



# Current Perspectives on Postoperative Cognitive Dysfunction in the Ageing Population

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## Abstract

Postoperative cognitive dysfunction (POCD) is defined as a prolonged cognitive function impairment that occurs within weeks to months of a surgical procedure. It is especially prevalent in the elderly population, leading to increased morbidity and mortality. As anaesthetic and surgical care continues to improve and become increasingly safer, a significantly greater number of older patients have elective surgical procedures today, yet this comes with an increased POCD risk as they go through the perioperative phases. Although the pathophysiology behind the development of POCD is still under investigation, current causative mechanisms include the mode of anaesthesia administered, anaesthetic used, cerebral hypoperfusion, hyperventilation and neuroinflammation. These findings lend an insight into the importance of being cognisant of the higher likelihood of POCD in at-risk patients, including the elderly, and taking precautions to include preoperative and postoperative cognitive testing, careful monitoring during anaesthesia, blood pressure control and early treatment of postoperative complications as they arise. In this review, we provide an update on the current understanding of the pathophysiology leading to POCD, identifying risk factors, prevention and treatment strategies, with a specific focus on the elderly population.

**Keywords:** Ageing, anaesthesia, frailty, geriatrics, postoperative cognitive dysfunction, postoperative delirium

## Introduction

Postoperative cognitive dysfunction (POCD) is a prolonged impairment in cognitive function that lasts weeks to months following surgery (1). First documented in the late 1800s, it is still a poorly understood problem in the medical community (2). POCD is especially prevalent in the elderly (3, 4). As such, the fragility of cognition in the elderly is already carefully monitored to prevent the manifestation of delirium or the progression to dementia, both of which increase morbidity and are main contributors to major financial burden on our healthcare system (5-7). POCD has been associated with increased mortality, and it can develop as a result of delirium (8). It is therefore crucial to examine any factors that may contribute to the cognitive decline in preoperative patients. With a rapidly increasing need for surgical procedures and an increase in the number of elderly patients undergoing elective surgical procedures that necessitate the use of anaesthetic medications, the medical community is responsible for exploring the risk factors, strategies for prevention and treatment of POCD.

## Epidemiology

The POCD incidence is estimated at 10%-54%. POCD occurs several weeks postoperatively and affects primarily the elderly (9). The ISPOCD1 study found an incidence of 25.8% one week and 9.9% three months postsurgery in patients >60 years who underwent major non-cardiac surgery (10). As the number of surgical procedures in the elderly population increases, so does the need to identify the POCD risk factors (11).

Preoperatively, some established POCD risk factors are similar to those of mild cognitive impairment (MCI), and they include diabetes, poor glycaemic control and low cognitive reserve (12-14). Other MCI risk factors such as obesity, sleep fragmentation and APOE4 homozygosity have shown to have weaker risk associations with POCD (15-17). In addition, preoperative history of cognitive or functional impairment, major coronary bypass surgery, pulmonary disease, alcohol abuse, electrolyte abnormalities, psychoactive medication or preoperative delirium (POD) have all been shown to increase the POCD risk (18-20). Chief among these is an increased risk due to pre-existing MCI, which has a prevalence of 38%-56% in elderly patients. Intraoperatively, cerebral desaturation, a prolonged exposure and depth of anaesthesia have been associated with an increased POCD risk (21). Finally, postoperative patients are at higher risk of developing POCD if they experience POD, infection, respiratory complications, poorly controlled pain or low haematocrit.

The effect of the type of surgery has been debated in POCD. Some factors that implicate the type of surgery are the length of procedure, postoperative complications, stress response or hospitalisation length of stay (22). Previous studies have described a higher incidence of POCD in major cardiac surgeries, such as coronary artery bypass graft, even reporting an incidence of 30%-80% a few weeks post cardiac surgery and 10%-60% three to six months post non-cardiac surgery in the elderly (23). However, recently Evered et al. (24) denied the importance of the surgery type in POCD. Most literature emphasises the need for specific epidemiological research on POCD, and for that reason, a precise definition is required.

### Clinical Presentation

The primary issue facing POCD is finalising a distinct definition. Until this task is complete, clinical identification of POCD will vary between medical professionals. Some general guidelines suggest considering POCD as form of mild cognitive impairment and looking for similar clinical signs to help with diagnosis. Using this concept, POCD can be considered a persistent cognitive dysfunction that gradually develops postoperatively after a period of at least 1 week (25). The ISPOCD1 study identifies POCD as the presence of postoperative deficits in at least one area of mental state, including concentration, attention, memory, executive function, visuospatial ability and psychomotor speed. To achieve a reliable diagnosis, appropriate pre- and postoperative cognitive testing must be performed. Several tests are available to assess the cognitive function and impairment such as the mini mental state exam, Montreal cognitive assessment, Cognistat exam and Postoperative Quality Recovery Scale, as well as several computerised examinations (26). At this point, clinical evidence that suggests a new cognitive decline in postoperative patients from a pre-established baseline can qualify as POCD at the treating physician's discretion.

### Pathophysiology

Although the pathophysiology behind the development of POCD has been debated, causative mechanisms are thought to be the following: the mode of anaesthesia application, anaesthetic choice, hypoperfusion, hyperventilation and neuroinflammation (27). Multiple studies have proposed a possible correlation between the mode of anaesthesia and the subsequent likelihood of developing POCD (Table 1). Specifically, long-term outcomes in patients receiving general anaesthesia or regional anaesthesia have been compared. The study by Mason et al. (28) is based on the hypothesis that general anaesthesia affects gene transcription, receptor efficacy, synaptic vesicle cycling, intracellular calcium homeostasis and anticholinergic effects. However, results did not statistically prove that regional anaesthesia is less likely to cause POCD. Another study involving 483 elderly patients found that POCD was less likely in patients who received regional anaesthesia than in those who received general anaesthesia 1 week postoperatively but that it did not vary significantly 3 months following general or regional anaesthesia (29). While limiting the depth of anaesthesia has been shown to reduce the risk of POD, no such research has been successful with POCD.

Additional research has attempted to correlate the incidence of Alzheimer's disease and specific modes of anaesthesia. Inhaled anaesthetics have been demonstrated to increase the formation of B-amyloid plaques and neurofibrillary tangles in animal models and *in vitro* studies. Such pathologies are typically present in Alzheimer's disease (30, 31). However, a subsequent meta-analysis showed no correlation between previous exposure to inhaled anaesthetics and the development of Alzheimer's disease.

The incidence of POCD is not correlated with the use or avoidance of sedating agents such as propofol when a patient is receiving anaesthesia (Table 2). With this in mind, the use of dexmedetomidine instead of a propofol supplementary for a peripheral nerve block is significantly associated with a reduced incidence of POCD (32). Interestingly, patients who received dexmedetomidine in place of Propofol were found to have a significantly lower postoperative creatinine and a significantly higher postoperative GFR (33). Dexmedetomidine also yielded a significantly lower number of cases of postoperative hyperactive delirium and postoperative agitation.

Another hypothesis addressing the development of POCD involves intraoperative cerebrovascular autoregulation and hypoperfusion. In patients receiving general anaesthesia, the mean arterial pressure may stray outside the range in which cerebrovascular autoregulation can be maintained (Table 3). A study that involved patients undergoing surgery with a cardiopulmonary bypass found that the duration of the longest

**Table 1. Comparing the outcomes of general to regional anaesthesia**

Study	Sample Characteristics (n, age)	Surgery Type	Comparing Pre- and Postoperative Cognition	Results and Conclusions
Mason et al. (28), The impact of general and regional anaesthesia on the incidence of postoperative cognitive dysfunction and postoperative delirium: A systematic review with meta-analysis.	<ul style="list-style-type: none"> <li>• Mean age &gt;50</li> <li>• 21 studies reviewed</li> </ul>	Orthopaedic, urological, vascular, abdominal, cardiovascular	Postoperative cognition -multiple cognitive function tests: all covered domains of cognition, including memory, executive function and calculation (mini mental state examination most common)	Delirium is unlikely to be influenced by the route of anaesthesia. Unable to draw conclusions regarding POCD because no accepted definition exists.
Rasmussen et al. (29), Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients.	<ul style="list-style-type: none"> <li>• Age &gt;60</li> <li>• 428 patients</li> </ul>	Orthopaedic, gynaecologic, vascular, urological, gastrointestinal	Four neuropsychological tests undertaken preoperatively and at 7 days and 3 months postoperatively. POCD was defined as a combined Z score >1.96 or a Z score >1.96 in two or more test parameters.	POCD significantly greater at 1 week in vs patients receiving GA RA. GA POCD: 33/156 (21.2% [15.0-28.4%]) vs RA POCD: 20/158 (12.7% [7.9-18.9%]) (p=0.04)
Seitz et al. (31) Exposure to general anaesthesia and risk of Alzheimer's disease: a systematic review and meta-analysis.	<ul style="list-style-type: none"> <li>• 15 case control studies reviewed</li> <li>• Mean age &gt;=50</li> </ul>	Cardiovascular, neurological	Excluded studies that examined POCD, postoperative delirium, or abnormalities on neuropsychological testing without a diagnosis of dementia (focused only on the outcome of development of AD)	No significant association between any exposure to GA and risk of AD (pooled OR: 1.05; 95% CI: 0.93-1.19, Z=0.80, p=0.43)

GA: general anaesthesia; RA: regional anaesthesia; AD: Alzheimer's disease

**Table 2. Comparison of intraoperative sedation using dexmedetomidine to propofol**

Study	Sample (n, age)	Surgery Type	Comparing Pre- and Postoperative Cognition	Results and Conclusions
Intraoperative sedation with dexmedetomidine is superior to propofol for elderly patients undergoing hip arthroplasty (32).	<ul style="list-style-type: none"> <li>• 296 patients</li> <li>• Age ≥65</li> <li>• Prospective, randomised controlled study</li> </ul>	Total hip arthroplasty	Preoperative and postoperative cognitive dysfunction was assessed with a mini mental state examination.	Patients sedated with dexmedetomidine had lower incidences of postoperative delirium and postoperative cognitive dysfunction than patients sedated with Propofol.
Intraoperative dexmedetomidine sedation reduces the postoperative agitated behaviour in elderly patients undergoing orthopaedic surgery compared to the Propofol sedation (33).	<ul style="list-style-type: none"> <li>• 855 patients</li> <li>• Age ≥65</li> <li>• Retrospective cohort study</li> </ul>	Orthopaedic surgery	Richmond Agitation-Sedation Scale	Incidence of agitation was lower in the dexmedetomidine group compared with the propofol group (6 [2.3%] vs. 17 [6.5%], p=0.027)

cerebrovascular autoregulation impairment was significantly associated with the occurrence of POCD (34). Currently,

there is no consensus on an optimal mean arterial pressure during cardiopulmonary bypass. Using near-infrared spec-

**Table 3. Exploring the role of haemodynamic status and cerebral oxygen delivery on postoperative cognitive dysfunction**

Study	Sample (n, age)	Surgery Type	Comparing Pre- and Postoperative Cognition	Results and Conclusions
Svagzdiene et al. (34) Cerebrovascular autoregulation impairment during cardiac surgery is related to postoperative cognitive dysfunction.	<ul style="list-style-type: none"> <li>• 59 patients</li> <li>• Observational study</li> </ul>	Coronary artery bypass graft surgery with CPB	Neuropsychological tests the day before and 10 days following surgery.	Duration of the single longest cerebrovascular autoregulation impairment event was found reliably associated with occurrence of POCD (p<0.05)
Ono et al. (35) Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality.	<ul style="list-style-type: none"> <li>• 450 patients</li> <li>• Age ≥65</li> <li>• Clinical study</li> </ul>	Coronary artery bypass graft and/or valve surgery with CPB	Major morbidity and operative mortality using the Society of Thoracic Surgeons National Cardiac Surgery Database definition	Duration and magnitude of blood pressure below the limits of cerebrovascular autoregulation was associated with major morbidity or operative mortality after cardiovascular surgery (odds ratio, 1.36; 95% confidence interval, 1.08-1.71; P ¼ .008)
Feinkohl et al. (38) Hypertension and Risk of Postoperative Cognitive Dysfunction (POCD): A Systematic Review and Meta-Analysis.	<ul style="list-style-type: none"> <li>• 24 studies reviewed, 4317 patients</li> <li>• Mean age, 63</li> </ul>	All surgery	Meta-analysis with variety of postoperative cognitive assessments	Hypertension was not significantly associated with POCD risk (RR 1.01; 95% CI 0.93, 1.09; p=0.82).

GA: general anaesthesia; RA: regional anaesthesia; CPB: cardiopulmonary bypass

troscopy to monitor cerebral oxygen saturation and the mean arterial pressure as a surrogate for cerebral blood flow, clinicians can monitor cerebral autoregulation in real time during surgery. Research has found a relationship between the mean arterial pressure falling below the lower limit of cerebral autoregulation and an increased incidence of major morbidity and operative mortality. Thus, the blood pressure management during cardiopulmonary bypass using physiologic endpoints to monitor cerebral autoregulation may optimise organ perfusion and improve postoperative outcomes (35).

Cognitive dysfunction has been linked to hyperoxia caused by hyperventilation following surgical procedures involving cardiopulmonary bypass. High oxygen content has been shown to be toxic to many organ systems, including cardiovascular, nervous, respiratory and gastrointestinal. High levels of oxygen increase free-radical formation and oxidative stress. Such stress is particularly damaging to the brain, as neurons have a higher rate of oxygen consumption and lower antioxidant defences (36). In a randomised controlled trial, patients were divided into one group receiving supplemental oxygen at a  $FiO_2$  of 0.35 (normoxic) and another group receiving a  $FiO_2$

of 1.0 (hyperoxic). It is currently suggested that monitoring and maintaining normal levels of oxygen intraoperatively, and avoiding a hyperoxic state, will reduce the incidence and presentation of POCD (37). The role of hypertension and risk of POCD is also being investigated, as one study found that hypertension is not associated with the POCD development, while also admitting that many confounding variables have not been adjusted for (38).

Anaesthesia during surgery is thought to produce a neuroinflammatory state that leads to POCD. The role of inflammation leading to neuronal dysfunction has been assessed. Systemic inflammation from bacterial LPS produces both working memory deficits and acute brain injury by acting on hippocampal neurons, causing hyperexcitation and permanent loss of membrane potential (39). Specifically, preoperative elevations in Il-6 and Il-8 were associated with poorer cognitive function postoperatively (40). POCD patients also had an increased plasma TNF- $\alpha$  and a decreased IGF-1 when compared to healthy patients (41). Neuroinflammation and oxidative stress secondary to anaesthesia are also thought to be caused by interrupted plasticity of neurons and

interference in glutamate signalling (Table 4). The need for neuroprotective agents is therefore justified. Although more research needs to be conducted before definitive results can be concluded, lidocaine, ketamine, Cox II inhibitors, minocycline, and dexmedetomidine currently show the most neuroprotective potential (42, 43). The use of remifentanyl instead of fentanyl is correlated with lower levels of inflammation (specifically IL-6) on postoperative Day 7, but no correlation was found between the remifentanyl use and a decreased incidence of POCD (44).

**Differentiating postoperative delirium from postoperative cognitive dysfunction**

Differentiating POCD from POD is an important step to guide future clinical research (Table 5). POD is a subset of

delirium and is defined in DSM-5 as a disturbance in attention and awareness, an acute change from baseline, and a disturbance in cognition that cannot be explained by an existing cognitive or otherwise attributable disorder. Millions are spent annually to alleviate the burden of POD, and current studies focus on addressing the risk of stratification, geriatric consultation, multidisciplinary programmes, optimising depth of anaesthesia, opioid-sparing pain management and polypharmacy avoidance (45). POCD also poses a significant burden on healthcare worldwide, but statistical analysis is thus far most limited by the inability of many POCD patients to adhere to study guidelines (46).

Although POCD currently has no agreed-upon diagnostic criteria, it broadly includes a prolonged impairment in cogni-

**Table 4. Exploring an inflammatory mechanism for the development of postoperative cognitive dysfunction during general anaesthesia**

Study	Sample (n, age)	Comparing Pre- and Postoperative Cognition	Results and Conclusions
Skvarc et al. (42) Postoperative Cognitive Dysfunction: An exploration of the inflammatory hypothesis and novel therapies.	<ul style="list-style-type: none"> <li>Multi-study review</li> </ul>	Meta-analysis with variety of postoperative cognitive assessments	Neuroinflammation and to surgery and anaesthesia is strongly implicated in POCD. Interruption of synaptic plasticity and glutamate signalling are potential mechanisms.
Nemeth et al. (43) Influence of the postoperative inflammatory response on cognitive decline in elderly patients undergoing on-pump cardiac surgery: A controlled, prospective observational study.	<ul style="list-style-type: none"> <li>42 patients</li> <li>Age ≥60</li> </ul>	Cognitive function and mood state were preoperatively and postoperatively (7 days following), tested with a set of five neurocognitive tests and two mood inventories.	The low inflammatory and high inflammatory groups did not vary in the scores of neurocognitive tests and frequencies of POCD (7 vs 8 cases, respectively, p>0.05).
Kline et al. (40) Perioperative inflammatory cytokines in plasma of the elderly correlate in prospective study with postoperative changes in cognitive test scores.	<ul style="list-style-type: none"> <li>31 patients</li> <li>Age ≥ 65</li> <li>Prospective non-interventional non-randomised study</li> </ul>	Digit Span Forward and Digit Span Backward cognition exams	Increase in inflammatory burden correlated with a greater decline in cognitive performance (IL6, IL8; r>-0.560; p≤ 0.008)
De Cosmoso et al. (44) Effect of remifentanyl and fentanyl on postoperative cognitive function and cytokines level in elderly patients undergoing major abdominal surgery.	<ul style="list-style-type: none"> <li>622 patients</li> <li>Age ≥60</li> <li>Randomised double-blind controlled study</li> </ul>	Stroop Colour Word Interference Test, Visual Verbal Learning Test, MMSE, Test of Rey	The use of remifentanyl did not reduce the incidence of POCD. IL-6 levels were lower the 7 <sup>th</sup> day after surgery for remifentanyl group (p=0.04)
Jiang et al. (41) Circulating TNF-α levels increased and correlated negatively with IGF-I in postoperative cognitive dysfunction.	<ul style="list-style-type: none"> <li>44 patients</li> </ul>	Mini Mental Status Exam	POCD was associated with lower IGF-1 levels (114.37±9.55 vs. 136.08±10.61 µg L <sup>-1</sup> , p<0.0001) and higher TNF-α levels (45.46±4.49 vs 39.27±4.99 ng L <sup>-1</sup> , p=0.0001). Combined monitoring of TNF- α and IGF-1 may give insight into POCD pathogenesis.

**Table 5. Comparing postoperative delirium to postoperative cognitive dysfunction**

	POD	POCD
Clinical Findings	Neuropsychological syndrome characterised by disturbance in attention and awareness, altered level of consciousness, acute change from baseline, disturbance in cognition, all not explained by pre-existing neurocognitive condition. There is evidence of an attributable cause.	No agreed consensus, but common findings include prolonged impairment of cognitive function after surgery with limitations in memory, attention, intellectual ability and executive function
Postoperative time to onset	24-72 hours	1 week-1 month
Research Diagnosis	Clinical findings and delirium assessment methods: CAM-ICU test, MMSE	Deterioration from preoperative cognition tests to postoperative cognition tests (MMSE, Richmond Agitation-Sedation Scale, t-MoCA, Digit Span Forward/Digit Span Backward, Stroop Colour Word Interference Test, Visual Verbal Learning Test)
Long-term complications	POCD	Additional research required

POD: postoperative delirium; POCD: postoperative cognitive dysfunction; CAM-ICU: Confusion Assessment Method for the ICU; MMSE: Mini Mental Status Exam; t-MoCA: Telephone Montreal Cognitive Assessment

tive function after surgery with deficits in memory, intellectual ability and executive function. While POD may develop between 24 and 72 hours following surgery, POCD may occur anywhere between 1 week to 1 month afterwards. Inadequate sample sizes renders many POCD clinical studies statistically insignificant, indicating the need for a structured consensus on a POCD definition (47). Research also indicates that many patients with POD may go on to develop POCD (48).

**Prevention and improving outcomes**

Outlining parameters to clinically assess POCD is required first to identify factors and guide the prevention of its development. This includes the incorporation of pre- and postoperative neuropsychological tests for POCD diagnosis into presurgical routine (49). Rasmussen et al. (23) point out that special considerations must be made when using neuropsychological exams. The tests must possess a high sensitivity for POCD and a clear definition of what constitutes as postoperative change. O’Brien et al. (1) state that change within one standard deviation from baseline may be a good starting point for identifying POCD. Finally, we should remember the preoperative setting is one of efficiency, and thus preoperative cognitive testing should not delay the process to the point that physicians will not use them regularly.

Knowing patient baselines can prove important for not only diagnosis of POCD, but also prevention. Several preoperative measures can be taken to prevent POCD and hopefully improve patient outcomes. For example, O’Brien et al. (1) has identified that cognitive training in preoperative patients reduces POCD incidence. They also point out that patients should be carefully assessed for factors such as polypharmacy that may predispose them to delirium. Also, assessing the patient for weakness or frailty may alert the healthcare team

to extra precautions to be taken. These kinds of interventions are especially important in patients with known risk factors for POCD as discussed above. Finally, Lu et al. (50) found that pretreatment with parecoxib sodium combined with dexmedetomidine followed by a continuous low dose infusion causes a decrease in the incidence of POCD in patients undergoing arthroscopy by over 10%. This combined therapy is theorised to improve the sleep quality as, well as provide the central nervous system protective, anti-inflammatory and improved analgesic effects. This intervention should be considered especially in high-risk patients, moving forward.

Intraoperatively, other aspects to consider to reduce the incidence are the extent and duration of anaesthesia. Two interventional approaches address this: minimise the length of exposure accompanied by careful monitoring while exposed. Chan et al. (51) have shown a decrease in POCD at 3 months with monitoring of the brain activity via bispectral index (BIS) and an appropriate adjustment of anaesthetics during the procedure. However, Radtke et al. (52) found that the BIS guided anaesthesia decreased the risk of POD, but not POCD. Chen et al. (53) also found that the use of inhaled versus total intravenous anaesthetics for cardiac surgery produced higher postoperative scores on the mini mental state exam. Apart from anaesthetics, it is appropriate to try and control other potential pathophysiological causes. Sun et al. (54), for example, conducted a study based on the hypothesis that intraoperative hypotension contributes to POCD. They found that controlling blood pressure intraoperatively with nicardipine and nitroglycerine or nicardipine with other antihypertensives, such as esmolol, reduced the incidence of POCD in patients with cardiac ablation.

Lastly, postoperative management is crucial to POCD prevention. Early identification and treatment of postoperative

complications, such as delirium and infection, may decrease the POCD risk. Special attention should be paid to polypharmacy and pain relief in elderly postoperative patients, which can be difficult in and of itself, in case this triggers the progression to POCD or delirium.

## Conclusion

With the rapid increase of the elderly population undergoing elective surgical procedures, understanding their vulnerabilities to POCD, and the morbidity and mortality it can cause, only increases in importance. POCD is a well-documented phenomenon that places patients in a daunting situation. The first step is undoubtedly settling upon a finite definition of POCD, independent of CI and POD. Despite that they share many of the same risk factors, establishing a POCD definition will allow for homogeneity among studies and create a clear path for POCD research. Current research presents several theories as to the pathogenesis of POCD, most prominent among them being increased inflammation, hypoperfusion and anaesthetic use during surgery. Prior to this, physicians can take precautions with patients to prevent POCD, such as pre- and postoperative cognitive testing, careful monitoring during anaesthesia, blood pressure control and early treatment of postoperative complications as they arise. The research and understanding of POCD could significantly change the perioperative, and especially the postoperative, experience for elderly patients from a time of fearful tension to the one of safety and healthy recovery.

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