Original Article

Influence of blood pressure on internal carotid artery blood flow during combined propofol-remifentanil and thoracic epidural anesthesia

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Abstract

Background and Aims: Anesthesia often reduces mean arterial pressure (MAP) to a level that may compromise cerebral blood flow. We evaluated whether phenylephrine treatment of anesthesia-induced hypotension affects internal carotid artery (ICA) blood flow and whether anesthesia affects ICA flow and CO_2 reactivity.

Material and Methods: The study included twenty-seven patients (65 ± 11 years; mean ± SD) undergoing esophageal resection (n = 14), stomach resection (n = 12), or a gastroentero anastomosis (n = 1) during combined propofol-remifentanil and thoracic epidural anesthesia. Duplex ultrasound evaluated ICA blood flow. Evaluations were before and after induction of anesthesia, before and after the administration of phenylephrine as part of standard care to treat anesthesia-induced hypotension at a MAP below 60 mmHg, and the hypocapnic reactivity of ICA flow was determined before and during anesthesia.

Results: Induction of anesthesia reduced MAP from 108 ± 12 to 66 ± 16 mmHg ($P < 0.0001$) and ICA flow from 340 ± 92 to 196 ± 52 mL/min ($P < 0.0001$). Phenylephrine was administered to 24 patients (0.1–0.2 mg) and elevated MAP from 53 ± 8 to 73 ± 8 mmHg ($P = 0.0001$) and ICA flow from 191 ± 43 to 218 ± 50 mL/min ($P = 0.0276$). Furthermore, anesthesia reduced the hypocapnic reactivity of ICA flow from 23 (18–33) to 14%/kPa (10–22; $P = 0.0068$).

Conclusion: Combined propofol–remifentanil and thoracic epidural anesthesia affect ICA flow and CO_2 reactivity. Phenylephrine partly restored ICA flow indicating that anesthesia-induced hypotension contributes to the reduction in ICA flow.

Keywords: Anesthesia, carotid artery, cerebrovascular circulation, hypotension

Introduction

Propofol reduces cerebral blood flow (CBF) by approximately 50% by lowered neuronal activity with maintained cerebral O_2 extraction fraction.[1,2] Also, propofol anesthesia reduces mean arterial pressure (MAP)[2,3] but it is unknown to what extent the reduction in CBF by propofol anesthesia is aggravated by a low MAP. According to the intraoperative goals, vasoactive medication should be considered if MAP decreases to below, e.g. 60 mmHg, or below 80% of the value before induction, in order to maintain organ blood flow.[4] However, MAP may also be kept low during the so-called hypotensive anesthesia in order to reduce surgical bleeding.[5]

We evaluated internal carotid artery (ICA) flow non-invasively by duplex ultrasound. In patients undergoing combined propofol–remifentanil and thoracic epidural anesthesia, we

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.JOACP_575_20

How to cite this article: Olesen ND, Egesborg AH, Frederiksen HJ, Kitchen CC, Svendsen LB, Olsen NV, *et al*. Influence of blood pressure on internal carotid artery blood flow during combined propofol-remifentanil and thoracic epidural anesthesia. J Anaesthesiol Clin Pharmacol 2022;38:580-7.

Submitted: 29-Sep-2020 **Revised:** 14-Apr-2021
Accepted: 14-May-2021 **Published:** 09-Sep-2022

evaluated the effect of induction of anesthesia on ICA flow and whether ICA flow is affected by hypotension. The primary outcome was the effect on ICA flow by the administration of phenylephrine when MAP decreased to below 60 mmHg. We hypothesized that an increase in MAP would elevate ICA flow. The arterial CO_2 tension ($PaCO_2$) is a potent cerebral vasodilator[6] although hypotension appears to attenuate cerebral CO_2 reactivity.[7] Thus, the CO_2 reactivity of the ICA was determined before and after induction of anesthesia, and ICA flow was 'corrected' for eventual changes in $PaCO_2$.

Material and Methods

Thirty consecutive patients, planned for open esophageal or stomach resection, aged ≥18 years were recruited for the study after providing written informed consent between December 2016 and July 2017. Ethical approval for the study was provided by the Ethical Committee E of the Capital Region (Videnskabsetiske Komité E for Region Hovedstaden, Kongens Vænge 2, DK-3400, Hillerød, Denmark; Chairperson: Cecilie Mejer Hjelm; October 18, 2016; protocol id: H-16036250) in accordance with the Declaration of Helsinki. This manuscript adheres to the applicable STROBE guideline. The conduct of the study and the safety of the patients were overseen by the authors. Preoperative hypertension was defined by medical history and treatment with antihypertensive medication. Exclusion criteria were inadequate visualization of the ICA, e.g., due to high bifurcation, above 15% obstruction of either ICA as evaluated by duplex ultrasound prior to inclusion, and neurologic disease considered to affect CBF including dementia, epilepsy, and stroke. Data from this study on the effect of a so-called mesenteric traction syndrome, in response to surgical manipulation of the viscera, on central hemodynamics and ICA flow will be published elsewhere.

No premedication was administered and surgery was after an overnight fast with the patients allowed to drink "clear" fluids until 2 h before the operation. A catheter was inserted in the left radial artery under the cover of local anesthesia. Also, under cover of local anesthesia, an epidural catheter was placed (T8-T10) and 15–30 mg bupivacaine administered followed by infusion of bupivacaine with morphine (2.5 and 0.05 mg/mL; 5 mL/h) and an hourly 15 mg bolus dose bupivacaine. Induction of anesthesia was by propofol with cisatracurium or suxamethonium for muscle relaxation and anesthesia was maintained by propofol and remifentanil. A tracheal tube was placed and ventilation aimed at maintaining an end-tidal CO_2 tension ($PetCO_2$) at the pre-anesthesia level (Dräger Primus, Drägerwerk, Lübeck, Germany). Guided by ultrasound, a central venous catheter was inserted through the internal jugular vein contralateral to the ICA insonation site. Blood volume was supported by lactated Ringer's solution and human albumin 5%. An anesthesia-induced reduction in MAP to below 60 mmHg was treated by bolus dose administration of phenylephrine or ephedrine or infusion of noradrenaline on the choice of the anesthesiologist as part of routine care.

Radial artery pressure derived stroke volume, cardiac output (CO), and total peripheral resistance by modified pulse-contour analysis (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). The ICA flow was evaluated by duplex ultrasound using a linear transducer at 8–12 MHz (Logiq E, transducer 12L, GE Medical System, Jiangsu, China). The left or right ICA was chosen for insonation according to image quality, i.e. low carotid bifurcation and absence of torsion. The head was turned to the contralateral side and the evaluation was conducted at least 1.5 cm distal to the bifurcation with an insonation angle ≤60° and pulsed-wave Doppler determined the angle-corrected time-averaged maximum blood velocity that corresponds to twice the mean velocity.[8] The mean of two to three recordings over approximately 20 s is reported. Software determined the vessel diameter (Brachial Analyzer for Research v. 6, Medical Imaging Applications LLC, Coralville, IA, USA) and flow was calculated as[8]:

$$\text{ICA blood flow} = \pi * (\text{diameter}/2)^2 * (\text{Time-averaged maximum blood velocity})/2$$

and conductance was ICA flow/MAP. The ICA flow was evaluated by a single ultrasonographer. Still images of the duplex ultrasound evaluation in a representative patient are presented in Figure 1.

Near-infrared spectroscopy determined forehead oxygenation (S_cO_2) on the left side and right deltoid muscle oxygenation (S_mO_2) (INVOS 5100C, Somanetics, Troy, MI, USA) while laser Doppler flowmetry evaluated forehead skin blood flow and oxygenation at a depth of 1–2 mm close to the hairline (VMS-LDF and VMS-OXY, Moor Instruments, Axminster, UK). Depth of anesthesia was evaluated by the Bispectral index (BIS; BIS Complete Monitoring Systems, Covidien, USA).

Central hemodynamic and skin variables were sampled at 100 Hz (Powerlab, ADInstruments, Bella Vista, Australia) and S_cO_2, S_mO_2, and BIS every 5 s on a PC with values averaged over 2 min. Immediately following the evaluation of ICA flow, arterial blood was sampled in pre-heparinized syringes (QS50, Radiometer, Copenhagen, Denmark) and analyzed for blood gas variables (ABL 725, Radiometer). For

patients undergoing esophageal resection, measurements were conducted before one-lung ventilation. Evaluation of MAP, HR, and ventilatory parameters were a part of standard of care.

The experimental protocol is presented in Figure 2. Evaluations were conducted at rest breathing room air, following intubation, during anesthesia-induced hypotension at a MAP below 60 mmHg when the anesthesiologist considered to administer 0.1–0.2 mg phenylephrine as part of standard care, and 3–5 min after administration. No attempt was made to reduce MAP deliberately (by, e.g., vasodilators). Cerebral CO_2 reactivity was evaluated by hyperventilation when the patients were awake and re-evaluated 60 min after incision and then, in random order, included both hypo-, normo-, and hyperventilation. The changes in ventilation were guided by an increase or a decrease in $PetCO_2$ by 1.5 kPa as evaluated by a face mask, and on the ventilator, respectively, and measurements were conducted after the value had been stable for 5 min. The only interventions conducted as part of the study were the changes in ventilation in order to evaluate CO_2 reactivity.

Statistical analysis

The minimal clinically important difference in ICA flow by phenylephrine treatment of hypotension was estimated to be 10% based on an association between near-infrared spectroscopy determined reduction in S_cO_2 by 10% and postoperative cognitive dysfunction.[9] A sample size calculation suggested that 27 patients were needed to detect a difference in ICA flow by 10% at a 5% significance level with a power of 80%.[10]

The primary outcome was the change in ICA flow by phenylephrine treatment of hypotension. Secondary outcomes were (1) the change in ICA flow by induction of anesthesia and (2) the change in hypocapnic ICA CO_2 reactivity by anesthesia.

Cardiovascular and anesthetic variables

Analysis of variables at the time points: at rest before induction, after induction of anesthesia, and before and after the administration of phenylephrine was by a repeated measure mixed model, fit by restricted maximum likelihood in a structured covariance model by compound symmetry, with time point as a fixed effect and the subject variable as a random effect and if significant, we evaluated changes from when the patients were awake and in response to phenylephrine (PROC MIXED; SAS 9.4, SAS Institute, Cary, NC, USA). Correction for multiple testing was by the Tukey–Kramer method. As the results may be confounded by hypertension, we also evaluated whether changes in MAP and ICA flow were similar for normo- and hypertensive patients by adding an interaction factor post-hoc. Analysis of plasma lactate concentration was after logarithmic transformation in order to obtain a normal distribution to allow for parametric tests.

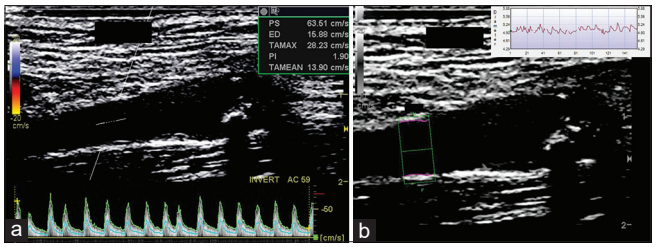

Figure 1: Duplex ultrasound images from a representative patient. Pulsed-wave evaluation of ICA time-averaged maximum blood velocity (a) and evaluation of ICA diameter using automated wall-tracking software (b)

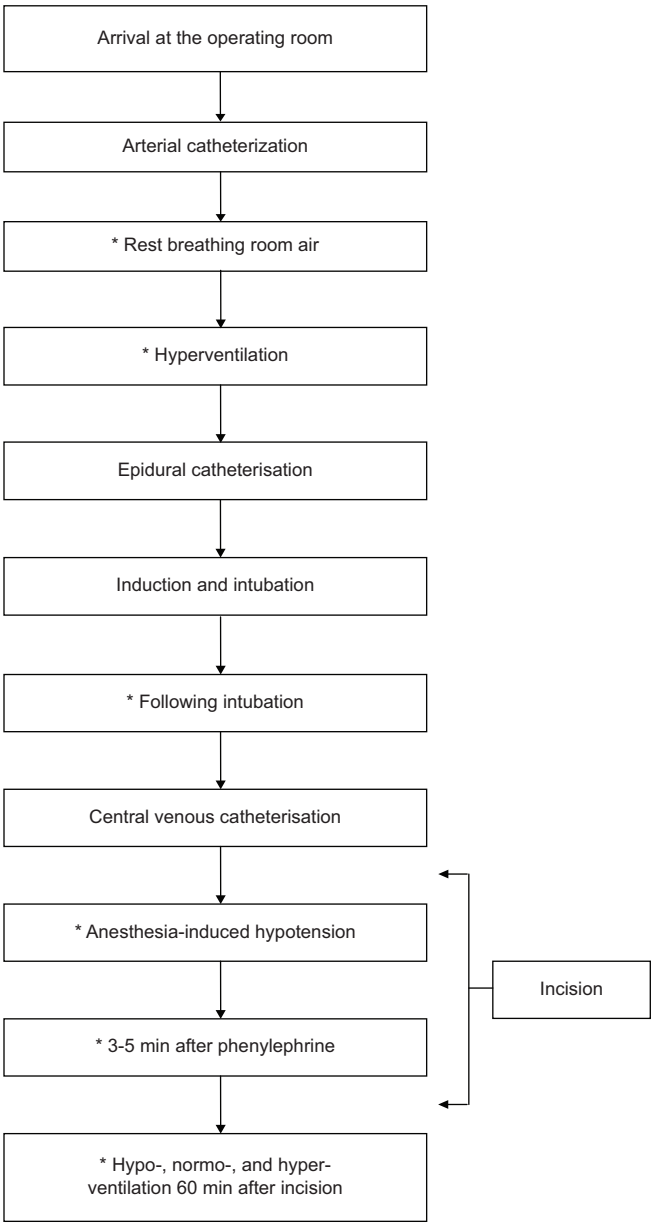

Figure 2: Experimental protocol. Evaluation of ICA flow and arterial gas variables are denoted by *. Evaluations during hypo-, normo-, and hyperventilation during anesthesia were conducted in random order

For the fraction of inspired oxygen, BIS, and the infusion rate of propofol and remifentanil, the change from before to after phenylephrine was evaluated by a Wilcoxon signed-rank test.

CO_2 reactivity

The ICA CO_2 reactivity was calculated as the change in flow *100/change in $PaCO_2$* baseline flow and similarly for S_cO_2. The ICA flow and conductance and S_cO_2 during anesthesia were 'corrected' for changes in $PaCO_2$ from the value at rest by the individually determined CO_2 reactivity to hypo- and hypercapnia during anesthesia as evaluated by linear regression. Comparison of ICA hypocapnic reactivity when patients were awake and during anesthesia was by a linear mixed model fit by restricted maximum likelihood with the change in ICA flow as the outcome and the fixed effect was the change in $PaCO_2$ with an interaction factor for the difference and the subject variable as a random effect.

Reproducibility of ICA flow

The intraclass correlation coefficient for intrarater reliability of ICA flow measurements was evaluated by two-way mixed models (model 3,1) with an absolute agreement for average measures (SPSS 25, Corp. 2013, Armonk, NY). Values are presented as mean ± SD or median (IQR) for not normally distributed data with changes reported as mean (95% CI) and statistical significance was set at $P < 0.05$.

Results

Fourteen patients underwent esophageal and 12 patients stomach resection, while surgery for one patient was gastroentero anastomosis due to carcinosis [Table 1]. Three patients were excluded from the analysis because the central venous catheter was placed at the chosen insonation side, due to the use of sevoflurane, or because the CO_2 reactivity was not evaluated due to early one-lung ventilation. For one patient, the evaluations were not conducted when he was awake and after intubation. Thirteen patients were hypertensive and treated with one, two to three drugs (n = 6, 4, and 1, respectively). Duration of anesthesia and surgery and fluid balance are presented in Table 2. No patient received red blood cells during the study period. The length of stay in hospital was 9 days (8–10) and there was no mortality within 1 month.

CO_2 reactivity

When the patients were awake, hyperventilation reduced $PaCO_2$ from 5.0 ± 0.5 to 3.9 ± 0.8 kPa while during anesthesia, $PaCO_2$ was 5.3 ± 0.6 kPa and reduced to 4.1 ± 0.7 kPa and elevated to 6.4 ± 0.5 kPa for the evaluation of CO_2 reactivity. The hypocapnic ICA CO_2 reactivity was 23%/kPa (18–33) when the patients were awake and decreased to 14%/kPa (10–22; P = 0.0068) during anesthesia while the hypercapnic reactivity was 24%/kPa (15–33). The CO_2 reactivity for S_cO_2 to hypocapnia when the patients were awake was 3.6%/kPa (2.4–5.3) and similar 3.6%/kPa (1.1–5.6; P = 0.7223) during anesthesia while the hypercapnic reactivity was 4.3%/kPa (1.0–6.9).

Induction of anesthesia and treatment of hypotension

Induction of anesthesia reduced MAP, heart rate, stroke volume, and thus, CO whereas total peripheral resistance remained unaffected at a BIS of 42 ± 11 [Table 3]. After tracheal intubation, 16 patients had received 0.2 mg (0.2–0.3) phenylephrine, 16 patients 10 mg (10–20) ephedrine while 5 patients had received no vasopressors. The ICA blood velocity was reduced with a stable diameter, and thus, the flow decreased by 144 mL/min (95% CI: 121–168; $P < 0.0001$) resulting in no change in vascular conductance. Induction of anesthesia did not affect S_cO_2, skin blood flow, and skin oxygenation whereas S_mO_2 increased. Additionally, $PaCO_2$ and PaO_2 increased while arterial hemoglobin and O_2 content decreased with no significant change in plasma lactate concentration.

Table 1: Patient characteristics (n=27)

Age (years)	65±11
Height (cm)	172±8
Weight (kg)	79±18
Body mass index (kg/m^2)	27±5
Male, n	14
Preoperative risk factors	
ASA physical status II/III, n	17/10
Arterial hypertension, n	13
Dyslipidemia, n	6
Diabetes mellitus type 2, n	3
Chronic obstructive pulmonary disease, n	3
Chronic heart failure NYHA II, n	2

Values are mean±SD or count. ASA, American Society of Anesthesiologists physical status classification. NYHA, New York Heart Association classification

Table 2: Intraoperative data (n=27)

Duration of anesthesia (min)	242 (204-283)
Duration of surgery (min)	194 (164-237)
Volume balance	
Saline (l)	0.9 (0.8-1.0)
Lactated Ringer's solution (l)	1.0 (0.8-1.1)
Human albumin 5% (l)	0.5 (0.5-1.0)
Total fluid administration (l)	2.4 (2.2-2.9)
Blood loss (l)	0.5 (0.3-0.7)
Diuresis (l)	0.5 (0.2-0.7)
Fluid balance (l)	1.4 (1.0-1.8)

Values are median (IQR)

Table 3: Hemodynamic, arterial, and anesthetic variables

	Awake (*n*=26)	Induction (*n*=26)	Hypotension (*n*=24)	Phenylephrine (*n*=24)	*P*
Mean arterial pressure (mmHg)	108±12	66±16*	53±8*	73±8*†	<0.0001
Heart rate (bpm)	79±11	66±12*	66±8*	62±9*	<0.0001
Stroke volume (mL)	102±45	78±23*	72±19*	82±24*	<0.0001
Cardiac output (l/min)	7.7±2.8	5.0±1.4*	4.6±1.4*	4.9±1.4*	<0.0001
Total peripheral resistance (mmHg*min/L)	16±7	15±6	13±4	17±6†	0.0107
ICA TAVMAX (cm/s)	52±13	36±9*	36±10*	38±12*	<0.0001
ICA diameter (mm)	5.4±0.9	5.3±0.8	5.2±0.8	5.4±0.9	0.877
ICA blood flow (mL/min)	340±92	196±52*	191±43*	218±50*†	<0.0001
ICA conductance (mL/[min*mmHg])	3.2±0.9	3.1±1.0	3.6±0.9*	3.0±0.7†	0.0037
Frontal lobe oxygenation (%)	66±8	68±9	64±9*	62±10*	<0.0001
Muscle oxygenation (%)	77±9	83±8*	78±9	78±8	<0.0001
Skin blood flow (PU)	113±79	128±101	97±55	103±64	0.4775
Skin oxygenation (%)	81±9	79±8	78±13*	77±12	0.018
Arterial CO_2 tension (kPa)	5.0±0.5	5.4±0.8*	5.4±0.7*	5.4±0.6*	0.0011
Arterial O_2 tension (kPa)	12±3	34±12*	23±8*	24±7*	<0.0001
Arterial hemoglobin (mM)	7.4±1.0	7.0±1.0*	6.7±1.0*	6.8±1.0*	<0.0001
Arterial O_2 content (mM)	7.2±0.9	7.0±1.0*	6.7±1.0*	6.7±1.0*	<0.0001
Arterial lactate (mM)	0.8 (0.7-1.2)	0.9 (0.6-1.2)	1.0 (0.7-1.2)	1.0 (0.8-1.2)	0.1661
Fraction of inspired O_2 (%)	21 (21-21)	55 (48-68)	46 (41-49)	45 (41-48)†	-
Bispectral index	-	42±11	41±9	41±9	-
Propofol (μg/(min*kg)	-	64 (57-72)	65 (56-77)	65 (56-77)	-
Remifentanil (μg/(min*kg)	-	0.3 (0.3-0.4)	0.3 (0.3-0.3)	0.3 (0.3-0.3)	-

*Values are during normocapnia when awake, after intubation, and before and after phenylephrine treatment of anesthesia-induced hypotension. Values are mean±SD or median (IQR). ICA, internal carotid artery; TAVMAX, time-averaged maximum blood velocity. P values represent the overall effect as estimated by a repeated measure mixed model. For fraction of inspired O2, Bispectral index, and propofol and remifentanil infusion, the effect of phenylephrine was evaluated by Wilcoxon signed-rank test. *P<0.05 vs. awake. †P<0.05 anesthesia-induced hypotension vs. after phenylephrine*

The evaluation before and after treatment of hypotension by 0.1 mg (0.1–0.2) phenylephrine was conducted for 24 patients, before (n = 15) or after (n = 9) incision while the level of anesthesia was maintained. The MAP had been below 60 mmHg for 4 min (1–6). The effect of phenylephrine was not evaluated in three subjects because one patient did not receive any sympathomimetic drugs while for two patients MAP was maintained by noradrenaline. At the evaluation during hypotension, the accumulated vasopressor administration had been 0.3 mg (0.2–0.4) phenylephrine for 19 patients and 20 mg (10–20) ephedrine for 19 patients, while two patients had received no vasopressors, and none had received noradrenaline. Before administration of phenylephrine, ICA conductance was increased while S_cO_2 was reduced as compared to when the patients were awake. Phenylephrine increased MAP and total peripheral resistance, while heart rate, stroke volume, and CO were unaffected. Changes in ICA blood velocity and diameter did not reach statistical significance, while ICA flow increased by 27 mL/min (95% CI: 3–51; P = 0.0276) with a reduction in conductance independent of correction for the small changes in $PaCO_2$. There was no significant change in S_cO_2, S_mO_2, skin variables, $PaCO_2$, PaO_2, arterial hemoglobin or O_2 content, plasma lactate concentration, or BIS in response to phenylephrine, while the fraction of inspired O_2 increased marginally.

As compared between the normo- and hypertensive patients, MAP was similar when the patients were awake (104 ± 13 vs. 111 ± 10 mmHg; P = 0.4812) and MAP was affected similarly by induction of anesthesia and by phenylephrine (P = 0.3005 for the interaction) with similar changes also in ICA flow (P = 0.9965 for the interaction). The intraclass correlation coefficient for intrarater reliability for the two to three measurements at each time point was 0.98 (95% CI: 0.97–0.99).

Discussion

This study evaluated whether treatment of hypotension attenuates the anesthesia-induced reduction in ICA flow. In middle-aged and elderly patients of whom approximately half were hypertensive, combined propofol–remifentanil and thoracic epidural anesthesia lowered MAP and reduced ICA flow by about 40%. Most of the reduction in ICA flow in response to anesthesia was likely due to a reduction in cerebral metabolism as there was little change in S_cO_2. Yet, phenylephrine treatment of anesthesia-induced hypotension at a MAP below 60 mmHg partly restored ICA flow as observed by a 15% increase. Thus, about 20% of the reduction in ICA flow induced by anesthesia appears to be in consequence of a low MAP as phenylephrine has no direct

effect on CBF,[10] and the blood–brain barrier seems to be preserved by propofol.[11]

Intraoperative cerebral hypoperfusion is of interest because postoperative cognitive dysfunction and delirium are common following major surgery, particularly in the elderly, and may relate to intraoperative hypotension[12] although that is not a universal finding.[13] Cerebral autoregulation is often considered to maintain CBF when MAP is kept between 60 and 150 mmHg.[14] However, CBF may be affected by a reduction in MAP even within the autoregulatory range[15] and it is unclear whether propofol affects the lower limit of cerebral autoregulation. A previous study demonstrated a 15% increase in ICA flow along with an increase in CO in response to a noradrenaline-induced elevation in MAP from 60–65 to 80–85 mmHg during major abdominal surgery during combined propofol–remifentanil and thoracic epidural anesthesia.[16] Combined with the findings of the present study, the results suggest that ICA flow is somewhat pressure passive with no clear lower limit of cerebral autoregulation. In the present study, induction of anesthesia attenuated CO and that may have contributed to the reduction in ICA flow.[17] In contrast to noradrenaline,[16] phenylephrine did not affect CO, possibly due to the beta-adrenergic effect of noradrenaline whereas phenylephrine is solely an alpha-adrenergic agonist. When the central blood volume and CO are reduced, S_mO_2 becomes affected before any change in MAP,[18] but in this study, S_mO_2 in addition to skin blood flow was maintained, indicating that CO was sufficient to secure oxygenation of tissues that are not autoregulated. Thus, the effect of phenylephrine on ICA flow was despite a low CO while $PaCO_2$ and the administration of propofol and remifentanil were unchanged.

It remains to be evaluated whether the observed 15% increase in ICA flow by phenylephrine is clinically important. The S_cO_2 was reduced during hypotension but remained low when MAP was restored by phenylephrine, possibly due to cutaneous vasoconstriction.[19] Hypotensive anesthesia is reported to be associated with an increase in markers of neuronal damage[20] but studies have probably been too small to detect an effect on the incidence of cognitive dysfunction.[21] During carotid endarterectomy in halothane-N_2O anesthesia, the acute critical lower level of regional CBF is reported at a two-thirds reduction at 18 mL/(100 g * min),[22] but the critical level is not known during propofol anesthesia. Propofol reduces CBF and cerebral metabolism similarly[2] and for resting subjects, a reduction in CBF by 30% provokes symptoms associated with cerebral hypoperfusion.[23] Postoperative cognitive complications could reflect prolonged relative cerebral hypoperfusion but that relation is not evaluated, and in addition to hypotension, cognitive complications may relate to hypoxia, drug-related effects, cerebral microemboli, inflammation, and other factors.[24] Future studies could evaluate the effect of maintaining MAP at different absolute or relative levels, using different vasopressors, on the risk of postoperative complications including cognitive dysfunction.

Propofol reduces CBF by about 40%[1-3,17] while epidural anesthesia[25] and remifentanil[26] are reported to reduce MAP with no effect on CBF. Similarly, we found that ICA flow was reduced by approximately 40% by propofol–remifentanil and epidural anesthesia at a BIS of about 40. The cerebral CO_2 reactivity, as determined by transcranial Doppler, appears unaffected by propofol,[6] although a reduction is also reported.[1] Here, the cerebral CO_2 reactivity was reduced during anesthesia which may reflect the low MAP as hypotension appears to reduce vessel reactivity.[7]

Limitations

The study was not designed to evaluate a difference between normo- and hypertensive patients. Chronic arterial hypertension may lower cerebral CO_2 reactivity[27] and elevate the limits for cerebral autoregulation although less so when hypertension is treated[28] and the preoperative MAP was similar among normo- and hypertensive patients. The sample size calculation was based on an association between near-infrared spectroscopy determined cerebral deoxygenation and postoperative cognitive dysfunction,[9] however, changes in CBF and S_cO_2 differ in response to different interventions.[19] The evaluation of ICA flow using duplex ultrasound is similar to, and correlates with, an evaluation by phase-contrast magnetic resonance imaging, albeit with large individual variability.[29] Cerebral autoregulation allows for regulation of CBF within 10 s after a change in MAP[30] whereby we consider ICA flow to have reached a steady-state 3–5 min after the administration of phenylephrine. The ICA has no extracranial branches and supplies about 80% of CBF[10] while the remainder is provided by the vertebral artery that was not evaluated. The reactivity of the intracerebral vessels may differ from that of the ICA whereby hypotension could affect regional CBF differently in different areas of the brain and the vertebral artery presents different regulation than that of the ICA.[31] Yet, propofol decreases regional flow throughout the brain.[2] In order to avoid severe hypotension, most patients had received vasopressors and that may have affected the results. Further, the administration of phenylephrine was not controlled. The effect of phenylephrine was evaluated after incision for some patients and surgical stimulation may increase regional neuronal activity and CBF, but we take the effect of surgery to be small as the increase in regional CBF is attenuated by propofol–remifentanil anesthesia combined with regional anesthesia.[32] The study would be improved by evaluation of internal jugular venous bulb O_2 saturation and only reactivity to hypocapnia was evaluated

when the patients were awake. Although ventilation aimed at the $PetCO_2$ as established when the patients were awake, $PaCO_2$ was slightly higher after induction of anesthesia but changes in ICA flow were similar with and without correction for the small change in $PaCO_2$.

Conclusion

Propofol–remifentanil combined with thoracic epidural anesthesia reduced the ICA CO_2 reactivity and ICA flow by about 40%, but phenylephrine treatment of anesthesia-induced hypotension restored about 20% of the reduction in ICA flow. The results indicate that part of the reduction in ICA flow in response to anesthesia is related to a reduction in MAP to below 60 mmHg.

Acknowledgments

For their invaluable help we thank the surgical and anesthetic personnel at the departments of Anesthesia and Surgical Gastroenterology, Rigshospitalet, Copenhagen, Denmark.

Ethical approval

Videnskabsetiske Komité E for Region Hovedstaden, DK-3400, Hillerød, Denmark; Chairperson: Cecilie Mejer Hjelm; October 18th 2016; protocol id: H-16036250.

The study was preregistered at clinicaltrials.gov. id: NCT02951273; principal investigator: N.D.O.; November 1, 2016. https://clinicaltrials.gov/ct2/show/NCT02951273?term=NCT02951273&rank=1

Financial support and sponsorship

This study was supported by University of Copenhagen. The funding source had no involvement in study design, collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Conflicts of interest

There are no conflicts of interest.

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