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Review Article

Postoperative Cognitive Dysfunction: Knowns and Unknowns

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ABSTRACT

Aim of review: The aim of this review was to summarize and discuss current status and challenges in our understanding of the diagnosis, risk factors, pathophysiologic mechanisms, and preventions for postoperative cognitive dysfunction (POCD).

Method: We searched and reviewed the articles about POCD published in the past 2 decades using PubMed and Google Scholar.

Recent findings: POCD affects a wide variety of cognitive domains, including attention, memory, executive function and speed of information processing, with the deficits in memory and a reduced ability to handle intellectual challenges being most obvious. The causes of POCD are thought to be multifactorial and may include the preoperative health status of the patient, the patients' preoperative level of cognition, perioperative events related to the surgery itself, and possible neurotoxic effects of anesthetic agents. There are many controversies about POCD, from how it is measured to how long it lasts, to its precise implications for patients, and whether POCD is linked to a long-term risk of developing dementia.

Summary: POCD is a topic of special importance in the geriatric surgical population. Unfortunately, no therapeutic interventions are available to prevent the onset of POCD, strategies for management of these patients should be a multimodal approach involving close cooperation between the anesthesiologist, surgeon, geriatricians, and family members to promote early rehabilitation and avoid loss of independence in these patients. Future researches focusing on the mechanisms involved in POCD are critical for better understanding and management of this cognitive dysfunction after surgery.

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More than sixty years ago, Bedford published a retrospective study of 1193 elderly patients who underwent surgery with general anesthesia during a 5-year period. He observed that cognitive decline occurred in about 10% of the older patients after surgery. Most of these patients had mild problems, but still can function independently. However, 18 cases (1.5%) experienced extreme dementia and remained confused until their death, leading to the conclusion that "operations for elderly people should be confined to unequivocally necessary cases" (1). Although the safety of perioperative care has been improved significantly, the descriptions of cognitive dysfunction in that case series are similar to the complaints of current patients suffering from postoperative cognitive dysfunction or decline (POCD). With the advances in surgical and anesthetic techniques, and in combination with the increased life expectancy, POCD has become an area of focus of anesthesia researches (2- 5). This is reflected partly by the increasing number of articles published on this topic. As the number of surgeries performed worldwide approaches 250 million per year, optimizing postoperative cognitive function

and preventing or treating POCD has become one major public health issue.

POCD affects a wide variety of cognitive domains, including attention, memory, executive function and speed of information processing, with the deficits in memory and a reduced ability to handle intellectual challenges being most obvious (2, 3). Although not limited to aged patients, the incidence and impact of POCD is more profound in aged patients (6). POCD should be distinct from postoperative delirium, which is most often a transient condition that develops acutely in the immediate postoperative period with marked fluctuation in attention and orientation, whereas POCD is much subtler and can be prolonged (6). In addition, POCD tends to be resolved in the majority of patients but certain patients suffered from long-lasting cognitive deficits, which is associated with poor patient outcomes, such as prolonged hospital stay, reduced quality of life, loss of social dependence, and increased mortality (2-5). Although POCD has become a topic of special importance in the geriatric surgical population, there has been a great number of interests and controversies about POCD from how it is measured to how long it lasts, to its precise implications for patients, and whether POCD is linked to a long-term risk of developing dementia.

Definition and Prevalence of POCD

Despite the fact that POCD is not a formal psychiatric diagnosis, the term of POCD is commonly used in the literature and is considered to be a mild neurocognitive disorder (7). It is a syndrome defined by a decline in cognitive performance on a set of neuropsychological tests from before to after surgery (8). Neuropsychological testing for POCD typically includes tests that assess multiple cognitive domains (3, 8). Classically, a series of five to ten different neuropsychological tests are used to measure different domains of cognitive functioning (3). 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, 8). The International Study of Postoperative Cognitive Dysfunction (ISPOCD) used in Study 1 and Study 2 consisted of four neuropsychological tests and seven variables from these four tests were used (2, 3). The advantages of this test battery are that the baseline performance of the patient and the general variability of a control population are taken into account in the way the outcome (Z-score) is calculated (2, 3). It also takes into account both the overall deterioration across all tests and the specific impairment in an individual test. The practice effect is minimized by using parallel, instead of identical versions of the test and by subtracting the average learning effect in the calculation of the Z score (Z=[Postoperative score − preoperative score] − [average learning effect from controls]/standard deviation [SD] for change from baseline in the controls). A composite Z-score is defined as the sum of the seven Z scores and normalized using the SD for that sum in the controls (Z-comp=[Z1 + Z2 + Z3 + Z4 + Z5 + Z6 + Z7]/SD for [Z1 + Z2 + Z3 + Z4 + Z5 + Z6 + Z7] in the controls). Patients were defined as having POCD when at least two Z scores in individual tests or the composite Z score (of all seven variables) were greater than 1.96. The exact value of 1.96 has been chosen as only 2.5% of the controls would have a Z-score>1.96 by chance and the value 1.96 can therefore be interpreted as a substantial deterioration. Also, there are other ways to define POCD, for example, using the 20% decline and 1SD rule to detect POCD, but yielded different sensitivity and specificity (9).

The incidence of POCD reported varies widely depending on the definition, composition of the test battery, and time of postoperative assessment (6). The prevalence of POCD reported to be 30-80% a few weeks and 10-60% after 3-6 months after cardiac surgery, respectively (10). For patients undergoing noncardiac surgery, the ISPOCD reported an incidence of POCD 25.8% at 1 week and 9.9% at 3 months in patients older than 60 yr (3). However, some authors even stated that POCD rarely occurs, but is only based on wrongful interpretations of the results of neuropsychological tests (11). 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 (12). Therefore, it is possible that the arbi-

trary definitions of cognitive decline have resulted in an overestimation of the incidence of POCD (11).

Methodological Limitations for POCD

Although the neuropsychological tests theoretically provide a highly sensitive mean to quantify changes in cognition, differences in test batteries, timing of assessment and criteria for defining neuropsychological decline generate considerable heterogeneity in the data, which limits our ability to compare the results of different studies (6, 13). At present, there is no evidence to suggest that the long-term incidence of cognitive decline differs from that of nonoperative controls. Estimating long-term cognitive decline can be difficult, as normal ageing and dementia interfere with studies with older population. Furthermore, a common problem in POCD studies is the lack of a control group to account for the potential practice effect of repetitive testing (3). In particular, there are no formal criteria to use in assessing and diagnosing this mental disorder associated with surgery, and there is no ideal test being internationally accepted for POCD diagnosis (6).

Duration of POCD

Apart from the disagreement on how POCD diagnosis is defined, it is also unclear how long it may last. This issue is difficult to address for several reasons. It is ethically unreasonable and practically impossible to randomize patients to surgery/anesthesia or placebo treatment group. Without a nonsurgical control group, it is unclear how much of the cognitive dysfunction in surgical patients is truly due to anesthesia, surgery, and perioperative care. The initial rapid decline in cognition seen in patients with POCD occurs much more rapidly than normal age-related cognitive decline. There are few studies investigating the long-term cognitive effects of anesthesia and surgery. Some patients who demonstrated POCD at 10-14 days postoperatively were found to have improved functional scores at 3 months, while others continued to demonstrate POCD symptoms at periods longer than 1 year (3). However, the ISPOCD reassessed a subgroup at 1-2 years after anesthesia and surgery and stated

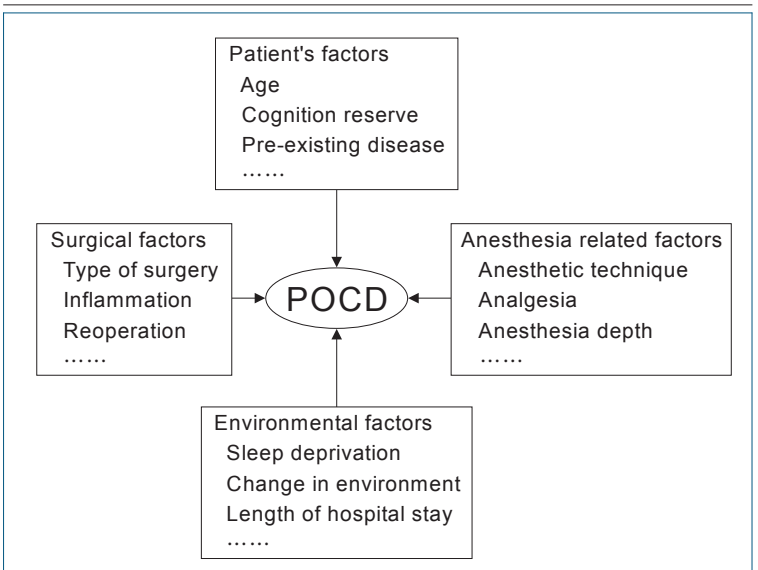

Figure. Proposed Mechanisms or Risk Factors for the Development of POCD.
The causes of POCD are multifactorial and may include the preoperative health status of the patient, perioperative events related to the surgery itself, possible neurotoxic effects of anesthetic agents, and the environmental factors.

that 10.4% of patients have POCD, while 10.6% occurred in non-surgical controls (2). The results of these long-term follow-up studies suggest that cognitive decline is permanent (14). Together, these studies suggest that in certain patients, POCD may be a long-term, possibly permanent alteration in cognitive functioning, and a POCD-dementia continuum is discussed.

Mechanisms Underlying POCD

The causes of POCD have not been clearly elucidated because it is a heterogeneous and multifactorial disorder involving a complex interrelationship between a vulnerable patient with preoperative risk factors and numerous precipitating factors in the perioperative period (15) (Figure). The large variability in cognitive dysfunction after surgery can be caused by inter-individual differences in the susceptibility of neural networks to surgery-induced deterioration. This susceptibility may be the result of genetics and environmental stimuli that influence the vulnerability for neuroinflammation or cause pre-existing neurodegeneration.

Through a combination of retrospective human studies, small prospective biomarker stud-

ies, and experiments in animals, it has been suggested that durable consequences of both anesthesia and surgery occur, and that these intersect with the normal processes of aging, and the abnormal processes of chronic neurodegeneration. It is highly likely that inflammatory cascades are at the heart of this intersection (16-20). In preclinical studies, it has been suggested that neuroinflammation drives early POCD, whereas resolution of neuroinflammation could allow reversal of POCD (20).

In a separate study, it has been shown that oxidative stress induced by hippocampal iron accumulation might induce cognitive impairment in a rat model of POCD (21). A more recent study suggested that surgery-induced Ang II release impairs blood-brain barrier integrity by activating NF-κB signaling pathway, which might contribute to the development of POCD (22). Moreover, it has been demonstrated that the APOEε4 allele was associated with a significantly increased POCD risk at about 1-week post-surgery, but the association disappeared at 1-3 months and 1-year postsurgery, respectively (23).

Our study reported that changes in neuronal phenotype, for example, the disruption in the parvalbumin-positive interneurons might contribute to the isoflurane-induced hippocampus-dependent cognitive impairment in aged mice (4). In addition, it has been suggested that epigenetic mechanism such as aberrant histone acetylation is involved in isoflurane exposure or anesthesia and surgery-induced cognitive impairments (24, 25).

Risk Factors of Developing POCD

Although the mechanisms responsible for POCD remain unclear, potential risk factors for POCD have been proposed. These can be divided into two categories: predisposing factors (advanced age, lower educational level, pre-existing cognitive impairments, cerebral vascualr disease, etc.) and precipitating factors (surgical type, postoperative pain, hypoperfusion and transient hypoxemia low perfusion, complications after surgery, use of anticholinergic medications, etc.) (2-6).

Predisposing Factors

Increasing age is considered to be the most important risk factor for the development of POCD (2, 3). The ISPOCD1 study analyzed the risk factors for POCD in patients with non-cardiac surgery and found that the incidence of POCD at 3 months after surgery was 7% in patients aged 60-69 and 14% in those over 69 years old (2). The POCD incidence in younger populations is relatively limited. In a study of 508 patients between 40 and 60 years of age, a prevalence of 6% was reported 3 months after non-cardiac surgery, while the prevalence reported in nonsurgical controls was 4% (26). There was a significant difference between all age groups and the age-matched control subjects. Indeed, elder patients are characterized by impairments in the function of many regulatory processes, including increased physical and mental frailty and decreased ability to cope with stresses such as anesthesia and surgery. Furthermore, older people more frequently have multiple conditions such as diabetes, renal insufficiency, cardiovascular diseases, and altered drug sensitivities, which increase the risk of developing POCD. These factors may explain why the elderly patients are at a greater risk than the younger part of the patient population.

Precipitating Factors

Postoperative cognitive dysfunction is the most common complication of cardiac surgery. It occurs in 30% to 80% of patients at discharge and 20% to 40% after 6 months to 1 year (10). It is reported that patients who underwent coronary artery bypass graft had a significantly higher incidence of POCD (43%) than patients who had a total hip joint replacement under general anesthetic (17%) at 1 week (27). After these procedures, POCD is probably a result of microembolic injury (28). Preventative operative strategies, such as off-pump coronary artery bypass grafting (CABG), can potentially reduce the incidence of postoperative neurological complications by avoiding manipulation of the ascending aorta. Although off-pump CABG is associated with reduced risk of stroke, there are no convincing differences in POCD between off-pump and on-pump CABG (29). 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 (6). Nevertheless, it is reported that the occurrence of POCD seems be independent on the type of surgery (30). Since the majority of the clinical investigation did not specifically determine the role of specific anesthetic (e.g., isoflurane versus desflurane) on the incidence of POCD. Such studies should be encouraged in the future clinical investigation.

For decades, it was assumed that volatile anesthetics were nontoxic and that their effects were rapidly reversed at the end of the procedure. There is now concern, however, that inhaled anesthetics may be neurotoxic to the aged brain. It has been demonstrated that clinical concentrations of two inhaled anesthetics, halothane and isoflurane, enhanced the oligomerization and aggregation of amyloid peptides in cell cultures (31). The in-vitro data indicated that inhaled anesthetic exposure might increase pathologic changes normally seen in Alzheimer's disease, especially in high-risk population like the elderly (32). Subsequent investigations revealed that isoflurane anesthesia activates enzymes called caspases, which may also contribute to the formation of neurofibrillary tangles and the production of beta amyloid, two key pathological features of Alzheimer's disease (33). These findings have led to concerns that inhaled anesthetics may alter the brain in some lasting way, possibly accelerate the course of Alzheimer's disease, and contribute to POCD in predisposed individuals (34).

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 (30). Rasmussen et al. (35) reported no significant difference in the incidence of cognitive dysfunction after 3 months, with 14.3% after general anesthesia and 13.9% after regional anesthesia. These findings suggested that factors other than anesthetic agents are responsible for the development of POCD (35). It has recently been demonstrating that the type of anesthesia (general versus regional) did not impact long-term cognitive outcome. However, all of the patients receiving regional anesthesia also received intravenous opioids and sedatives during the surgical procedure; it is not known whether regional anesthesia with no additional intravenous agents would improve postoperative cognitive outcome. Another study suggested the POCD incidence was higher in patients receiving spinal plus isoflurane anesthesia than those with spinal plus desflurane anesthesia (36). In addition, short-term POCD, diagnosed approximately 1 week after surgery, appears to be more common after general anesthesia. The available evidence is insufficient to determine whether any specific anesthetic agent is associated with a reduced risk of POCD. Future studies will be necessary to better understand whether there is a relationship between general anesthesia and POCD risk, and whether certain subgroups of patients (such as older patients, those with more cerebrovascular disease, or those with less cognitive reserve for other reasons) are at higher risk of developing POCD after general versus regional anesthesia. As it is ethically unacceptable to perform surgery without anesthesia (not to mention difficulty in recruitment!) and also challenging to administer anesthesia without surgery, in the real world the two are forever locked together as agents of any cognitive change after surgical interventions.

Prevention and Treatment of POCD

Potential prophylactic intervention may include minimal invasive surgery, multi-modal non-opioid pain management and pharmacological manipulation of the inflammatory response and sleep architecture. Meanwhile, nurses can provide important services by making older adults more aware of the problem, educating them about POCD, guiding decision making for future surgeries, intervening to help alleviate symptoms through nonpharmacological interventions, and implementing research focused on older adults' experiences with POCD. Drugs with various mechanisms of action, such as lidocaine (37), ketamine (38), and magnesium (39) have been tested over time but with different results. However, there is currently no evidence to suggest using the specific pharmacological agent to reduce the incidence of POCD.

Conclusion

POCD is a topic of special importance in the geriatric surgical population, although some clini-

cians have challenged the importance of POCD because the cognitive decline seems to be elusive. Notably, recent work has also suggested surgery may be associated with cognitive improvement in some patients, termed postoperative cognitive improvement (40). As for POCD, no definite therapeutic interventions are available to prevent the onset of POCD, strategies for management of these patients should be a multimodal approach involving close cooperation between the anesthesiologist, surgeon, geriatricians, and family members to promote early rehabilitation and avoid loss of independence in these patients. Future clinical and basic researches focusing on the mechanisms and pathways involved are critical for better understanding and management of this cognitive dysfunction after surgery.

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References

1. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955;269:259-63.
2. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology* 2009;110:548-55.
3. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; 351:857-61.
4. Li XM, Su F, Ji MH, Zhang GF, Qiu LL, Jia M, et al. Disruption of hippocampal neuregulin 1-ErbB4 signaling contributes to the hippocampus-dependent cognitive impairment induced by isoflurane in aged mice. *Anesthesiology* 2014;121:79-88.
5. Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. *Anesthesiology* 2011;115:727-32.
6. Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand* 2010;54:951-6.
7. Silverstein JH, Steinmetz J, Reichenberg A, Harvey PD, Rasmussen LS. Postoperative cognitive dysfunction in patients with preoperative cognitive impairment: which domains are most vulnerable? *Anesthesiology* 2007;106:431-5.
8. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT, et al. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001;45:275-89.
9. Lewis MS, Maruff P, Silbert BS, Evered LA, Scott DA. The sensitivity and specificity of three common statistical rules for the classification of post-operative cognitive dysfunction following coronary artery bypass graft surgery. *Acta Anaesthesiol Scand* 2006;50: 50-7.
10. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta Anaesthesiol Scand* 2010;54:663-77.
11. Rasmussen LS, Siersma VD; ISPOCD GROUP. Postoperative cognitive dysfunction: true deterioration versus random variation. *Acta Anaesthesiol Scand* 2004;48:1137-43.
12. Sauër AM, Kalkman C, van Dijk D. Postoperative cognitive decline. *J Anesth* 2009;23:256-9.
13. Funder KS, Steinmetz J, Rasmussen LS. Methodological issues of postoperative cognitive dysfunction research. *Semin Cardiothorac Vasc Anesth* 2010;14: 119-22.
14. Evered LA, Silbert BS, Scott DA, Maruff P, Ames D. Prevalence of dementia 7.5 years after coronary artery bypass graft surgery. *Anesthesiology* 2016;125: 62-71.
15. van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. *Anaesthesia* 2012;67:280-93.
16. Zhang J, Tan H, Jiang W, Zuo Z. Amantadine alleviates postoperative cognitive dysfunction possibly by increasing glial cell line-derived neurotrophic factor in rats. *Anesthesiology* 2014;121:773-85.
17. Qiu LL, Ji MH, Zhang H, Yang JJ, Sun XR, Tang H, et al. NADPH oxidase 2-derived reactive oxygen species in the hippocampus might contribute to microglial activation in postoperative cognitive dysfunction in aged mice. *Brain Behav Immun* 2016; 51:109-18.
18. Qiu LL, Luo D, Zhang H, Shi YS, Li YJ, Wu D, et al. Nox-2-mediated phenotype loss of hippocampal parvalbumin interneurons might contribute to postoperative cognitive decline in aging mice. *Front Aging Neurosci* 2016;8:234.
19. Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL. Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning. *Brain Behav Immun* 2014;38:202-10.
20. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, et al. Role of interleukin-1beta in postoperative cognitive dysfunction. *Ann Neurol* 2010;68:360-8.
21. Pan K, Li X, Chen Y, Zhu D, Li Y, Tao G, et al. Deferoxamine pre-treatment protects against postoperative cognitive dysfunction of aged rats by depressing microglial activation via ameliorating iron accumulation in hippocampus. *Neuropharmacology* 2016; 111:180-194.
22. Li Z, Mo N, Li L, Cao Y, Wang W, Liang Y, et al. Surgery-induced hippocampal angiotensin ii elevation causes blood-brain barrier disruption via MMP/TIMP in aged rats. *Front Cell Neurosci* 2016;10:105.
23. Cao L, Wang K, Gu T, Du B, Song J. Association between APOE epsilon 4 allele and postoperative cognitive dysfunction: a meta-analysis. *Int J Neurosci* 2014;124:478-85.
24. Ji M, Dong L, Jia M, Liu W, Zhang M, Ju L, et al. Epigenetic enhancement of brain-derived neurotrophic factor signaling pathway improves cognitive impairments induced by isoflurane exposure in aged rats. *Mol Neurobiol* 2014;50:937-44.
25. Jia M, Liu WX, Sun HL, Chang YQ, Yang JJ, Ji MH, et al. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, attenuates postoperative cognitive dysfunction in aging mice. *Front Mol Neurosci* 2015;8:52.
26. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology* 2002;96:1351-7.
27. Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, et al. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. *Anesthesiology* 2015;122:1224-34.
28. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. *J Am Coll Cardiol* 2013;62:531-9.
29. Jensen BO, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel DA. Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: a randomized trial. *Circulation* 2006;113:2790-5.
30. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg* 2011; 112: 1179-85.
31. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology* 2004;101:703-9.
32. Zhang B, Tian M, Zheng H, Zhen Y, Yue Y, Li T, et al. Effects of anesthetic isoflurane and desflurane on human cerebrospinal fluid Aβ and τ level. *Anesthesiology* 2013;119:52-60.
33. Wang H, Dong Y, Zhang J, Xu Z, Wang G, Swain CA, et al. Isoflurane induces endoplasmic reticulum stress and caspase activation through ryanodine receptors. *Br J Anaesth* 2014;113:695-707.
34. Zhang Y, Xu Z, Wang H, Dong Y, Shi HN, Culley DJ, et al. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. *Ann Neurol* 2012;71:687-98.
35. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* 2003;47:260-6.
36. Zhang B, Tian M, Zhen Y, Yue Y, Sherman J, Zheng H, et al. The effects of isoflurane and desflurane on cognitive function in humans. *Anesth Analg* 2012;114:410-5.
37. Lin D, Cao L, Wang Z, Li J, Washington JM, Zuo Z. Lidocaine attenuates cognitive impairment after isoflurane anesthesia in old rats. *Behav Brain Res* 2012;228:319-27.
38. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiol Scand* 2009;53:864-72.
39. Mathew JP, White WD, Schinderle DB, Podgoreanu MV, Berger M, Milano CA, et al. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. *Stroke* 2013; 44:3407-13.
40. Nadelson MR, Sanders RD, Avidan MS. Perioperative cognitive trajectory in adults. *Br J Anaesth* 2014;112:440-51.