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REVIEW ARTICLE

Brain white matter lesions and postoperative cognitive dysfunction: a review

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Abstract

Postoperative cognitive dysfunction (POCD) is a serious complication of anesthesia and surgery, and the major risk factor of POCD is aging. Although the exact pathophysiology of POCD remains unknown, two possible and reliable mechanisms have been proposed: neuroinflammation and neurodegeneration, i.e., amyloid β accumulation and/or tau protein phosphorylation, by surgery and/or general anesthetics. White matter lesions (WML) are produced by chronic cerebral hypoperfusion, frequently observed in elderly people, and closely related to cognitive decline. As recent studies have revealed that WML are a significant risk factor for POCD in humans, and we previously also demonstrated that persistent hypocapnea or hypotension caused neuronal damage in the caudoputamen or the hippocampus in a rat model of chronic cerebral hypoperfusion, which features global cerebral WML without neuronal damage and is recognized as a good model of human vascular dementia especially in elderly people, we hypothesize that in addition to those two previously proposed mechanisms, perioperative vital sign changes that cause reductions in cerebral blood flow might contribute to POCD in patients with WML, whose cerebral blood flow is already considerably decreased.

Keywords White matter lesion · Postoperative cognitive dysfunction · Chronic cerebral hypoperfusion · Aging

Postoperative cognitive dysfunction

Postoperative cognitive dysfunction (POCD) is a serious complication of anesthesia and surgery. It occurs in > 10% of non-cardiac surgical patients over the age of 60 years [1], can sometimes last for months or longer [1, 2], and is associated with increased mortality [2, 3]. Various risk factors for POCD have been identified, but aging is the most reliable, and hence is considered to be a major risk factor for POCD [1–3]. Although the exact pathophysiology of POCD remains unknown, some possible mechanisms have been proposed: General anesthetics, such as isoflurane and sevoflurane, and surgery were reported to increase ß-amyloid protein (βAP) production and tau protein phosphorylation in the brain in preclinical studies [4–7]. In human studies, it was found that the amount of βAP in the cerebrospinal fluid was increased in patients who underwent sevoflurane- or isoflurane-based anesthesia, but not in those subjected to desflurane-based anesthesia [8, 9]. βAP accumulation and intraneuronal neurofibrillary tangles, which are composed of aberrantly phosphorylated tau proteins, are considered to be two major etiologies for Alzheimer's disease (AD). On the other hand, the majority of researchers consider that neuroinflammation is the major causative factor responsible for POCD. Neuroinflammation can be induced not only by inhalational anesthetics [10], but also by surgery itself [11, 12], because preclinical studies have demonstrated that even non-neurological surgery can disrupt the blood–brain barrier and facilitate the migration of macrophages into the brain through the activation of the tumor necrosis factor α (TNF-α)/nuclear factor kB signaling pathway. Valentin et al. demonstrated that dexamethasone decreased the risk of POCD and the serum S100 protein level in elderly patients (60–87 years old) who underwent non-cardiac and non-neurological surgery [13]. However, these hypotheses cannot fully explain why aging is the only obvious risk factor for POCD in spite of the findings of preclinical studies that during normal aging microglia develop a more inflammatory phenotype, which is known as "microglial priming" [14, 15], and surprising results that the incidence of POCD

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was not different between general anesthesia and regional anesthesia [16] and POCD was independent of type of surgery and anesthetic [17].

We hypothesize that the reduction in cerebral blood flow (CBF) that occurs during anesthesia and surgery might also be involved in the pathophysiology of POCD, especially in elderly patients, whose CBF is already generally decreased, even in the absence of cerebral infarctions. Therefore, we have investigated the effects of changes of vital signs that cause reductions in CBF on the risk of POCD, using a rat chronic cerebral hypoperfusion (CCH) model.

Brain white matter lesions and postoperative cognitive dysfunction

WML are produced by CCH, even in the absence of cerebral infarctions, and develop with age, particularly in patients with arterial hypertension, diabetes mellitus (DM), or cardiovascular disease [18]. WML are found in 27–87% of > 65-year-old brains and have been demonstrated to be closely correlated with cognitive decline [19]. These lesions are associated with diseases that affect cerebral small blood vessels, such as radiological lacunar infarctions, and are frequently observed in stroke patients, and considered to be one of the most common causes of vascular cognitive impairment and dementia [20–24]. In fact, WML are the core pathology in Binswanger's disease, a form of vascular dementia, and are partly responsible for AD [18, 20–24]. Interestingly, several reports suggested that some form of brain vascular pathology existed in up to 80% of sporadic late-onset AD [24].

WML exhibit hyperintensity on T_2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging. Diffusion-weighted imaging and diffusion tensor imaging are also useful for detecting WML [18, 25]. The WM was once believed to be less vulnerable to ischemia than gray matter, but it has since been demonstrated that WM, especially oligodendrocytes and myelinated axons, is also vulnerable to ischemia [26, 27]. In addition, the pathophysiology of ischemic damage in the WM is quite different from that of ischemic damage in the gray matter [27, 28], and WM can be independently damaged in addition to Wallerian degeneration secondary to neuronal damage. Based on these findings, some researchers emphasize the importance of "total brain protection", in which both gray matter and WM are protected from acute brain ischemia [27, 29].

Recent studies have shown that preoperative WML are a serious and significant risk factor for postoperative delirium and POCD in humans [30–32]. Interestingly, DM and pre-existing cerebral, cardiac, or vascular disease are common risk factors for both WML [18] and POCD [33, 34].

A rodent model of chronic cerebral hypoperfusion

Unlike the gray matter, which is composed of neuronal cell bodies and glial cells, the WM is composed of axons and glial cells, especially myelinated oligodendrocytes, and in humans the WM comprises about half of the volume of the central nervous system, which is about a three–four-fold greater proportion than that found in rodents [28]. Therefore, some researchers have suspected that old rodent brains do not necessarily reflect the brains of elderly people [18]. A rodent model of CCH, which can be induced in rat or mouse brains by permanent occlusion of both common carotid arteries, is characterized by cognitive impairment and global cerebral WML with little gray matter damage; i.e., neuronal damage or cerebral infarctions, and it is considered to be a well-established model of human vascular dementia [18, 20, 22, 35–37]. In such a model, CBF decreases to 40–82% of normal levels over a prolonged period without cerebral infarctions, which typically occur when CBF is reduced to < 20% of normal levels. There is ample evidence to suggest that oxidative stress and inflammatory responses play pivotal roles in WML [38]. Hypoperfusion-induced inflammatory events cause peripheral leukocyte recruitment; the activation of microglia and astrocytes; and upregulated expression of inflammatory mediators, such as TNF-α and interleukin 1β [38, 39]. WML can be ameliorated by various agents, such as nimesulide (a cyclooxygenase-2 inhibitor) [40], cyclosporine A [41] and FK 506 (immunosuppressants) [42], and edaravone (an antioxidant) [43].

A rodent model of chronic cerebral perfusion and postoperative cognitive dysfunction

We previously demonstrated that the neurons of the caudoputamen, which play an essential role in the acquisition of motor, perceptual, and cognitive skills, as well as in spatial working memory, were damaged by long-term hypocapnia ($PaCO_2$ was maintained at 20–25 mmHg for 2 h) during mechanical ventilation in a rat model of CCH [36], and the damage was prevented by pre-administering ketamine [37]. In these studies, the CCH per se induced marked microglial activation and axonal damage in some brain regions, such as the caudoputamen, optic tract, corpus callosum, and cerebral cortex, without causing neuronal damage. In addition, no neuronal damage was seen in the control rat group (the normal cerebral perfusion group) subjected to hypocapnea or the CCH group

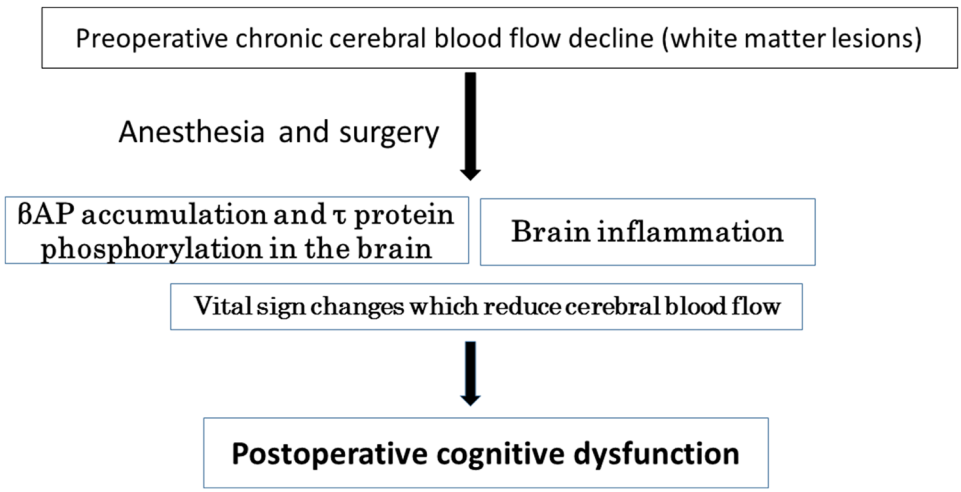

Fig. 1 shows a putative mechanism for postoperative cognitive dysfunction (POCD). Patients with preoperative white matter lesions, such as elderly patients, are at risk of developing POCD. In addition to neuronal inflammation and/or neurodegeneration, such as anesthetic/surgery-induced β-amyloid protein (βAP) accumulation or tau protein phosphorylation, perioperative vital changes that cause reductions in CBF might contribute to the development of POCD

maintained under normocapnia ($PaCO_2$ at 35–45 mmHg for 2 h). Interestingly, it was once believed that there were no *N*-methyl-D aspartate (NMDA) glutamate receptors in myelinated oligodendrocytes, but recent studies have revealed that an unusual type of NMDA glutamate receptor is expressed in these cells. Normal NMDA receptors, which are expressed in neurons, are usually composed of NR1 and NR2A-NR2C subunits, but the unusual NMDA receptors are composed of NR1, NR2, and NR3A subunits [44, 45]. The NR1/NR3 subunit-based NMDA receptors are less sensitive to Mg^{2+} block, and they exhibit a substantial current even at the resting potential and are more sensitive to glycine than glutamate. Interestingly, in accordance with the result of our animal study, a recent systemic review and meta-analysis has revealed that intraoperative ketamine administration has some protection towards POCD in humans [46].

Moreover, we have recently shown that 2 h of isoflurane-induced hypotension (mean arterial pressure: <60 mmHg) caused hippocampal CA1 neuronal damage in CCH rats [47]. As the hippocampus plays a crucial role in long-term episodic memory [48], these findings suggest that even anesthetic-induced persistent hypotension can cause cognitive dysfunction in patients with pre-existing low CBF levels. Our results seem quite natural because patients with WML and pre-existing reductions in CBF are quite vulnerable to further reductions in CBF, even if they have not suffered any apparent cerebral infarctions. Such changes in CBF can lead to neuronal damage, i.e., cerebral infarctions. Our results may also explain why aging is the most obvious risk factor for POCD because WML develop with age, and most elderly people have WML.

As far as we know, there have been few preclinical and some clinical reports, which investigate the effect of intraoperative hypotension and/or hypocapnea on POCD, both of which can decrease the cerebral blood flow [49], but unfortunately most of these clinical reports are old and unconvincing: As for the effect of intraoperative hypocapnea, Wollman and Orkin found that extreme hypocapnea ($PaCO_2$: 12–38 mmHg, mostly below 24 mmHg) during anesthesia caused prolonged cognitive dysfunction even in young or middle-aged patients (19–56 years) [50], but most of other studies were unable to find any significant effect of hypocapnea on postoperative cognitive function [51, 52]. As for the effect of intraoperative hypotension, Thompson et al. reported that intraoperative deliberate hypotension, where the mean arterial pressure (MAP) was reduced to 50 mmHg for around 1.5 h, did not affect postoperative cerebral function [53], but the sample size was small and the patients were not so old (58 ± 4 years). Niazi found a significant decline in Mini Mental State Examination scores of patients (21–50 years) when their MAPs were kept around 50 mmHg for about 1 h during operations [54]. A recent randomized controlled pilot trial has revealed that intraoperative hypotension is not associated with POCD in elderly patients [55]. In this study, however, although the intraoperative average MAP in the target group (92 ± 9 mmHg) was significantly higher than that in the No-target group (hypotensive group), the average MAP in the No-target group was 85 ± 11 mmHg, and thus the cerebral blood flow even in the No-target group would have been well preserved. Unfortunately, none of these studies checked pre-existing patients' WML.

In conclusion, our experimental results and the finding that preoperative WML are a significant risk factor for POCD suggest that in addition to βAP production in the brain and cerebral inflammation induced by anesthesia/surgery, perioperative vital changes that cause reductions in CBF, such as persistent hypotension and/or hypocapnea, might contribute to the development of POCD, especially in patients whose CBF is already reduced, such as elderly patients (Fig. 1).

References

1. 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. Lancet. 1998;351:857–61.
2. 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.
3. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology. 2009;110:548–55.
4. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, Frosch MP, Crosby G, Tanzi RE. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. Ann Neurol. 2008;64:618–27.
5. Dong Y, Zhang G, Zhang B, Moir RD, Xia W, Marcantonio ER, Culley DJ, Crosby G, Tanzi RE, Xie Z. The common anesthetic sevoflurane induces apoptosis and increases beta-amyloid protein. Arch Neurol. 2009;66:620–31.
6. Zhang B, Dong Y, Zhang G, Moir RD, Xia W, Yue Y, Tian M, Culley DJ, Crosby G, Tanzi RE, Xie Z. The inhalation anesthetic desflurane induces caspase activation and increases amyloid beta-protein level under hypoxic conditions. J Biol Chem. 2008;283:11866–75.
7. Jiang JUE, Jiang H. Effect of the inhaled anesthetics isoflurane, sevoflurane and desflurane on the neuropathogenesis of Alzheimer's disease (Review). Mol Med Rep. 2015;12:3–12.
8. Zhang B, Tian M, Zheng H, Zhen Y, Yue Y, Li T, Li S, Marcantonio ER, Xie Z. Effects of anesthetic isoflurane and desflurane on human cerebrospinal fluid Aβ and τ level. Anesthesiology. 2013;119:52–60.
9. Liu Y, Pan N, Ma Y, Zhang S, Guo W, Li H, Zhou J, Liu G, Gao M. Inhaled sevoflurane may promote progression of amnestic mild cognitive impairment: a prospective, randomized parallel-group study. Am J Med Sci. 2013;345:355–60.
10. Wu X, Lu Y, Dong Y, Zhang G, Zhang Y, Xu Z, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-alfa, IL-6, IL-1beta. Neurobiol Aging. 2012;33:1364–78.
11. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, Jonsson Fagerlund M, Charo IF, Akassoglou K, Maze M. Resolving postoperative neuroinflammation and cognitive decline. ANN Neurol. 2011;70:986–95.
12. Vacas S, Degos V, Feng X, Maze M. The neuroinflammatory response of postoperative cognitive decline. Br Med Bull. 2013;106:161–78.
13. Valentin LS, Pereira VF, Pietrobon RS, Schmidt AP, Oses JP, Portela LV, Souza DO, Vissoci JR, Luz VF, Trintoni LM, Nielsen KC, Carmona MJ Effects of single low dose of dexamethasone before noncardiac and nonneurologic surgery and general anesthesia on postoperative cognitive dysfunction- a phase III double blind, randomized clinical trial. PLos One. 2016. https://doi.org/10.1371/journal.pone.0152308.
14. Norden DM, Godbout JP. Microglia of the aged brain: primed to be activated and resistant to regulation. Neuropahtol Appl Neurobiol. 2013;39:19–34.
15. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol. 2008;84:932–9.
16. Guay J. General anaesthesia does not contribute to long-term postoperative cognitive dysfunction in adults: a meta-analysis. Indian J Anaesth. 2011;55:358–63.
17. 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.
18. Nakao S, Xu Y. White matter injury in global cerebral ischemia. In: Carmichael S Jr and Baltan S, editor. White matter injury in stroke and cns disease. New York: Springer; 2014. 181–96.
19. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The cardiovascular health study. Stroke. 1996;27:1274–82.
20. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke. 1997;28:652–9.
21. Schmidt R, Scheltens P, Erkinjuntti T, Pantoni L, Markus HS, Wallin A, Barkhof F, Fazekas F. White matter lesion progression: a surrogate endpoint for trials in cerebral small-vessel disease. Neurology. 2004;63:139–44.
22. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701
23. ">Desmond DW. Cognition and white matter lesions. Cerebrovasc Dis. 2002;13(Suppl 2):53–7.
24. ">Duncombe J, Kitamura A, Hase Y, Ihara M, Kakaria RN, Horsburgh K. Chronic cerebral hypoperfusion: a key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodent models and human vascular cognitive impairment and dementia. Clin Sci. 2017;131:2451–88.
25. Schmidt R, Grazer A, Enzinger C, Ropele S, Homayoon N, Pluta-Fuerst A, Schwingenschuh P, Katschnig P, Cavalieri M, Schmidt H, Langkammer C, Ebner F, Fazekas F. MRI-detected white matter lesions: do they really matter? J Neural Transm. 2011;118:673–81.
26. Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. Stroke. 1996;27:1641–46.
27. Dewar D, Yam P, McCulloch J. Drug development for stroke: Importance of protecting cerebral white matter. Eur J Pharmacol. 1999;375:41–50.
28. Matute C. Glutamate and ATP signaling in white matter pathology. J Anat. 2011;219:53–64.
29. Kubo K, Nakao S, Jomura S, Sakamoto S, Miyamoto E, Xu Y, Tomimoto H, Inada T, Shingu K. Edaravone, a free radical scavenger, mitigates both gray and white matter damages after global cerebral ischemia in rats. Brain Res. 2009;1279:139–46.
30. Hatano Y, Narumoto J, Shibata K, Matsuoka T, Taniguchi S, Hata Y, Yamada K, Yaku H, Fukui K. White matter hyperintensities predict delirium after cardiac surgery. Am J Geriatr Psychiatry. 2013;21:938–45.
31. Maekawa K, Baba T, Otomo S, Morishita S, Tamura N. Low pre-existing gray matter volume in the medial temporal lobe and white matter lesions are associated with postoperative cognitive dysfunction after cardiac surgery. PLoS One. 2014. https://doi.org/10.1371/journal.pone.0087375.
32. Kant IMJ, de Bresser J, van Montfort SJT, Slooter AJC, Hendrikse J. MRI markers of neurodegenerative and neurovascular changes in relation to postoperative delirium and postoperative cognitive decline. Am J Geriatr Psychiatry. 2017;25:1043–61.
33. Feinkohl I, Winterer G, Pischon T. Diabetes is associated with risk of postoperative cognitive dysfunction: a meta-analysis. Diabetes Metab Res Rev. 2017. https://doi.org/10.1002/dmrr.2884.
34. Rundshagen I. Postoperative cognitive dysfunction (review). Dtsch Artebl Int. 2014;111:119–25.
35. Ihara M, Tomimoto H, Kinoshita M, Oh J, Noda M, Wakita H, Akiguchi I, Shibasaki H. Chronic cerebral hypoperfusion induces MMP-2 but not MMP-9 expression in the microglia and vascular endothelium of the white matter. J Cereb Blood Flow Metab. 2001;21:828–34.

36. Miyamoto E, Tomimoto H, Nakao S, Wakita H, Akiguchi I, Miyamoto K, Shingu K. Caudoputamen is damaged by hypocapnia during mechanical ventilation in a rat model of chronic cerebral hypoperfusion. Stroke. 2001;32:2920–5.
37. Miyamoto E, Nakao S, Tomimoto H, Wakita H, Yamada M, Masuzawa M, Takahira K, Sakamoto S, Shingu K. Ketamine attenuates hypoxia-induced neuronal damage in the caudoputamen in a rat model of chronic cerebral hypoperfusion. Neurosci Lett. 2004;354:26–9.
38. Dewar D, Underhill SM, Goldberg MP. Oligodendrocytes and ischemic brain injury. J Cerebr Blood Flow Metab. 2003;23:263–74.
39. Wang J, Zhang HY, Tang XC. Huperzine a improves chronic inflammation and cognitive decline in rats with cerebral hypoperfusion. J Neurosci Res. 2010;88:807–15.
40. Wakita H, Tomimoto H, Akiguchi I, Lin JX, Miyamoto K, Oka N. A cyclooxygenase-2 inhibitor attenuates white matter damage in chronic cerebral ischemia. Neuroreport. 1999;10:1461–5.
41. Wakita H, Tomimoto H, Akiguchi I, Kimura J. Protective effect of cyclosporin a on white matter changes in the rat brain after chronic cerebral hypoperfusion. Stroke. 1995;26:1415–22.
42. Wakita H, Tomimoto H, Akiguchi I, Kimura J. Dose-dependent, protective effect of FK506 against white matter changes in the rat brain after chronic cerebral ischemia. Brain Res. 1998;792:5–13.
43. Ueno Y, Zhang N, Miyamoto N, Tanaka R, Hattori N, Urabe T. Edaravone attenuates white matter lesions through endothelial protection in a rat chronic hypoperfusion model. Neuroscience. 2009;162:317–27.
44. Káradóttir R, Cavelier P, Bergersen LH, Attwell D. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. Nature. 2005;438:1162–6.
45. Matute C. Oligodendrocyte NMDA receptors: a novel therapeutic target. Trends Mol Med. 2006;12:289–92.
46. Hovaguimian F, Tschopp C, Beck-Schimmer B, Puhan M. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction. Acta Anaesthesiol Scand. 201862:1182–93.
47. Yamamoto T, Iwamoto T, Kimura S, Nakao S. Persistent isoflurane-induced hypotension causes hippocampal neuronal damage in a rat model of chronic cerebral hypoperfusion. J Anesth. 2018. https://doi.org/10.1007/s00540-018-2458-z.
48. Bird CM, Burgess N. The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci. 2008;9:182–94.
49. Pappa M, Theodosiadis N, Tsounis A, Sarafis P. Pathogenesis and treatment of post-operative cognitive dysfunction. Electron Phys. 2107;9:3768–75.
50. Wollman SB, Orkin LR. Postoperative human reaction time and hypocarbia during anesthesia. Brit J Anaesth. 1968;40:920–6.
51. Blenkarn GD, Briggs G, Bell J, Sugioka K. Cognitive function after hypocpnic hyperventilation. Anesthesiology. 1972;37:381–6.
52. Murrin KR, Nagarajan TM. Hyperventilation and psychometric testing. A preliminary study. Anaesthesia. 1974;29:50–8.
53. Thompson GE, Miller RD, Stevens WC, Murray WR. Hypotensive anesthesia for total hip arthroplasty. Anesthesiology. 1978;48:91–6.
54. Niazi AA. Postoperative cognitive function and controlled hypotensive anesthesia in patients undergoing septoplasty. Egypt J Anaesth. 2016;32:61–6.
55. Langer T, Santini A, Zadek F, Chiodi M, Pugni P, Cordolcini V, Bonanomi B, Rosini F, Marcucci M, Valenza F, Marenghi C, Inglese S, Pesenti A, Gattinoni L. Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. J Clin Anesth. 2019;52:111–8.