Ornim NCS abstract 2015

Optoacoustic cerebral blood flow (CBF) Monitoring During Induction of Anesthesia in Humans

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CBF is an important variable in Neurocritical care but a non-invasive monitor of CBF has not been available. A recently developed approach is based on an opto-acoustic adaptation of near infrared spectroscopy. Our objective was to determine whether the optoacoustic CBF monitor would detect changes in CBF which are known to occur with propofol(decrease) and subsequent endotracheal intubation (increase)(1).

METHODS: 57 patients scheduled for elective non-intracranial surgery were enrolled. Patients with intracranial disease were excluded. A Cerox3215F (Ornim, Israel) optoacoustic CBF monitor was used. On arrival in the operating room, the optoacoustic transducers were applied bifrontally. Baseline values were obtained. Subsequently changes in CBF from baseline were determined at three points: two minute baseline, the lowest value over three minutes after propofol injection and the highest value over five minutes after laryngoscopy. SaO_2 and mean arterial pressure were determined at the same time points. Data were evaluated by repeated measures ANOVA.

RESULTS: Mean dose of propofol given was 213 $\pm$ 77.1 mg/kg. CBF decreased to 83$\pm$14% of baseline after propofol ($P<0.001$) and increased to 146$\pm$34% of baseline after endotracheal intubation ($P<0.001$). Concurrently SaO_2 remained >95% across all measurement times. At each measurement time MAP was 105 $\pm$ 15 mmHg (baseline), 84$\pm$ 18(propofol) ($P<0.001$), and 96 $\pm$ 22mmHg (laryngoscopy) ($P=0.11$)

CONCLUSIONS: Our data are congruent with TCD observations (1) made under similar conditions and similar experimental paradigm. This supports the notion that optoacoustic monitoring yields valid real-time measures of changes in CBF in humans. Further validation research compared against other quantitative measures of CBF would be appropriate.

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<figure> of CBF changes

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

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

Abstract and Keywords

BACKGROUND. Past transcranial Doppler studies have documented the effects of the sequence of anesthesia induction followed by intubation on cerebral blood flow 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: 72 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 minutes prior to induction. Subsequent changes in CFI from baseline were determined at two time points: the lowest value over three minutes after propofol injection but before laryngoscopy; and the highest value over five minutes after the start of laryngoscopy. CFI data were evaluated using Friedman's test.
RESULTS: The median dose of propofol [IQR] given was 200 mg [200-200]. CFI decreased to 84+22% of baseline after propofol and increased to 148+58% of baseline after endotracheal intubation (both $P < 0.001$), Concurrently, SaO_2 remained >95% across all measurement times. MAP decreased significantly after intravenous induction of anesthesia from 100±20 to 84±17 mmHg ($p<0.001$) and did not change significantly from baseline with endotracheal intubation, 103±30 mmHg ($p=0.617$).
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
Optoacoustic monitor
Cerebral blood flow
Anesthesia
Propofol
Endotracheal intubation
Bariatric surgery

Introduction

Cerebral Blood Flow (CBF) is an important parameter in neuroanesthesia and neuro-critical 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 blood flow[1, 2]. The commercially available acousto-optic monitor (Cerox®, Ornim Medical) continuously generates a value for cerebral blood flow in arbitrary units between 0 and 100, called the cerebral flow index (CFI), which reflects changes in cerebral blood flow in a small volume of brain tissue beneath the probe.

Previous studies have documented significant changes in CBF velocity (CBFV) known to occur during anesthetic induction and intubation in the operative setting [3]. In the absence of intracranial pathology, a decrease in CBFV occurs upon induction with thiopental [4-6] and propofol [7-9], driven mainly by specific effects of both drugs to decrease cerebral metabolic rate with a matched decrease in CBF. In patients with brain tumors Kofke et al.reported corresponding changes in MAP and CBFV with thiopental induction (decrease) and subsequent endotracheal intubation (increase).[3] Brain tumor patients were selected in that study because of concern at the time of oligemic intracranial hypertension arising with intubation. This was not observed, hence the conclusion made 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, 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.

The present study, was not designed to validate the acousto-optic CBF monitor against another gold standard CBF monitor; but rather, as an early step in its evaluation in acute care, ascertain whether similar changes to those seen by Kofke et al.[3] with transcranial Doppler ultrasonography are observed with the acousto-optic CBF monitor, using a similar propofol-based anesthetic paradigm. Specifically, using the acousto-optic method to measure 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 Cerox probe placement were excluded. A total of 79 patients were enrolled from November 2013 through June 2014.

A Cerox 3215F (Ornim Medical, Kefar 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. Cerebral flow index (CFI) was recorded continuously for at least 2 minutes prior to induction of anesthesia, and for at least 5 minutes after 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 mean arterial pressures 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.

Baseline CFI values were obtained for at least 2 minutes prior to induction. Subsequent changes in CFI from baseline were determined at two time points: the lowest value over three minutes after propofol injection but before laryngoscopy; and the highest value over five minutes after the start of laryngoscopy.

Descriptive statistics included counts, median, and IQR for continuous measurements, and counts with percent for categorical measurements. The distribution of measurements between patients that 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 □=0.05. Data are presented as either median [IQR] or mean ± 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 of which differ only in gender distribution from the analysis group). The data summary which follows is based on the remaining 73 patients. Demographic data are displayed in table 1.

The median age was 51.5 years [40.0-60.5]. The patients undergoing spine surgery were significantly older than the bariatric patients (p=0.047, Dunn's post hoc test). BMI was significantly higher among bariatric patients (p<0.001, Dunn's post hoc test). There was a borderline 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% (Table 3).

CFI decreased to 84±23% of baseline after propofol (p< 0.001) and increased to 147±59% of baseline following endotracheal intubation (p< 0.001).(Figure 1) This was seen in all surgical subgroups. MAP decreased significantly after intravenous induction of anesthesia from 100±20 to 84±17 mmHg (p<0.001) then returned to a value not significantly different from baseline following endotracheal intubation 103±30 mmHg (p=0.617). (Figure 2) The MAP pattern varies 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, Figure 1). The use of vasoactive agents did not affect the CFI and MAP patterns overall or for any specific subgroup. Concurrently SaO2 remained >95% for the duration of monitoring in all subjects.

Discussion

We have shown that the acousto-optic monitor can detect CFI changes reflecting expected proportionate changes in cerebral blood flow occurring during intravenous induction of anesthesia followed by laryngoscopy. The present study was not designed however, 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, and with concomitant nociceptive input such as laryngoscopy and endotracheal intubation [3, 10]. Other factors which would be expected to have an effect on CBF are arterial P_aCO_2 and the potential vasoactive properties of drugs given perioperatively. The time frame of the measurements would suggest that there was not enough time for significant changes in $PaCO_2$ to arise. 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.

Although we have no direct measure of absolute cerebral blood flow in our subject population, our data are congruent with observations made using transcranial Doppler (TCD) measurements of flow-velocity changes in the middle cerebral artery (MCAFV) under similar experimental conditions[3, 10]. Although TCD is also not a direct measure of flow because the technique cannot detect the caliber of intracranial vessels, a good correlation between MCAFV and actual CBF has been established using Xenon-CT CBF[11, 12] such that changes in blood flow velocity reflect changes in CBF. The acousto-optic monitor appears to be able to detect these same expected changes in CBF. In addition it offers several benefits as 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.

This study's obvious limitation 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 cerebral blood flow, and in the monitoring of the progress of their treatment. Further validation studies are needed in patients with intracranial pathology.

Figure 1
Changes in Cerebral Flow Index (CFI) on induction and intubation relative to baseline for each surgical procedure and overall (means and standard deviations). CFI was significantly decreased from baseline on induction (P<0.001), and increased from baseline after intubation
(P<0.001).

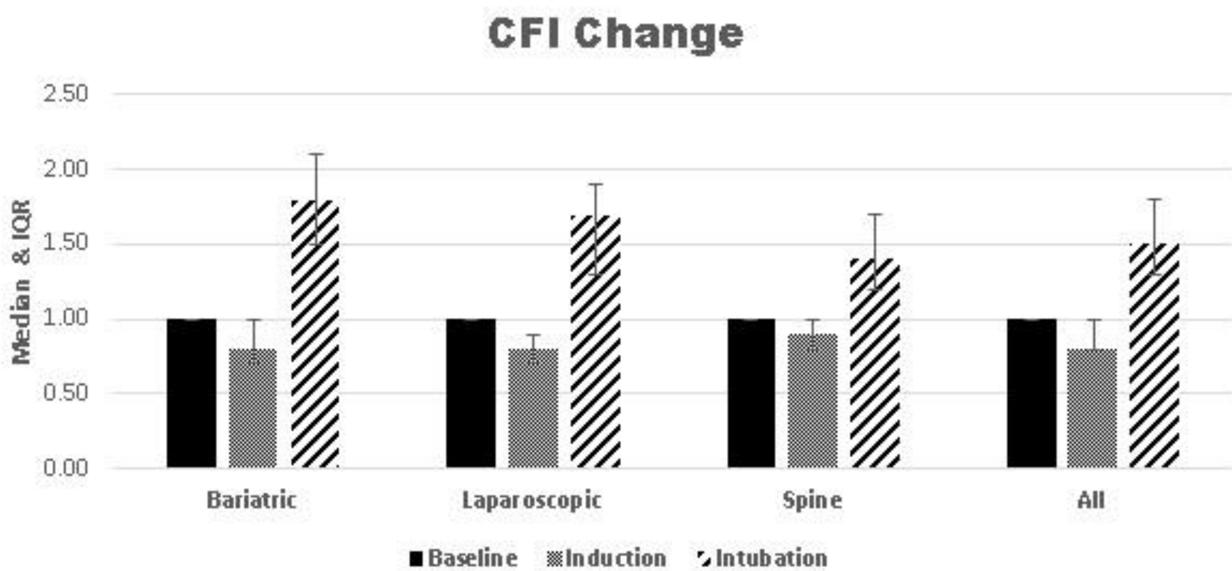
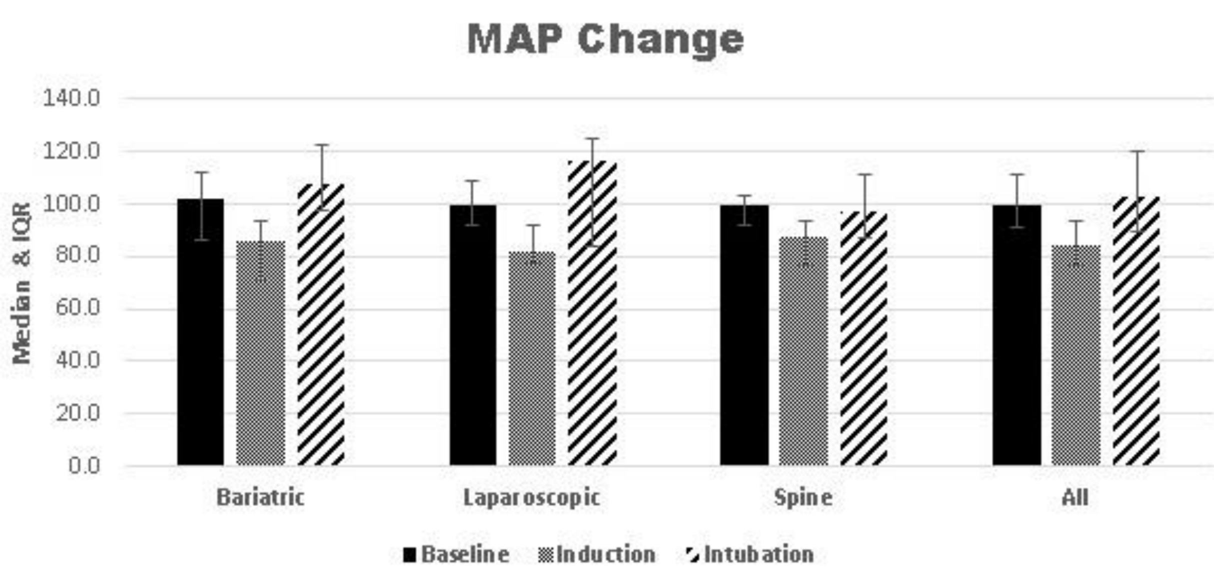


Figure 2
Changes in Mean Arterial Pressure (MAP) on induction and intubation relative to baseline for each surgical procedure and overall (means and standard deviations). MAP was significantly decreased from baseline on induction (P<0.001), and not significantly different to baseline after endotracheal intubation (P=0.617).



Conflicts of Interest

Marlon Schwarz, Giovanni Rivera, Mary Hammond and Kirk Jackson declare that they have no conflict of interest.

Limor Barkan, Zmira Silman and Moshe Kamar are employees of Ornim Medical Ltd.

W. Andrew Kofke has received funding for the present study from Ornim Medical Ltd.

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