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Invited review article

Postoperative cognitive decline

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Abstract
Memory loss and lack of concentration are symptoms that frequently occur in patients who have undergone a surgical procedure. Although cognitive function can be assessed using neuropsychological tests, reliable diagnosis of postoperative cognitive decline (POCD) appears to be difficult. Therefore, the true incidence of POCD is unknown. Severe POCD, which is apparent even without neuropsychological testing, is reported most frequently after cardiac and hip-replacement surgery. In these cases, POCD probably reflects microembolic brain injury. Apart from the nature of the surgical procedure, advanced age is the most important risk factor for POCD. The anesthetic technique is not a determinant of POCD: the risk of POCD appears to be similar after both general and regional anesthesia.

Key words Postoperative cognitive decline · POCD · Neuropsychological tests

Introduction

After a surgical procedure, patients frequently report memory loss and lack of concentration. Some patients indicate that they are "just not the same" even if they underwent their surgery several years previously. Symptoms of subtle cognitive decline after surgery are usually described as "postoperative cognitive decline (POCD)." Patients often attribute these symptoms to their anesthesia.

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Cognition

Cognitive functions such as perception, language processing, attention and memory functions, and abstract thinking are crucial for daily life activities, varying from everyday tasks such as driving and cooking to complex social interaction. One speaks of cognitive dysfunction when these processes do not go smoothly. Patients often describe their dysfunction as memory loss, lack of concentration, or slowness in executive and abstract functions.

Measuring cognition

There are many tests to measure cognitive performance [1,2]. These vary from the well-known "mini mental state examination (MMSE)" to more advanced and sometimes computerized neuropsychological tests. Examples are the measurements of reaction time or verbal and nonverbal memory. Every test, however, has its limitations. The MMSE has a ceiling effect: most patients obtain the maximum score and this test is therefore not suited to detect subtle cognitive decline. Often a series of five to ten different neuropsychological tests are used to measure different domains of cognitive functioning. These domains may include verbal and language skills, memory and learning, attention, concentration and perception, visual and spatial skills, visual motor and manual skills, numerical skills, executive functions, and composite measures [3]. There are even neuropsychological tests for laboratory animals; for example, tests measuring the time a thirsty rat needs to track down drinking water [4]. These tests are used in experimental settings to study disturbances in learning and memory functions, attributed to, for example, the use of anesthetics.

Definition and prevalence of POCD

After the patient has completed one or more neuropsychological tests, the presence or absence of POCD needs to be determined [1]. For some tests, tables are available with normal values, allowing a comparison of the patient's performance with that of groups similar in age, sex, and educational level.

In daily practice patients are often tested only when the suspicion of POCD has arisen after the operation. For research purposes, patients are tested several times before and after an operation to determine the presence or absence of POCD. The postoperative performance will then be compared to the preoperative performance. However, a person's cognitive performance varies by nature and so will the scores obtained by repeated neuropsychological testing in that person. Besides the phenomena of natural fluctuation in cognitive test performance and regression to the mean there can be learning effects as well, as seen in the frequently used word-learning tasks [1]. To correct for these effects information is needed about test-retest reliability and parallel versions of the tests used. Moreover, there is no consensus about the extent of the decline in test performance that is needed to speak of POCD. Therefore the prevalence of this condition depends on the definition used [5–7]. Some researchers even state that POCD rarely occurs, but is only diagnosed based on wrongful interpretations of the results of neuropsychological tests [8]. An alarming prevalence of POCD, of more than 30% at 1 year after coronary bypass surgery, decreases to 10% when applying a more conservative definition [6,9].

By including nonsurgical controls in a study, who repeatedly undergo the same neuropsychological tests, the natural fluctuation in test results can be corrected for. In this way a more reliable estimate of the prevalence of POCD can be obtained.

In a well-designed observational study in 1218 patients more than 65 years of age, undergoing major, noncardiac surgery, the incidence of POCD was quantified [10]. The authors also recruited 321 controls, who did not undergo an operation, but who were also repeatedly tested with neuropsychological tests. One week after the operation a prevalence of POCD of 26% was found. This decreased to 10% at 3 months postoperatively. A similar prevalence was found 12 months after the operation. At every time interval an incidence of POCD of 3%, according to the definition used, was found in the nonsurgical controls. Other studies show that from 1 year after surgery onward the prevalence of POCD increases again. However, it is unknown whether this can be attributed to the surgery or to natural aging effects and other unrelated factors [11].

Risk factors

Over the years a number of risk factors for the development of POCD have been identified. Cardiac surgery and specific orthopedic procedures are interventions with a relatively high incidence of POCD [11–13]. In general, larger and more invasive operations, such as abdominal, thoracic, and vascular surgery, present a larger risk than smaller, simpler procedures, such as outpatient surgery [14].

Irrespective of the type of surgery, advanced age is a major determinant of POCD [10–12, 15]. Only few studies have looked at younger populations. In a study of 508 patients between 40 and 60 years of age a prevalence of 6% was reported 3 months after noncardiac surgery, while the prevalence reported in the 183 nonsurgical controls was 4% [16]. Hardly any studies of POCD are conducted in patients younger than 40 years of age.

Oxygen saturation and blood pressure frequently drop during operations and in the first days and nights postoperatively. Although this has been subjected to extensive research, these parameters do not seem to be determinants of POCD [10]. Genetic make-up, such as the presence of apolipoprotein-E4 (the "Alzheimer") allele, appears to play no evident role as a risk factor for POCD either [17,18].

Several other risk factors, including lower educational level, a history of previous cerebral vascular accident, POCD at hospital discharge [15], the postoperative pain treatment regimen [19], and a history of alcohol abuse [20] are reported to influence the occurrence and severity of POCD at varying postoperative intervals.

Pathophysiology

It is a tempting idea to attribute POCD to the use of intravenous or volatile anesthetics. Although the regularly used hypnotics and analgesics cannot be traced in the blood anymore within a few days after an operation, it is conceivable that they may cause structural changes to the nerve system, which remain present for a longer period of time. Some evidence has been found in animal studies, and in in vitro experiments, that volatile anesthetics contribute to POCD through enhancement of the oligomerization and cytotoxicity of Alzheimer disease-associated peptides [21,22]. The theory that anesthetics may modulate new cell production and lead to POCD through anesthetic-induced suppression of neurogenesis has been disproved by Tung et al. [23]. However, there are no clinical studies supporting these in vitro findings so far.

A surprising, but consistent, finding which argues against general anesthetics as a cause of POCD is the

fact that the incidence of POCD after regional anesthesia and after general anesthesia is similar [24,25]. In 19 trials patients were randomized to general or regional techniques. In only 1 of these studies a small difference in the incidence of POCD was detected, in favor of patients allocated to regional anesthesia [25]. A limitation of these studies is the fact that patients operated under regional anesthesia frequently received sedatives, usually low-dose benzodiazepines or propofol.

Nevertheless, these findings suggest that factors other than anesthetic agents are responsible for the development of POCD. POCD after hip replacement procedures is associated with fat emboli arising from the bone marrow of the femur during insertion of the prosthesis [26]. Mostly emboli get stuck in the lung capillaries, but they can also end up in the brain. This most likely coincides with an open foramen ovale, which can be found in around 25% of the population.

POCD after cardiac surgery is attributed to the use of cardiopulmonary bypass (CPB) [27]. The use of CPB itself or manipulation of the aortic root can cause microemboli. Just as in the example of hip replacement surgery, emboli can be detected intraoperatively in the carotid artery or the arteria cerebri media with the use of Doppler echography. Magnetic resonance imaging and postmortem findings in patients after cardiac surgery reveal multiple small defects in the brain, most likely caused by these microembolic processes [27]. In a clinical trial comparing coronary bypass operations with and without CPB, POCD was also found in patients randomized to offpump coronary bypass surgery [9,28]. Thus, the role of CPB in the development of POCD is probably not as crucial as always suspected.

There is conflicting evidence on the effect of the processing of cardiotomy blood with a cell saver versus direct reinfusion through the cardiotomy suction reservoir. A study done by Djaiani et al. [29] showed a significant reduction in POCD with a cell saver, but a study done by Rubens et al. [30] failed to show the benefit of a cell-saver on cognitive outcome.

Independent of the kind of surgical procedure (cardiac or noncardiac) or anesthetic regimen, it is known that surgery-induced tissue damage activates the peripheral immune system, resulting in the release of inflammatory mediators. This inflammatory response contributes to POCD through the per- and postoperative secretion of cortisol, cytokines, and other inflammatory mediators [31–33].

Consequences for the patient

A small proportion of patients experience severe cognitive decline after their operation, without the focal signs consistent with cerebral infarction [12,13]. These patients are sometimes unable to resume their work, or they have to be admitted to long-term care facilities. After cardiac surgery the incidence of this severe POCD is about 3% [12]. The percentage of patients with severe POCD after noncardiac surgery is unknown, but is probably lower.

A high proportion of patients self report postoperative cognitive impairment through questionnaires. This impairment does not necessarily affect their daily activities. Compared with the strict criteria based on neuropsychological testing, subjective reporting overestimates the incidence of POCD [16,34].

Depression is often associated with subjective cognitive decline [16,34]. However, no clear association has been established between depression and POCD according to neuropsychological tests [16]. Also, there is no apparent relationship between a decline in neuropsychological test results and quality of life [9,12]. This confirms that the diagnosis "POCD", as established by means of neuropsychological tests, has little significance in real life for the individual patient, but is merely an outcome measure in research settings.

Conclusion

Cognitive functioning is a soft outcome measure, and it is extremely difficult to measure subtle differences in cognitive performance. The true prevalence of POCD is therefore uncertain. Cardiac surgery and certain orthopedic interventions in particular can be complicated by cognitive decline. After these procedures, POCD is probably a result of microembolic injury. There is little evidence that POCD is caused by general anesthesia.

References

1. van Dijk D, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R. Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. J Thorac Cardiovasc Surg. 2000;120: 632–9.
2. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The assessment of postoperative cognitive function. ISPOCD Investigators. The International Study of Postoperative Cognitive Dysfunction. Acta Anaesthesiol Scand. 2001;45: 275–89.
3. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anesthesiology. 2007;106:572–90.
4. Dieleman JM, de Lange F, Houston RJ, Biessels GJ, Bar PR, Mackensen GB, Grocott HP, Kalkman CJ. Cardiopulmonary bypass and long-term neurocognitive dysfunction in the rat. Life Sci. 2006;79:551–8.
5. Selnes OA, Pham L, Zeger S, McKhann GM. Defining cognitive change after CABG: decline versus normal variability. Ann Thorac Surg. 2006;82:388–90.

6. Keizer AM, Hijman R, Kalkman CJ, Kahn RS, van Dijk D. The incidence of cognitive decline after (not) undergoing coronary artery bypass grafting: the impact of a controlled definition. Acta Anaesthesiol Scand. 2005;49:1232–5.
7. Lewis MS, Maruff P, Silbert BS, Evered LA, Scott DA. The influence of different error estimates in the detection of postoperative cognitive dysfunction using reliable change indices with correction for practice effects. Arch Clin Neuropsychol. 2007;22: 249–57.
8. Selwood A, Orrell M. Long term cognitive dysfunction in older people after non-cardiac surgery. BMJ. 2004;328:120–1.
9. van Dijk D, Jansen EW, Hijman R, Nierich AP, Diephuis JC, Moons KG, Lahpor JR, Borst C, Keizer AM, Nathoe HM, Grobbee DE, de Jaegere PP, Kalkman CJ. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. Octopus Study Group. JAMA. 2002;287: 1405–12.
10. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD Investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998;351:857–61.
11. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395–402.
12. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med. 1996;335:1857–63.
13. Bitsch MS, Foss NB, Kristensen BB, Kehlet H. Acute cognitive dysfunction after hip fracture: frequency and risk factors in an optimized, multimodal, rehabilitation program. Acta Anaesthesiol Scand. 2006;50:428–36.
14. Canet J, Raeder J, Rasmussen LS, Enlund M, Kuipers HM, Hanning CD, Jolles J, Korttila K, Siersma VD, Dodds C, Abildstrom H, Sneyd JR, Vila P, Johnson T, Munoz CL, Silverstein JH, Nielsen IK, Moller JT. Cognitive dysfunction after minor surgery in the elderly. ISPOCD2 Investigators. Acta Anaesthesiol Scand. 2003;47:1204–10.
15. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108:18–30.
16. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, Kuipers HM, Hanning CD, Siersma VD, Kristensen D, Canet J, Ibanaz MT, Moller JT. Postoperative cognitive dysfunction in middle-aged patients. ISPOCD2 Investigators. Anesthesiology. 2002;96:1351–7.
17. Abildstrom H, Christiansen M, Siersma VD, Rasmussen LS. Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. ISPOCD2 Investigators. Anesthesiology. 2004;101:855–61.
18. Silbert BS, Evered LA, Scott DA, Cowie TF. The apolipoprotein E epsilon4 allele is not associated with cognitive dysfunction in cardiac surgery. Ann Thorac Surg. 2008;86:841–7.
19. Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am J Geriatr Psychiatry. 2007;15:50–9.
20. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Hyde TF, Reddy DM, Hudetz AG, Warltier DC. Postoperative cognitive dysfunction in older patients with a history of alcohol abuse. Anesthesiology. 2007;106:423–30.
21. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, Pidikiti R, Keller JM, Eckenhoff MF. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology. 2004;101:703–9.
22. Hanning CD, Blokland A, Johnson M, Perry EK. Effects of repeated anaesthesia on central cholinergic function in the rat cerebral cortex. Eur J Anaesthesiol. 2003;20:93–7.
23. Tung A, Herrera S, Fornal CA, Jacobs BL. The effect of prolonged anesthesia with isoflurane, propofol, dexmedetomidine, or ketamine on neural cell proliferation in the adult rat. Anesth Analg. 2008;106:1772–7.
24. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. JAMA. 1995;274:44–50.
25. Wu CL, Hsu W, Richman JM, Raja SN. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Reg Anesth Pain Med. 2004;29:257–68.
26. Edmonds CR, Barbut D, Hager D, Sharrock NE. Intraoperative cerebral arterial embolization during total hip arthroplasty. Anesthesiology. 2000;93:315–8.
27. Newman MF, Mathew JP, Grocott HP, Mackensen GB, Monk T, Welsh-Bohmer KA, Blumenthal JA, Laskowitz DT, Mark DB. Central nervous system injury associated with cardiac surgery. Lancet. 2006;368:694–703.
28. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW, Grobbee DE, de Jaegere PP, Kalkman CJ. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. Octopus Study Group. JAMA. 2007; 297:701–8.
29. Djaiani G, Fedorko L, Borger MA, Green R, Carroll J, Marcon M, Karski J. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. Circulation. 2007;116:1888–95.
30. Rubens FD, Boodhwani M, Mesana T, Wozny D, Wells G, Nathan HJ. The cardiotomy trial: a randomized, double-blind study to assess the effect of processing of shed blood during cardiopulmonary bypass on transfusion and neurocognitive function. Circulation. 2007;116:I89–I97.
31. Denicoff KD, Rubinow DR, Papa MZ, Simpson C, Seipp CA, Lotze MT, Chang AE, Rosenstein D, Rosenberg SA. The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. Ann Intern Med. 1987;107:293–300.
32. Rasmussen LS, O'Brien JT, Silverstein JH, Johnson TW, Siersma VD, Canet J, Jolles J, Hanning CD, Kuipers HM, Abildstrom H, Papaioannou A, Raeder J, Yli-Hankala A, Sneyd JR, Munoz L, Moller JT. Is peri-operative cortisol secretion related to postoperative cognitive dysfunction? ISPOCD2 Investigators. Acta Anaesthesiol Scand. 2005;49:1225–31.
33. Wan,Y, J Xu, D Ma, Y Zeng, M Cibelli, M Maze. Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology. 2007;106:436–43.
34. Keizer AM, Hijman R, van Dijk D, Kalkman CJ, Kahn RS. Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. Ann Thorac Surg. 2003;75:835–8.