Postoperative cognitive dysfunction after cardiac surgery

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Key points
Postoperative cognitive dysfunction (POCD) is common after cardiac surgery.
No international consensus exists for the diagnostic criteria of POCD.
The pathophysiology behind POCD is multi-factorial but as yet unclear.
The previous assumption that cardiopulmonary bypass has a significant role in POCD is overstated.
POCD after cardiac surgery may be attributable to natural disease progression in a high-risk population.

Nearly 40 000 people in the UK and many more worldwide have cardiac surgery annually. Adverse neurological outcomes post-cardiac surgery have been well recognized for many years and are an important cause of post-operative morbidity and mortality. They have been classified by The American College of Cardiology and the American Heart Association into Types 1 and 2. Type 1 neurological injury is attributable to brain death, non-fatal stroke, and new transient ischaemic attack, whereas delirium and postoperative cognitive dysfunction (POCD) are classified as Type 2 neurological injuries. The two most significant clinical neurological abnormalities after cardiac surgery are stroke and POCD. The reported incidence of stroke in patients undergoing isolated coronary artery bypass graft (CABG) is 1.6%. However, quantifying the incidence of POCD is more complex. In this review, we will solely focus on the relationship between POCD and cardiac surgery.

Definition and diagnosis
Bedford introduced the concept of POCD in 1955. However, POCD is difficult to diagnose, as there is still no international consensus. POCD is a decline in cognitive function after surgery and anaesthesia from the preoperative baseline level. It can affect different cognitive domains such as attention, memory, learning, visual spatial, motor skills, and executive function. It may also be accompanied by behavioural change. A clinical suspicion of POCD may be confirmed with neuropsychological testing completed several weeks after surgery and compared with baseline tests performed preoperatively. There is no international agreement on what test batteries should be used for the diagnosis of POCD. Different POCD studies have used a diverse compilation of neuropsychological tests, with each test reflecting different aspects of the cerebral cortex. A recent review article by Ghoneim and Block on assessment of cognition after anaesthesia and surgery highlighted the most commonly used neuropsychological tests.

Some of the diagnostic tools that have been used are listed below:
- Trial making test measures visual attention and task switching.
- Letter-digit coding test analyses speed of information processing.
- Boston naming test looks at word finding ability.
- Stroop-word interference test assesses interference susceptibility.
- Four boxes test examines psychomotor speed.
- Paper and pencil memory scanning test measures sensorimotor speed.
- CERAD word list memory test.
- Visual verbal learning test examines memory.

A number of analytic criteria have been suggested to determine the difference between normal variation in cognitive function and POCD. The criteria routinely used are a percentage change from baseline in a defined number of neuropsychological tests (usually a decline >20% in two or more tests) or an absolute decline from baseline scores greater than a defined proportion of the standard deviation (SD) of the two or more tests (usually >1SD, calculated from baseline scores). The inherent issue with the percentage change method is that those patients with initial low baseline scores require a much smaller change to fulfil the criteria. The reliable change index is often used—it compares the change score to the normal test–retest variation in an age-matched control population. The reliable change index has the advantage of correcting for the learning effect that arises from repeat testing.

Incidence and significance
POCD is now the most frequent significant neurological sequela post-cardiac surgery.
Postoperative cognitive dysfunction after cardiac surgery

Quoted incidences are dependent on varying factors: timing of measurements, the type of surgery (cardiac vs non-cardiac), the exact assessment used, and its sensitivity. POCD can be sub-classified into short term and long term. Short-term POCD is usually transitory and is defined as cognitive decline lasting up to 6 weeks post surgery. This occurs in 20–50% of patients undergoing cardiac surgery. However, POCD can be long term which is defined as a subtle deterioration in cognitive function 6 months after surgery. This occurs in 10–30% of cardiac patients. As mentioned earlier, there are no gold standard tests for POCD. Hence, the incidences quoted vary greatly and the diagnosis of POCD is not uniform.

The issue of POCD is important as patients’ perception of their general health correlates directly with neurocognitive function. POCD itself heralds a loss of independence, quality of life, and withdrawal from society. If present at 3 months after operation, it is associated with major long-term consequences and financial implications such as a higher risk of leaving the labour market and dependency on social welfare payments, and also increased mortality at a median of 8.5 yr. According to a Danish study, POCD only 1 week after surgery increases the risk of leaving the labour market prematurely. POCD also leads to a prolonged hospital stay.

Possible aetiology and mechanisms of POCD post-cardiac surgery

The pathophysiology and causes of POCD post-cardiac surgery have been widely researched over the years and many theories have been suggested. Nevertheless, it is still poorly understood. The causes of POCD post-cardiac surgery are most likely multi-factorial, and could be related to a variety of surgical, anaesthetic, and patient factors.

Surgical factors

The difference in surgical technique between on- and off-pump cardiopulmonary bypass (CPB) surgery has been comprehensively discussed. For many years, it has been assumed that one of the main causes of POCD was cerebral microemboli during CPB. However, no clear advantage of on-pump (CPB) surgery compared with off-pump in the incidence in POCD could be proved in the Randomized On/Off Bypass Study Group of 2203 patients. Also, when CPB was used, there was no difference between pulsatile and non-pulsatile flow in relation to cognitive decline post cardiac surgery.

Cerebral autoregulation occurs if cerebral perfusion pressure is within the physiological range. The optimal target arterial pressure during CPB has not yet been defined. During CPB, mean arterial pressure (MAP) is usually maintained at ~60 mm Hg; this is an arbitrary figure dependant on patient age, preoperative arterial pressure and medical history. This could be too low for chronic hypertensive patients who have a rightward shift in their autoregulatory curve, and may therefore lead to watershed stroke from global hypoperfusion. A recent 2011 study found that increased perfusion pressure equivalent to physiological conditions was associated with less early POCD (P-value of 0.012), but still there is little evidence to guide clinicians. Joshi and colleagues were able, with the use of cerebral oximetry, to determine the cerebral lower limit of autoregulation by examining the response of individual patients’ cerebral oxygen saturations to various changes in arterial pressure. They found that preoperative arterial pressure and clinical history were both imprecise methods of predicting the MAP at the lower limit of autoregulation, because of the wide variability that exists. In a previous study, this group showed that perioperative strokes were more common in patients with impaired autoregulation. Thus, real-time continuous cerebral blood flow autoregulation monitoring may provide a rational means for individualizing MAP during CPB. Further studies are required to ascertain whether using a real-time lower limit of autoregulation-guided assessment and intervention can improve neurological outcome.

Embolic material can be derived from CPB but also from aortic lesions. Aortic arteriosclerosis itself may be a source of emboli, especially at cannulation and cross-clamp, and should therefore be identified and avoided. Two separate studies comparing the use of blood processed via a cell saver during CPB in order to minimize microembolization, to unprocessed blood returned directly back to the patient via the CPB circuit, were unable to find a statistical difference in the incidence of POCD. A technique for looking at new acute cerebral infarction due to emboli may be magnetic resonance diffusion-weighted imaging (DWI). Studies using DWI have shown a positive relationship between new cerebral ischaemic regions postcardiac surgery and the development of POCD. However, it is difficult to correlate the volume and location of cerebral ischaemia to the development of POCD. Thus, using DWI to predict POCD has been controversial and the evidence is not sufficient. Cognitive decline can still occur without obvious infarct.

Inducing hypothermia in cardiac surgery decreases cerebral metabolic rate. It also decreases cerebral blood flow and disrupts the blood–brain barrier. On a cellular level, hypothermia attenuates the neuroinflammatory response, inhibits free radical generation, and reduces apoptosis. Hence, hypothermia can be neuroprotective. However, during fast rewarming, cerebral oedema can occur because of cerebral hyperthermia disrupting autoregulation mechanisms. The resulting increase in intracranial pressure may impair perfusion and oxygenation to brain tissues leading to POCD.

During CPB, hypothermia may also result in alterations to acid–base balance, which in turn affect cerebral blood flow. There are two techniques used to regulate acid–base balance during CPB: pH-stat and alpha-stat. They differ according to how arterial CO₂ and in turn pH is managed: blood gas measurements are either made on blood warmed to 37°C (alpha-stat) or on values corrected to the patient’s actual temperature (pH-stat). pH-stat has been implicated as a causative factor in POCD; this may be attributable to the fact that it requires CO₂ to be added to the CPB circuit leading to cerebral vasodilation above metabolic demands and subsequent loss of autoregulation. In addition, increased cerebral blood flow may result in increased embolic load and a greater risk of cerebral embolization. However, some centres report...
improved results using pH-stat during deep hypothermic CPB, and comparative trials are awaited.

The duration of surgery has been found to be associated with POCD. Surgery itself initiates the stress response and systemic inflammation. Activation of macrophages, neutrophils, and platelet aggregation leads to up-regulation of adhesion molecules and cytokine production, resulting in destruction of the blood–brain barrier and making the brain more susceptible to ischaemic insults. It is postulated that systemic inflammation can lead to inflammation of the neurones resulting in POCD. In particular, being on CPB during cardiac surgery activates the inflammatory response by direct contact between blood and the artificial surfaces of the CPB circuit. Despite this, the inflammatory response is similar whether CPB is used or not, which may be attributable to other factors including sternotomy, graft harvesting, and pericardial incision.

Extreme haemodilution (decrease in haematocrit of >12% from baseline) during cardiac surgery may have adverse neurocognitive outcomes especially in the elderly and should be avoided if possible.

Anaesthetic factors

Anaesthetic agents bring about a reversible loss of consciousness as an effect, but intracellulary the consequences may be more long term. Conflicting evidence exists as to whether i.v. or volatile agents are implicated in the development of POCD, if at all. Human studies examining the role of anaesthetic agents in POCD are difficult because usually we cannot detach anaesthesia from the insult of surgery. Hence, what type of anaesthetic agent may be best in terms of development of POCD is still uncertain, although there is some evidence, from small studies, that volatile anaesthesia in cardiac surgery could have a better cognitive outcome than propofol based anaesthesia,14 which is converse to non-cardiac surgery. This could be attributable to pre- and post-conditioning by volatile anaesthesia, as it is known to mitigate the ischaemia-reperfusion injury of different organs occurring in CPB with cardioplegic arrest.

Great interest exists in the potential role of intra-operative monitoring in POCD. Devices such as cerebral oximetry may be used to maintain regional cerebral oxygen saturation (rSO2) within predefined limits, as cognitive decline after cardiac surgery may be associated with decreases in cerebral oxygen desaturations.15 There is also some evidence that targeting depth of anaesthesia and decreasing cumulative deep hypnotic time may improve neurological outcome by getting the advantage of neuroprotection of anaesthetic agents and minimizing neurotoxic effects in non-cardiac patients. This hypothesis is not yet proved in the cardiac patients and still remains hotly debated and will be discussed further.

Patient factors

Current thinking and future development is moving towards attempting to understand the role of patient susceptibility in POCD. Some of these factors are easily identifiable before operation and should be considered in the work up of the patient.

The most important risk factor associated is age; numerous studies have proved there is a strong relationship between increasing age and POCD. Greater incidence in the elderly could be attributable to changes in their vasculature and auto regulation of cerebral blood flow. Age is also linked to the risk factors for cerebrovascular disease, which contributes to POCD, such as diabetes, atherosclerosis, and hypercholesterolaemia. All these risk factors can contribute to priming of the immune system, so that patients are already in a pro-inflammatory state when subjected to cardiac surgery, leading to amplification of systemic and neuronal inflammation. This precipitates widespread neuronal dysfunction contributing to POCD. In addition, elderly patients may already display a degree of pre-existing cognitive decline.

Initial preoperative low-baseline scores during neuropsychological testing are associated with age, hypertension, and low-education levels, indicating mild cognitive decline: this may increase the risk of POCD. In patients undergoing CAGB, 20–46% have some degree of preoperative cognitive impairment. Patients with pre-existing magnetic resonance imaging evidence of cerebral small vessel disease also have a higher risk of POCD. Thus, preoperative cognitive dysfunction may be an indication of cerebrovascular disease per se. Some studies comparing patients’ neurological outcomes after CAGB with outcomes of non-surgical coronary artery disease patients have shown that cognitive decline is similar in both groups. This suggests that the cognitive dysfunction seen post-cardiac surgery may be simply a reflection of the natural history of a patient population already at high risk for cognitive decline secondarily to their cerebrovascular and cardiovascular disease.2

The term cognitive reserve has been coined, and this relates to the resilience of the brain to an insult or pathology. It is thought to be because of individual differences in cognitive processes or neural networks underlying task performance that allows some people to cope better than others with brain stressors. Equally as important to the quantity of available synapses is anatomical variability at the level of the neural networks. The more neurone synapses we form throughout life from education, particularly in early childhood, the greater the defense against brain injury, thus a higher level of education offers some protection against POCD. This may be attributable to the fact that we need to damage more neurones to reach the threshold where we start to see clinical symptoms of cognitive decline. POCD is also associated with low preoperative cognitive function and neurodegenerative conditions like Parkinson’s disease and Alzheimer’s disease.

There are also some genetic variables that come into play and are suggestions that patients with apoprotein E4 genotype are more susceptible to POCD. Furthermore, certain C-reactive protein (CRP) and P-selectin genotypes are more prone to POCD. All these genotypes display a higher incidence of inflammation and have higher CRP levels and platelet activation, indicating that strategies to decrease perioperative inflammation may be useful.13

Preoperative left ventricular dysfunction with an ejection fraction of <30% is associated with POCD because poor cardiac function...
can precipitate secondary low cerebral flow. However, this association is unclear.

**Methods to minimize POCD in cardiac surgery**

**Preoperative**

To prevent POCD, the focus should be on identification of high-risk patients, with meticulous preoperative assessment. In some cases, preoperative cognitive screening has been suggested. However, this may have resource implications as these neurocognitive test batteries require the assistance of specially trained neuropsychologists and are very time consuming. Such assessments, however, may help patients and clinicians in the decision-making process before surgery and could allow the planning of individualized surgical and anaesthetic techniques.

**Intra-operatively**

Intra-operatively, different surgical and anaesthetic strategies can be considered and used, as elucidated from the factors discussed above. In order to minimize POCD, the main goal should be to maintain haemodynamic stability and preserve cerebral blood flow and perfusion pressure to ensure adequate oxygen delivery. Surgically, minimally invasive procedures may result in a reduced surgical stress response and in theory could reduce the degree of systemic inflammation. There are also technological advances in CPB circuits which may reduce the migration of emboli.

Pharmacologically, as mentioned above, volatile anaesthetic agents may offer some protection against POCD. However, larger better design randomized control trials are needed to determine if there are indeed beneficial effects. Another anaesthetic agent that has been investigated is the N-methyl-D-aspartate (NMDA)-receptor antagonist, ketamine. It has been shown that the incidence of early POCD was lower after receiving a single dose of ketamine at anaesthetic induction. However, this study was small. Opiates contributed to delirium after operation but did not increase the risk of POCD.

Lidocaine was thought to be potentially neuroprotective in cardiac surgery by decreasing the inflammatory response associated with CPB by crossing the blood–brain barrier and modulating cerebral inflammation. There is no evidence for this and when administered to diabetic patients they were in fact more likely to suffer cognitive decline in the 6-week postoperative period.12

It is well established that peri-insult hyperglycaemia leads to worse clinical outcome in the setting of strokes and traumatic brain injury. In a recent study of 525 patients undergoing CABG, it was found that hyperglycaemia was associated with a decrease in cognitive performance at 6 weeks, although this effect was not reproducible in diabetic patients.13 Possible mechanisms involve neuronal lactic acidosis with subsequent lipid peroxidation and intracellular calcium accumulation, under anaerobic conditions. Other theories include the excitatory neurotransmitter glutamate and corticosteroid production, which are both pivotal in neuronal death.

Many advanced intra-operative cerebral monitoring devices are currently available. These can be used to guide manipulation of physiology in order to assist in the reduction of the incidence of POCD. They are discussed below. Compared with monitoring other organs such as the heart during anaesthesia, monitoring the brain is less developed and less regularly used. It is also pertinent that we understand that it is not the process of monitoring, but the subsequent anaesthetic interventions which may decrease the risk of POCD and improve outcome.

Cerebral oximetry is a non-invasive monitor which uses near-infrared spectroscopy technology to estimate rSO2. It utilizes the varying absorbance spectrum of oxygenated and deoxygenated haemoglobin. An example of such a monitor is the Invasive Cerebral Oximeter (Somanetics/Covidien, MI, USA). This particular device assumes that blood in the brain is 70% venous and 30% arterial. It does not directly look at brain function, but indicates the balance between brain oxygen supply and demand. Normal range of rSO2 is between 60 and 80%. The most common intervention trigger may be either an absolute decrease of rSO2 to ≤50%, or a 20% decrease from the baseline rSO2. However, different targets for rSO2 less used have been identified in other studies.

In one study, patients with significant intra-operative decreases in rSO2 were shown to have higher incidences of POCD and poorer outcomes with prolonged hospital length of stay. These patients had desaturations of more than 3000 s below 50%, showing that it is the total burden of cerebral hypoxia (i.e. total time spent below a rSO2 threshold) that is important rather than a reduction to an absolute rSO2 threshold. However, other trials have been unable to reproduce similar results, despite showing a lower incidence of organ morbidity and mortality when rSO2 values are maintained. Hence, more trials are required. Of recent interest, preoperative baseline rSO2 has been also used to predict patient’s morbidity and mortality after surgery.16 This can actually be useful for risk stratification of patients before operation if considered in conjunction with the other risk factors. Some have suggested that the brain may be an ‘index organ’.17 Cerebral desaturations have correlated with many adverse systemic outcomes such as prolonged ventilation and renal failure. Therefore, rSO2 may be a marker of the adequacy of perfusion within other organs and measures to improve rSO2 may optimize systemic perfusion too. It is important to note that because of the brain having a preferential perfusion, normal cerebral saturations may occur in the context of significant impairment in oxygen delivery to other organs such as the kidney and gut.

A number of interventional protocols aimed at improving outcomes post surgery as have been suggested, such as Murkin’s protocol18 (see Fig. 1), can be implemented when the rSO2 decreases >20% compared with baseline or an absolute decrease <50% occurs. The use of these protocols may shorten hospital stay and decrease major organ morbidity and mortality. However, it has not been proved that this reduces the incidence of POCD.

To measure depth of anaesthesia, both the raw electroencephalography (EEG) and processed EEG such as the bispectral index (BIS) have been utilized. The usage of BIS is controversial but
POCD has been linked to an increase in cumulative deep hypnotic time, which is defined as the amount of time BIS is <45. This could be attributable to anaesthesia ‘overdose’ causing neurotoxicity. An accumulation of cumulative deep hypnotic time is associated with an increase in 1-yr mortality. Moreover, BIS may also play a role in titrating anaesthesia to avoid haemodynamic instability and hypoperfusion caused by anaesthetic agents. Also when hypertension occurs with optimal depth of anaesthesia, it could be treated with a vasodilator instead deepening anaesthesia, which could be neurotoxic.

Post operation

Postoperative hypoxia may be a risk factor for the development of early POCD. Postoperative complications such as infection, particularly of the respiratory tract, have also been associated with a higher level of POCD. Also, by ensuring the patient’s modifiable cerebrovascular disease risk factors are strictly controlled, the possibility of late POCD can be reduced. Prudent postoperative management should include encouraging a good diet and exercise with regular checks and control of arterial pressure and cholesterol.

Conclusion

POCD is a serious complication of cardiac surgery associated with a wide range of surgical, anaesthetic, and patient factors. As there is no evidence POCD can be treated successfully, emphasis should be on prevention. The use of different modalities of perioperative monitoring may facilitate a reduction in the incidence and severity of POCD. Greater research is required into the pathophysiology of POCD. Once diagnosed, we should aim to provide supportive care and educate patients and their families.

Declaration of interest

None declared.

References

17. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth* 2009; 103 (Suppl.): i3–i13

Please see multiple choice questions 25–28.