagonist properties temporarily alter neurotransmission by acting at a
number of sites at a cellular level to achieve deep sedation and amnesia during the operation. The long-term effects of these agents with regard to cognitive function are not well understood, and thus their influence on POCD in the context of CABG surgery is hard to determine. A very early report suggested the potential for pathological changes in the brain in association with anesthetic agents, and more recent animal models have added weight to this proposition. Many of these studies have been conducted in young animals, but anesthesia-induced alteration to neural pathways has also been associated with memory impairment in aged rats. Other features have been described. For example, hypoxic challenge would normally be mediated by the capacity of the brain to autoregulate its own blood supply and also through astrocyte-derived upregulation of hypoxia-protective factors (eg, via hypoxia-inducible factor pathway). However, a recent study suggested that anesthetic agents might suppress this response. If so, this could help to explain why there is no straightforward relationship between cerebral oximetry measures during surgery and later POCD; other factors need to be accounted for simultaneously.

Exposure to general anesthesia has already been implicated in altered gene expression in human brains with potential for POCD for a number of days postsurgery, and even with mechanisms associated with the development of Alzheimer disease. In support of this finding, having an optimized depth of anesthesia (assessed by using the bispectral index and cerebral oximetry) for noncardiac surgery reduced the incidence of POCD over the course of 1 year. On the other hand, a randomized, controlled study of general versus epidural anesthesia in older adults undergoing noncardiac surgery demonstrated equivalent POCD incidence at 1 week and 6 months after surgery. There is limited evidence available in CABG surgery, but bispectral index data (reflecting the depth of anesthesia) were unrelated to POCD incidence in a recent study. We may currently only conclude that there is a complex relationship between POCD and anesthetic agents, the effect of underlying illness, the acute trauma of surgery, and the hospital environment.

All anesthetics used for cardiac surgery will induce hypotension and render the patient apneic, requiring mechanical ventilation with its attendant effects on oxygenation, ventilation-perfusion mismatch, and reduction in venous return to the heart. Indeed, because approximately one-fifth of patients undergoing noncardiac surgery also experienced significant cerebral oxygen desaturation intraoperatively, we might consider that the origins of desaturation extend beyond the specifics of CABG surgery. The task of maintaining cardiac output, mean arterial pressure, and cerebral oxygenation continues after surgery into postoperative intensive care. Consistent with this, stroke risk was reportedly highest in the days immediately after surgery, peaking on the second postoperative day. This could be explained in part by the delayed effects of surgical complications, eg, movement of lodged emboli, but also by factors such as prolonged ventilation. For example, efforts at recruiting areas of collapsed lung space by raising intrathoracic pressure (to 40 cm H2O) have been shown to decrease brain frontal lobe oxygenation in the context of low mean arterial pressure. Other perioperative complications that could contribute to stroke and POCD risk include an air embolus from lines or injury from carotid arterial cannulation, the onset of atrial fibrillation, and perhaps also biochemical and metabolic derangement including poor glycemic control.

It is worth remembering that the physiological response in patients who have a stroke outside of the surgical environment is an increase in arterial pressure to maintain perfusion to penumbral regions around the areas of infarct. This response might be tempered in the context of cardiac surgery and continued ventilation in intensive care.

Notwithstanding the currently tentative evidence with regard to anesthesia and cognition in humans, this factor should not be ignored, not the least because of its potential to cloud our interpretation of the relationship between the intricacies of cardiac surgery and POCD. For example, repeated episodes of deep sedation may increase the risk of delirium, which reportedly affects up to 30% of patients undergoing cardiac surgery. A number of pathophysiological processes are implicated in delirium, including an acute increase in the biomarkers of stress and inflammation and more chronic underlying brain pathology. The important point is that most studies of patients undergoing CABG surgery have poorly controlled for the possibility that unrecognized delirium may have influenced the reported incidence of POCD. Indeed, multiple regression identified delirium as significantly associated with worse POCD, suggesting a mediated relationship between intraoperative factors (eg, cerebral oxygen desaturation) and POCD in some patients.

In summary, there have been many attempts at modifications in perioperative technique to improve the outcome following CABG surgery. The equivocal success of these approaches suggests that no one modification is likely to alter the outcome of POCD independently of other factors. Moreover, although the influence of anesthesia on POCD might not be as strong as some surgical factors, there are profound changes to neurotransmitter systems and physiology, and acute alterations to some patients’ behavioral state, which limit the degree to which POCD may be reliably identified in the immediate postoperative period. Indeed, 1 study of POCD reports that investigators were unable to administer the Mini Mental State Examination and thus excluded 5 postoperative patients, presumably those most vulnerable to POCD, owing to the requirement for sedation/ventilation at the planned time of testing (48 hours post-CABG surgery). On a more positive note, the simple presence of neuromonitoring in cardiac surgery has potential to reduce the incidence of brain injury and POCD in older surgical patients generally, suggesting that part of the effect could be the increased attention that the surgical team pays to protecting the patient’s brain.

Preoperative Cognitive Variability – Chronic Influences on Brain Function

There are a great number of environmental and genetic influences on brain function that introduce considerable variability in cognition whether or not CABG surgery is performed. It is important to first acknowledge that a degree of cognitive decline and brain atrophy are seen in normal aging. Based on this, cognitive reserve is a term frequently applied to explain any discrepancy between the predicted and observed
degree of cognitive deficit recorded in any group of patients under investigation. It is determined by factors such as pre-morbid intelligence, education, socioeconomic status, mood, and, in general, by the extent of cognitive stimulation throughout life. However, the usefulness of cognitive reserve to any individual at any given time may be reduced by acute biochemical changes that alter baseline patterns of neural connectivity, as well as by increased psychological stress, as well. Such factors are associated with surgery in general, and, as such, POCD and mood disorders are not distinct to patients undergoing CABG surgery.

Superimposed on this background variability, cardiovascular disease imposes an additional burden on neurological and cognitive function (Figure 3 illustrates the relationship between hypertension and cognition). The extent of brain atrophy in individuals with atherosclerotic disease is similar to that seen in the general population of aging adults, but added to this is decreased regional perfusion and ischemic vascular lesions, which often take the form of subcortical small-vessel disease and may be clinically silent, albeit associated with subtle cognitive dysfunction. Patients presenting for CABG surgery have similar cardiovascular risk factors and therefore are predisposed to baseline changes in cognition. Indeed, MRI studies of patients undergoing CABG surgery show that a large proportion have small brain infarcts before surgery. In 1 study, although half (45%) of patients showed new ischemic brain lesions following CABG surgery, a significant proportion (38%) had preexisting lesions likely to be the result of small deep cerebral infarcts. Most strikingly, the presence of new lesions was not associated with a detectable new neurological deficit. The long-term case-controlled studies by Selnes and colleagues at Johns Hopkins have been particularly influential in this matter, showing that the longitudinal cognitive profile is similar in patients who have undergone CABG surgery and those whose cardiovascular disease was medically managed, suggesting no additional burden of CABG surgery on long-term cognitive function.

In addition to a slowly progressive decline in cognitive function linked to cardiovascular pathology, patients undergoing CABG have a rate of preoperative stroke of ~6%, as estimated from 2 recent studies. The extent to which this influences POCD is not clear, because few studies have examined this factor. However, preoperative stroke is associated with a less favorable postoperative course, suggesting that these patients may therefore be more vulnerable to POCD. More importantly, it is possible that the inclusion of patients with unidentified preoperative brain infarct in previous studies of cognition in CABG surgery may have biased the results toward POCD.

Vascular explanations for dementia irrespective of CABG surgery are widely acknowledged and based on the finding of brain infarcts on autopsy studies, associated also with MRI demonstration of increased microinfarct incidence, and on the presence of cerebral microbleeds associated with hypertensive vasculopathy and amyloid angiopathy. Autopsy studies of individuals who have had cardiac surgery have revealed a similar picture of vascular pathology. Although CABG surgery cannot be excluded as a factor in the development of dementia, neither can it be assumed that it is directly and solely related, because many of the neuropathological correlates are not unique to surgical patients. Two important lines of evidence support this. First, the apolipoprotein E genotype associated with dementia is reportedly unrelated to POCD incidence in patients undergoing CABG surgery. Second, a recent epidemiological study in Canada reported that the proportion of patients with ischemic heart disease who subsequently received a diagnosis of dementia during 3 to 8 years of follow-up was 7.6% for those who were treated with CABG surgery and 12.1% for those who received conservative medical management only; this difference was not statistically significant.

Factors Relating to Methods – Taking a Cognitive Neuroscience Approach

Numerous neuropsychological tests are available, usually designed to tap a domain of cognitive function. However, post-CABG brain lesions visible on imaging have a wide distribution, potentially affecting any lobe in the brain and the cerebellum; although frontal and parietal lesions were the most commonly observed. This suggests that a specific profile of cognitive deficit following CABG surgery would be unlikely.

First, it is necessary to take a step back and summarize the main underlying pathophysiology. We have argued that chronic, progressive changes in the brain are associated with normal aging, and, pathologically, with underlying cardiovascular disease. Against this background, CABG surgery is associated with acute insult to the brain. In particular, 2 main interacting mechanisms have been implicated in intraoperative brain vulnerability, namely, hypoperfusion and microemboli. Specifically, it has been hypothesized that decreased perfusion limits the washout of microemboli, contributing to the development of infarction in arterial borderzones of the brain. Microemboli are typically small and shower the brain, instead of causing the type of focal
hypoxia-ischemia associated with overt neurological deficit. Cumulative regional damage might nevertheless result in larger lesions; indeed, it has been noted that small capillary/arteriolar dilations, taken as evidence of microemboli in neuropathological studies, tend to cluster together, and that this might result from small fragments breaking away from larger emboli lodged upstream.91 Conceivably, this could introduce a time lag between microemboli generation and neurological damage and thus help to explain the occurrence of early postoperative stroke,1 and perhaps also why POCD has not been fully accounted for by high-intensity transient signal rate32 and cerebral oxygen desaturation12 recorded intraoperatively. End arteries supplying deep arterial borderzone areas may be at particular risk from microemboli, especially in the older patients in whom these vessels show greater tortuosity.92 Such diffuse and subtle damage, incorporating deep white matter, may lead to disconnection of neural networks and perhaps partly explains the presence of transient processing speed slowing demonstrated in a recent meta-analysis.8 The effect on the brain of more generalized complications of CABG surgery, such as transient cerebral desaturations, neuroinflammation, and hemodilution, is far from clear, but would also be expected to result in variable deficit.

Despite the expected lack of specificity in the cognitive profile of patients undergoing CABG surgery, the use of a general screening instrument, such as the Mini-Mental State Examination, is unlikely to be sufficiently sensitive to subtle change in cognitive state.93 Instead, the evidence suggests the necessity of testing multiple domains of function and of including time-sensitive measures of attention and processing speed using computer-based measures. Furthermore, combining information obtained from MRI and neuropsychological methods has obvious appeal in delineating a profile of deficit when it occurs. Visual rating scales that estimate the extent of white matter lesions94 have allowed correlation between lesions and neuropsychological outcome in noncardiac surgery populations.95 However, any brain damage in cardiac surgery may also result in more subtle pathology that is invisible to the human eye. More fine-grained analysis is possible by using MRI sequences and analytic techniques focused on subtle change in grey matter (voxel-based morphometry) and white matter (diffusion tensor imaging). Other techniques such as electrophysiology (event-related potentials), transcranial Doppler, and functional MRI have potential for exploring acute derangement in neurovascular coupling. In addition, more recently developed surrogate markers of brain autoregulatory function, eg, near-infrared spectroscopy,96 are being increasingly applied with the prediction that they might provide more sensitive measures of intraoperative brain vulnerability,97 and thus potential for POCD.

An often cited methodological issue is the variability in choice of criteria for determining significant change in test scores.4 This is compounded by the lack of control groups in many studies, which prevents the underlying rate of cognitive change with repeated assessments, aging, and cardiovascular disease from being addressed, and may therefore lead to an overestimate of the incidence of POCD. Indeed, studies in which appropriate control groups have been included have reached the conclusion that long-term cognitive decline is not solely attributable to CAGB surgery.5 Others have accounted for genetic and environmental influences on cognition by the use of twin controls.98 At ≥1.5 years after CAGB surgery, there was no overall group difference in cognitive function between 232 male patients and their twins, but, when data were stratified by age, it was found that those who underwent surgery earlier in life (between 63 and 70 years of age) showed a slight improvement in cognitive function postoperatively, whereas those in older age groups (71 to 83 years) did not.

Longitudinal studies with multiple preoperative test points would establish the background rate of cognitive change against which CAGB surgery occurs, but would require an unacceptable delay in surgery so that there would be sufficient time between administrations. Long-term population-based studies would allow an opportunity to prospectively acquire multiple data points in individuals who go on to require CAGB surgery, but would necessitate multicenter cooperation and considerable funding to provide the large numbers of participants required. Innovative approaches to make assessment more convenient have been piloted and may provide an answer to such issues. For example, telephone99 and Internet-based assessment that patients may complete at home pre- and postoperatively have been described, obviating the need for frequent hospital admissions. Ultimately, the use of age- and socioeconomic status–matched controls combined with statistical techniques that simultaneously account for multiple medical factors such as previous stroke may provide the best solution.

Finally, the timing of the postoperative cognitive assessment will have a profound impact on the conclusions that are drawn. Cognitive testing performed in the immediate postoperative period may suggest a considerable burden of POCD in some patients, but may also reflect delirium and resolve once the individual is through this acute postoperative phase. It may also reflect the use of opioid analgesic and sedative medications that are required before hospital discharge. Similarly, limiting assessment to the first postoperative year may not permit the detection of any increased risk of dementia in this population.

Conclusions: Shifting the Research Paradigm
If we restrict our research focus to POCD incidence early after CAGB surgery, then our potential to understand the wider, possibly modifiable issues is limited. The alternative is that we accept the more dynamic, complex picture of the underlying, interacting factors influencing cognition. This may allow us to harness other (nonsurgical) mechanisms to optimize outcome.

Older populations with greater comorbidities are undergoing CAGB surgery and yet the incidence of perioperative stroke is declining.3 By contrast, efforts at improving intraoperative neuroprotection, as described above, have provided somewhat mixed results with regard to POCD. The findings can be understood if POCD also reflects preexisting cognitive change (see Figure 4). In other words, CAGB surgery may ultimately have little impact on the established individual trajectory of neurological and cognitive function that is already set in motion, with improvement in both cardiac output and sense of health and motivation even benefiting cognition in some people, at least in the short term. Critically, however,
this interpretation suggests that any attempts to protect the brain must occur earlier in life, and be aimed at controlling the progression of cardiovascular disease, eg, lowering blood pressure and controlling diabetes mellitus; and perhaps also by increasing cognitive reserve preoperatively through promoting cognitive activity\(^{100}\) in an attempt to cushion the acute effects of surgery. Simply stated, the best method of neuroprotection may be understanding potential for POCD beyond the operating room.

We speculate that those who demonstrate POCD may have exceeded a threshold of preexisting vulnerability over which the brain’s compensatory systems become increasingly susceptible to the hit of CABG surgery. If this were the case, it might be possible to devise ways of predicting which patients will have a worse cognitive outcome than others, and using this as a means to focus increased perioperative investigation, treatment, and monitoring. For example, we could start by modifying existing cardiac surgery risk scales to include more markers of preoperative neurological and cognitive function. This may allow the surgeon and patient to consider the risk of POCD more realistically. It has already been shown that the preoperative level of cognitive function is associated with the risk of developing postoperative cognitive dysfunction\(^{101}\) in an attempt to cushion the acute effects of surgery. Simply stated, the best method of neuroprotection may be understanding potential for POCD beyond the operating room.

Finally, we point out that research into POCD following CABG surgery has thus far been driven by a few cardiothoracic specialist centers, mainly involving surgeons, anesthetists, and neurologists. However, increasing recognition that multiple factors are likely to interact to influence brain function in the context of CABG surgery suggests that an interdisciplinary approach is the key to future progress. In other words, POCD incidence after CABG surgery is apparently determined by the company the atheromatous coronary artery keeps, and thus should be investigated by the company the surgeon keeps, including contribution from psychologists, radiologists, geneticists, and epidemiologists. This and other recommendations made herein reflect the original aims of the 1995 Consensus Statement.\(^{1}\) However, what is now required is an updated perspective based on the analysis of findings published under the past 17 years of Consensus Statement influence, and taking into account developments in related fields of research, predominantly cognitive neuroscience. Addressing all of the factors identified in this review may provide us with a significant future challenge, but neglecting to consider them may no longer be acceptable.

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Disclosures

None.

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