neurocritical care society Neurocrit Care
DOI 10.1007/s12028-015-0201-2

ORIGINAL ARTICLE

Acousto-Optic Cerebral Blood Flow Monitoring During Induction of Anesthesia in Humans

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Abstract
Background Past transcranial Doppler (TCD) studies have documented the effects of the sequence of anesthesia induction followed by intubation on cerebral blood flow (CBF) velocity. The purpose of this study was to determine whether acousto-optic CBF monitoring would detect changes in CBF which are known to occur with propofol and subsequent endotracheal intubation.
Methods Seventy-two patients scheduled for elective non-intracranial surgery were evaluated. A Cerox 3215F (Ornim Medical) acousto-optic CBF monitor was used. The acousto-optic transducers were applied bifrontally prior to induction. Baseline cerebral flow index (CFI) values were obtained for at least 2 min prior to induction, set to a unitless value of 100. Subsequent relative changes in CFI from baseline were determined at the lowest value over 3 min after propofol injection but before laryngoscopy; and the highest value over 5 min after the start of laryngoscopy. CFI data were evaluated using Friedman's test.
Results The median dose of propofol [interquartile range] given was 200 mg [160–250]. CFI decreased to 84 % of baseline after propofol and increased to 147 % of baseline after endotracheal intubation (both $p < 0.001$); MAP decreased after intravenous induction of anesthesia from 103 ± 15 to 86 ± 15 mmHg ($p < 0.001$) and then returned following endotracheal intubation to 104 ± 20 mmHg.
Conclusions Our data are congruent with previous observations made with TCD under similar experimental conditions. Such observations support the notion that acousto-optic monitoring yields valid real-time measures of changes in CBF in humans. Further validation against other quantitative measures of CBF would be appropriate.

Keywords Near-infrared spectroscopy · Acousto-optic monitor · Cerebral blood flow · Anesthesia · Propofol · Endotracheal intubation · Bariatric surgery

Introduction

Cerebral Blood Flow (CBF) is an important parameter in neuroanesthesia and neurocritical care. Unfortunately, a non-invasive real-time bedside monitor of CBF has not been available for routine clinical use. A recently developed approach is based on an acousto-optic adaptation of near-infrared spectroscopy, in which an ultrasound signal is used to "acoustically tag" infrared light emitted at a precise frequency from a laser source. The ultrasound-tagged light allows the signal to be localized to a specific depth in the tissue being monitored such that a measurement of the Doppler shift in the light reflected can be used to determine brain blood flow [1–3]. The commercially available acousto-optic monitor (Cerox®, Ornim Medical) continuously generates a value for CBF in relative units of change after being initially set at a baseline of 100, and called the cerebral flow index (CFI). The CFI is thought to accurately reflect changes in CBF and as a monitor can reflect relative changes in CBF in a small volume of brain tissue beneath

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Published online: 23 September 2015

the probe. The technique performs as expected in Monte Carlo simulations and in vitro experiments [3]. Studies in piglets with dynamically induced changes in CBF indicate an encouraging correlation between acousto-optic CFI and laser Doppler [4], and human studies suggest an appropriate CFI response compared to ^{133}Xe-SPECT in humans given acetazolamide, altogether suggesting a potential use for acousto-optic CBF assessment in Neurocritical care.

Previous studies using transcranial Doppler (TCD) have documented significant changes in CBF velocity (CBFV) during anesthetic induction and intubation in the operative setting [5, 6]. In the absence of intracranial pathology, a decrease in CBFV and CBF occurs upon induction with thiopental [7–9] and propofol [10–14], driven mainly by specific effects of both drugs to decrease cerebral metabolic rate with a matched decrease in CBF [13]. In patients with brain tumors, Kofke et al. reported corresponding changes in mean arterial pressure (MAP) and CBFV with thiopental induction (decrease) and subsequent endotracheal intubation (increase) [5]. Brain tumor patients were included in that study because of concern at the time of oligemic intracranial hypertension arising with intubation. This was not observed and hence was concluded that elevated ICP with induction of anesthesia and intubation is likely from hyperemia.

While thiopental and propofol both produce a decrease in MAP on induction, with the noxious stimulation of laryngoscopy producing an increase back towards baseline, cerebral autoregulation is assumed to be relatively intact [15, 16]; hence, the effects on CBF are not primarily driven by the simultaneous changes in MAP but by changes in level of neural activity with coupled changes in CBF [13], an observation which can be attenuated by the type and depth of concomitant anesthetic or analgesic [6].

The present study was designed not to validate the acousto-optic CBF monitor against another gold standard CBF monitor, but rather, as an early step in its evaluation for use in acute care, to ascertain whether similar changes to those seen by Kofke et al. [5] with TCD are observed using the acousto-optic CBF monitor, using a similar propofol-based anesthetic paradigm. Specifically, using the acousto-optic method to measure dynamically arising relative changes in CFI, we hypothesized that decrements in CFI would arise after propofol injection and that increments in CFI would arise with laryngoscopy and endotracheal intubation.

Methods

The protocol was approved by the Institutional Review Board of the University of Pennsylvania. Patients between the ages of 18 and 80, scheduled for elective non-intracranial surgery without intracranial pathology under general anesthesia with endotracheal intubation, were selected, and informed consent was obtained. Patients with intracranial pathology including tumor, pneumocephalus, pneumocranium, or significant cerebral atrophy, and patients with hematoma, laceration or implants at the intended site for acousto-optic probe placement were excluded. A total of 79 patients were enrolled from November 2013 through June 2014.

A Cerox 3215F (Ornim Medical, Kfar Saba, Israel) acousto-optic CBF monitor was used. Prior to or upon arrival in the operating room, the acousto-optic transducers (probes) were applied bifrontally onto cleaned skin, using proprietary adhesive mountings and standard ultrasound gel. Baseline CFI values were obtained for at least 2 min prior to induction. Subsequent changes in CFI from baseline were determined at two time points: the lowest value over 3 min after propofol injection but before laryngoscopy; and the highest value over 5 min after the start of laryngoscopy. After monitoring was completed, the probes were removed and the site inspected.

General anesthesia was induced using propofol, with added intravenous lidocaine, midazolam, opiates, ketamine, and neuromuscular blockade at the discretion of the attending anesthesiologist. The computerized anesthetic record (Epic Systems Corporation, Verona, WI) continuously recorded the patients' vital parameters and their non-invasive MAP throughout induction and intubation and were available for comparison with the CFI.

In many cases, vasoactive agents (usually vasopressors) were given to patients to support their blood pressures during induction of general anesthesia. We recorded the instances where vasoactive agents were given prior to the start of, or during, CFI monitoring, but not where agents were given after monitoring had ceased. Agents used were typically phenylephrine and/or ephedrine but included vasopressin and epinephrine. The impact of vasoactive agents on CFI was evaluated.

Descriptive statistics included counts, median, and interquartile range [IQR] for continuous measurements, and counts with percent for categorical measurements. The distribution of measurements between patients who underwent different procedures was compared using the Kruskal–Wallis test followed by Dunn's post hoc test for continuous measurements, and the Chi-square test for categorical measurements.

The differences in CBF and MAP values from baseline at the two time points were compared using Friedman's test. Statistical significance was defined as $p = 0.05$. Data are presented as either median [IQR] or mean $\pm$ SD. Data were analyzed using SPSS Statistics for Windows (Version 22.0, 2013, IBM Corp, Armonk, NY).

Results

Seventy-nine patients were enrolled. Data from 72 patients were analyzed (7 patients were excluded due to technical errors in CFI recordings). The data summary which follows is based on the remaining 72 patients. Demographic data are displayed in Table 1.

The median age was 51.5 years [IQR [40.0–60.5]]. The patients undergoing spine surgery were significantly older than the bariatric patients ($p = 0.047$, Dunn's post hoc test). Body mass index (BMI) was significantly higher among bariatric patients ($p < 0.001$, Dunn's post hoc test). There was a trend for higher percentage of females among bariatric surgeries ($p = 0.088$).

Anesthetics employed during induction of anesthesia are summarized in Table 2.

Subjects undergoing bariatric surgery received significantly higher doses of propofol ($p < 0.005$). There were no significant differences in the doses of fentanyl and lidocaine between procedure types.

There were significant differences ($p = 0.002$, Chi square) in the percentage of subjects that received vasoactive agents: among bariatric surgeries 82.4 %; among laparoscopies 63.2 %, and among spine surgery 33.3 %.

CFI decreased to 84 % [IQR [75–98]] of baseline after propofol ($p < 0.001$) and increased following endotracheal intubation to 147 % [IQR [125–184]] of baseline ($p < 0.001$) (Fig. 1). This pattern was seen in all surgical subgroups. MAP decreased significantly after intravenous induction of anesthesia from 103 ± 15 mmHg to 86 ± 15 mmHg ($p < 0.001$) and then returned following endotracheal intubation to 104 ± 20 mmHg, not significantly different from baseline (Fig. 2). The MAP pattern varied between surgeries; only bariatric surgery cases demonstrated a significant reduction in MAP after induction ($p = 0.012$). The MAP reduction was not statistically significant for laparoscopy and spine cases ($p = 0.131$, $p = 0.082$, respectively). The use of vasoactive agents did not affect the CFI and MAP patterns overall or for any specific subgroup. Concurrently, SaO_2 remained >95 % for the duration of monitoring in all subjects.

Discussion

In the prior report in 104 patients without brain tumors by Kofke et al. [5], TCD CBFV values were 63.6 ± 16.3, 47.8 ± 12.5, and 65.5 ± 16.2 cm/s for baseline, induction, and intubation, respectively. Similar to our CFI observations with propofol, induction with (mostly) thiopental produced a decrease to 80 % of the baseline. In the TCD report, intubation increased flow velocity back to baseline, whereas in the current CFI study, we observed a somewhat greater increase with intubation. Our data, showing a decrease with propofol and a subsequent increase with intubation, are congruent with the observations using TCD measurements of CBFV changes in the middle cerebral artery under similar conditions [5, 17].

The present study was not designed to provide quantitative validation versus another CBF technology. Our goal was to assess whether the system provided information congruent with prior studies reflecting known effects of propofol and endotracheal intubation; and the data support that conclusion.

Induction with agents such as thiopental and propofol is associated with up to a 50 % decrease in CBF which is largely and rapidly reversed by systemic redistribution of the drug [13], and its CBF decreasing effects may be lessened with concomitant nociceptive input such as laryngoscopy and endotracheal intubation [5, 6, 17]. That the increase in CBF with laryngoscopy is due to neural activation is supported by reports of increased bispectral index with intubation after induction of anesthesia [18, 19]. However, notably, these observations are not reproduced when higher doses of hypnotic or analgesic are given [20–22]. Other factors which would be expected to have an effect on CBF are arterial $PaCO_2$ and the potential vasoactive properties of drugs given perioperatively. We did not record the end-tidal CO_2 before and after laryngoscopy, partly due to the unreliability of the measure with mask ventilation before laryngoscopy. The time frame of the measurements would suggest that there was not enough time for significant changes in $PaCO_2$ to arise. With a 1 min laryngoscopy, one might anticipate no more than a

Table 1 Demographic characteristics by procedure type

	Bariatric ($N = 17$)	Laparoscopic ($N = 19$)	Spine ($N = 36$)	Total ($N = 72$)	p value*
Age: median [IQR]	45.0 [39.0–53.0]	51 [37.0–56.0]	56.5 [44.5–70.0]	51.5 [40.0–60.5]	0.046
BMI: median [IQR]	46.9 [41.1–53.6]	28.6 [28.3–30.8]	29.2 [25.7–32.3]	30.8 [27.8–37.2]	0.000
Female: N (%)	13 (76.5 %)	11 (57.9 %)	16 (44.4 %)	40 (55.6 %)	0.088

* p value by Kruskal–Wallis, except for male:female ratios with p value by Chi-square test

Table 2 Use of anesthetic drugs by procedure type

	Bariatric $N = 17$		Laparoscopic $N = 19$		Spine $N = 36$		Total $N = 72$		p value
	N	Median [IQR]	N	Median [IQR]	N	Median [IQR]	N	Median [IQR]	
Propofol (mg)	17	250 [200–300]	19	200 [150–240]	36	200 [150–200]	72	200 [160–250]	<0.001
Lidocaine (mg)	17	80 [60–80]	19	80 [60–100]	36	80 [60–100]	72	80 [60–100]	0.788
Fentanyl (mg)	17	200 [150–200]	18	200 [200–300]	33	200 [200–200]	68	200 [200–200]	0.752
Rocuronium (mg)	16	77.5 [55–95]	15	70 [50–105]	9	90 [60–100]	40	72.5 [50–100]	0.948
Hydromorphone (mg)	15	1.8 [1.6–2.4]	16	2 [1.3–2.1]	6	2 [2–2]	37	2 [1.6–2]	0.984
Midazolam (mg)	9	2 [2–2]	8	2 [2–2]	8	2 [2–2]	25	2 [2–2]	0.556
Cisatracurium (mg)	1	22 [22–22]	4	11 [8–36]	16	15 [12–19]	21	14 [12–20]	0.269
Ketamine (mg)	13	70 [50–100]	1	140 [140–140]	6	47.5 [40–55]	20	65 [42.5–100]	0.116
Vecuronium (mg)	0	[−]	0	[−]	7	10 [10–10]	7	10 [10–10]	NA
Remifentanil (mg)	0	[−]	0	[−]	3	0.2 [0.2–0.2]	3	0.2 [0.2–0.2]	NA
Morphine (mg)	0	[−]	0	[−]	1	10 [10–10]	1	10 [10–10]	NA

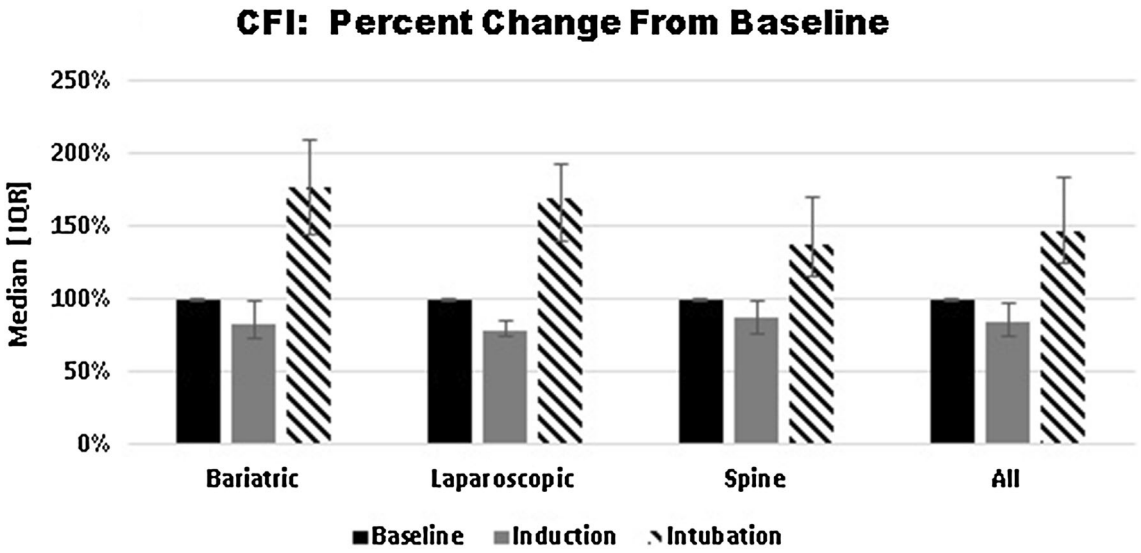

Fig. 1 Relative changes in cerebral flow index (CFI) on induction of anesthesia and intubation relative to baseline value of 1.0 for each surgical procedure and overall (medians and interquartile ranges). CFI was significantly decreased from baseline on induction ($p < 0.001$) and increased from baseline after intubation ($p < 0.001$)

3–4 mmHg rise of $PaCO_2$, which might account for up to a 9 % increase in CBF [23], less than we and others have observed with laryngoscopy, but nonetheless possibly a contributing factor.

Vasopressors were given to support blood pressure in some patients after propofol injection, and we observed no significant effect of this on CFI. Given the rationale for their use (to keep MAP within normal limits), we would not expect, and did not observe a significant difference in MAP between those who had received vasopressors and those who had not. Notably, although CBF increased with intubation, no changes in MAP were observed. This likely reflects the mixture of ongoing hemodynamic depression with propofol, titrated pressor administration, and some nociception-related pressor effects, altogether leading to minimal intubation-associated blood pressure changes. This would suggest that the CFI changes with intubation were not due primarily to hypertension but more likely to neural activation with nociception as suggested by Abdallah et al. [6].

Although TCD is also not a direct measure of flow because the technique cannot detect the caliber of intracranial vessels, a good correlation between CBFV and actual CBF has been established using Xenon-CT

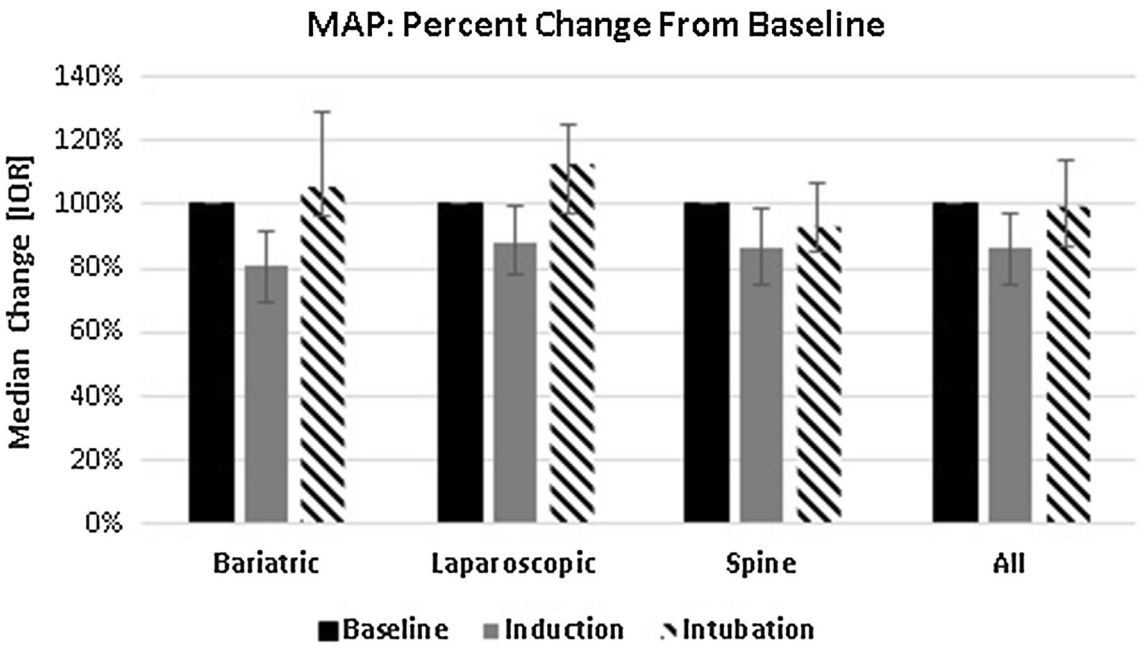

Fig. 2 Relative changes in mean arterial pressure (MAP) on induction of anesthesia and intubation relative to baseline value of 100 % for each surgical procedure and overall (medians and interquartile ranges). MAP was significantly decreased from baseline on induction ($p < 0.001$) and not significantly different to baseline after endotracheal intubation ($p = 0.617$). Absolute values for MAP are *cited in the text*

CBF [24, 25] such that changes in CBFV reflect acute changes in CBF. The acousto-optic monitor appears to be able to detect the same expected changes in CBF. In addition, it offers several benefits compared to TCD due to its relative ease of use, especially by non-specialist operators. TCD is associated with operator-dependent variability related to difficulty reproducing and maintaining a constant insonation angle over time.

The obvious limitation of this study is that it did not directly validate the acousto-optic monitor versus a gold standard CBF measure such as XeCT CBF or PET CBF. However, we do provide an initial assessment indicating that the device appropriately detects known changes in CBF in a dynamic clinical situation. Further studies are needed to determine the temporal and spatial resolution of the acousto-optic monitor, as well as to assess whether it can make clinically useful measurements when intracranial physiology is disturbed by pathophysiologic factors other than anesthetics.

The potential to measure CBF non-invasively, in real time, and without the need to transport the patient for imaging may make the acousto-optic CBF trend monitor a potentially clinically useful tool in screening for adverse events related to changes in CBF, and in the monitoring of the progress of their treatment. It may find its best role for evaluating acute effects of therapy on changes from a baseline CBF. Further validation studies are needed in patients with intracranial pathology.

Acknowledgments This work was supported by a Grant from Ornim Ltd, 15 Atir Yeda St., Kfar Saba, Israel 4464312.

Compliance with Ethical Standards

Conflict of interest Marlon Schwarz, Giovanni Rivera, Mary Hammond, and Kirk Jackson declare that they have no conflicts of interest. Zmira Silman is an employee of Ornim Medical Ltd. W. Andrew Kofke has received funding for the present study from Ornim Medical Ltd.

References

1. Schytz HW, Guo S, Jensen LT, et al. A new technology for detecting cerebral blood flow: a comparative study of ultrasound tagged NIRS and 133Xe-SPECT. Neurocrit Care. 2012;17:139–45.
2. Mahan GD, Engler WE, Tiemann JJ, Uzgiris E. Ultrasonic tagging of light: theory. Proc Natl Acad Sci USA. 1998;95:14015–9.
3. Tsalach A, Metzger Y, Breskin I, Zeitak R, Shechter R. In: Ultrasound modulated light blood flow measurement using intensity autocorrelation function: A Monte-Carlo simulation. Photons Plus Ultrasound: Imaging and Sensing 2014; San Francisco, CA: SPIE, 2014.
4. Ron A, Racheli N, Breskin I, et al. In: Measuring tissue blood flow using ultrasound modulated diffused light. Photons Plus Ultrasound: Imaging and Sensing 2012; San Francisco, CA, 2012.
5. Kofke W, Dong M, Bloom M, Policare R, Janosky J, Sekhar L. Transcranial Doppler ultrasonography with induction of anesthesia for neurosurgery. J Neurosurg Anesthesiol. 1994;6:89–97.
6. Abdallah C, Karsli C, Bissonnette B. Fentanyl is more effective than remifentanil at preventing increases in cerebral blood flow velocity during intubation in children. Can J Anesth. 2002;49:1070–5.

7. Pierce E, Lambertsen C, Deutsch S. Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest. 1962;41:1664–71.
8. Michenfelder J. The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology. 1974;41:231–6.
9. Kassell N, et al. Alterations in cerebral blood flow, oxygen metabolism, and-electrical activity produced by high dose sodium thiopental. Neurosurgery. 1980;1:598.
10. Vandesteene A, Trempont V, Engelman E, et al. Effect of propofol on CBF and metabolism in man. Anaesthesia. 1988;45(Suppl):42–3.
11. Alkire MT, Haier RJ, Barker SJ, et al. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology. 1995;82:393–403 **discussion 27A**.
12. Oshima T, Karasawa F, Satoh T, Oshima T, Karasawa F, Satoh T. Effects of propofol on cerebral blood flow and the metabolic rate of oxygen in humans. Acta Anaesthesiol Scand. 2002;46:831–5.
13. Ludbrook GL, Visco E, Lam AM. Propofol: relation between brain concentrations, electroencephalogram, middle cerebral artery blood flow velocity, and cerebral oxygen extraction during induction of anesthesia. Anesthesiology. 2002;97:1363–70.
14. Jung HS, Sung TY, Kang H, Kim JS, Kim TY. Cerebral blood flow change during volatile induction in large-dose sevoflurane versus intravenous propofol induction: transcranial doppler study. Korean J Anesthesiol. 2014;67:323–8.
15. Engelhard K, Werner C, Möllenberg O, Kochs E. Effects of remifentanil/propofol in comparison with isoflurane on dynamic cerebrovascular autoregulation in humans. Acta Anaesthesiol Scand. 2001;45:971–6.
16. Harrison JM, Girling KJ, Mahajan RP. Effects of propofol and nitrous oxide on middle cerebral artery flow velocity and cerebral autoregulation. Anaesthesia. 2002;57:27–32.
17. Dong ML, Kofke WA, Policare RS, et al. Transcranial Doppler ultrasonography in neurosurgery: effects of intracranial tumour on right middle cerebral artery flow velocity during induction of anaesthesia. Ultrasound Med Biol. 1996;22:1163–8.
18. Yoo KY, Jeong CW, Kim WM, et al. Cardiovascular and arousal responses to single-lumen endotracheal and double-lumen endobronchial intubation in the normotensive and hypertensive elderly. Korean J Anesthesiol. 2011;60:90–7.
19. Yoo KY, Jeong CW, Jeong HJ, et al. Thiopental dose requirements for induction of anaesthesia and subsequent endotracheal intubation in patients with complete spinal cord injuries. Acta Anaesthesiol Scand. 2012;56:770–6.
20. Alanoğlu Z, Tolu S, Yaļcin Ş, Batislam Y, Özatamer O, Tüzüner F. Different remifentanil doses in rapid sequence anesthesia induction: BIS monitoring and intubation conditions. Adv Clin Exp Med. 2013;22:47–55.
21. Choi EM, Min KT, Lee JR, Lee TK, Choi SH. Effect of a single dose of esmolol on the bispectral index to endotracheal intubation during desflurane anesthesia. Korean J Anesthesiol. 2013;64:420–5.
22. Lee SY, Min JJ, Kim HJ, Hong DM, Kim HJ, Park HP. Hemodynamic effects of topical lidocaine on the laryngoscope blade and trachea during endotracheal intubation: a prospective, double-blind, randomized study. J Anesth. 2014;28:668–75.
23. Warach S, Gur RC, Gur RE, Skolnick BE, Obrist WD, Reivich M. The reproducibility of the 133Xe inhalation technique in resting studies: task order and sex related effects in healthy young adults. J Cereb Blood Flow Metab. 1987;7:702–8.
24. Kofke WA, Brauer P, Policare R, Penthany S, Barker D, Horton J. Middle cerebral artery blood flow velocity and stable xenon-enhanced computed tomographic blood flow during balloon test occlusion of the internal carotid artery. Stroke. 1995;26:1603–6.
25. Brauer P, Kochs E, Werner C, et al. Correlation of transcranial Doppler sonography mean flow velocity with cerebral blood flow in patients with intracranial pathology. J Neurosurg Anesthesiol. 1998;10:80–5.