Internal carotid artery blood flow response to anesthesia, pneumoperitoneum and head-up tilt during laparoscopic cholecystectomy

Maria Skytioti M.D.[1], Maja Elstad M.D. Ph.D.[2], Signe Søvik M.D. Ph.D.[3]

[1]Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway. ORCID: 0000-0001-7792-5907

[2]Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway. ORCID: 0000-0003-0544-7154

[3]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway & Department of Anesthesia and Intensive Care, Akershus University Hospital, Lørenskog, Norway. ORCID: 0000-0003-4524-2268

Corresponding author Signe Søvik

Department of Anesthesia and Intensive Care, Division of Surgery

Akershus University Hospital, P.O. Box 1000, 1478 Lørenskog, Norway

Phone number: +47 679 69622, email address: signe.sovik@medisin.uio.no

Clinical trial number and registry URL: Not applicable

Prior Presentations: None

Acknowledgements: Not applicable

Word counts: Abstract (max 300): 300

Introduction (max 500): 497

Discussion (max 1500): 1479

Number of Figures: **2**

Number of Tables: **1**

Abbreviated title: Carotid flow during laparoscopic cholecystectomy

Funding: Support was provided from institutional and/or departmental sources and by the Research Council of Norway (M. Elstad, Grant #230354)

Conflicts of interests: The authors declare no competing interests

Abstract

Background Little is known about how implementation of pneumoperitoneum and head-up tilt position contributes to general anesthesia-induced decrease in cerebral blood flow in humans. We investigated this question in patients undergoing laparoscopic cholecystectomy, hypothesizing that cardiorespiratory changes during this procedure would reduce cerebral perfusion.

Methods In a non-randomized, observational study of 16 patients (ASA≤II) undergoing laparoscopic cholecystectomy, internal carotid artery blood velocity was measured by Doppler ultrasound at four timepoints: Awake, after anesthesia induction, after induction of pneumoperitoneum, and after head-up tilt. Vessel diameter was obtained each time, and internal carotid artery blood flow, our main outcome variable, calculated. We recorded pulse contour estimated mean arterial blood pressure (MAP), heart rate (HR), stroke volume (SV) index, cardiac index, end-tidal carbon dioxide ($ETCO_2$), bispectral index, and ventilator settings. Results are medians (95% CI).

Results Internal carotid artery blood flow decreased upon anesthesia induction from 350 ml min^{-1} (273-410) to 213 ml min^{-1} (175-249) (-37%, $p<0.001$), and tended to decrease further with pneumoperitoneum (178 ml min^{-1} (127-208), -15%, $p= 0.026$). Tilt induced no further change [171 ml min^{-1} (134-205)]. $ETCO_2$ and bispectral index were unchanged after induction. MAP decreased with anesthesia, from 102 (91-108) to 72 (65-76) mmHg, and then remained unchanged [Pneumoperitoneum*:* 70 (63-75); Tilt: 74 (66-78)]. Cardiac index decreased with anesthesia and with pneumoperitoneum [overall from 3.2 (2.7-3.5) to 2.3 (1.9-2.5) l min^{-1} m^{-2}]; tilt induced no further change [2.1 (1.8-2.3)]. Multiple regression analysis attributed the fall in

internal carotid artery blood flow to reduced cardiac index (both HR and SV index contributing) and MAP ($p<0.001$). Vessel diameter also declined ($p<0.01$).

Conclusions During laparoscopic cholecystectomy, internal carotid artery blood flow declined with anesthesia and with pneumoperitoneum, in close association with reductions in cardiac index and MAP. Head-up tilt caused no further reduction. Cardiac output independently affects human cerebral blood flow.

Key words: Carotid artery, internal; Cerebrovascular circulation; Cholecystectomy; Laparoscopy; Pneumoperitoneum, Artificial

Cerebral blood flow is regulated by an interplay of neurovascular coupling, oxygen and carbon dioxide reactivity, sympathetic innervation, and autoregulation that buffers variations in mean arterial pressure (MAP).[1] Numerous cardiorespiratory changes induced by anesthesia and mechanical ventilation may therefore affect cerebral flow, and surgical techniques may compound the problems. Little is known about how implementation of pneumoperitoneum with carbon dioxide and head-up tilt positioning contributes to general anesthesia-induced decrease in cerebral blood flow in humans. Here, we investigated this question in patients undergoing laparoscopic cholecystectomy.

Although artificial pneumoperitoneum during laparoscopic cholecystectomy is usually well-tolerated, the method alters the patient's cardiovascular[2 3] and respiratory physiology,[4 5] challenging the control of cerebral blood flow. General anesthesia, mechanical ventilation, the reverse Trendelenburg position and pneumoperitoneum may together lead to hemodynamic compromise. Insufflation of carbon dioxide increases systemic vascular resistance (SVR),[2] while increased intraperitoneal and intrathoracic pressures reduce venous return to the right heart, and hence stroke volume (SV) and cardiac output (CO). Pneumoperitoneum shifts the diaphragm cephalad, causing airway pressures to increase and functional residual capacity and lung compliance to decrease due to formation of basal atelectasis.[6] Positive end expiratory pressure (PEEP) employed to preserve oxygenation and improve respiratory mechanics may further compromise venous return.[7] The head-up position improves respiratory mechanics but does not favor venous return to the heart. In the presence of hypovolemia and hypotension, hypocapnia may aggravate cerebral hypoperfusion,[8] the cerebrovasculature being highly reactive to the arterial partial pressure of carbon dioxide ($PaCO_2$).[9-11]

No direct monitoring of cerebral blood flow is in routine clinical use, hence its optimization has customarily rested on indirect measures such as arterial blood pressure and arterial blood gases. Several studies have however found that also within the classic autoregulation plateau region (60–150 mmHg),[12] fluctuations in MAP are associated with fluctuations in cerebral arterial blood velocity.[13 14] Indeed, the autoregulation plateau seems to be narrow, sloped, less effective during hypotension than hypertension, and with poorer buffering for rapid than for slow MAP changes.[1 13 15] Many aspects of cerebral autoregulation however remain unresolved.

In healthy, awake humans, blood flow in the internal carotid artery (ICA) was found to decline in association with reductions in CO, despite unchanged MAP.[18] Experimental studies using cerebral blood velocity[16 19-21] or xenon imaging [17] as index for cerebral perfusion support these findings. In surgical populations, the relationship between CO and cerebral blood flow is not well characterized.

We wanted to investigate if cerebral blood flow would be affected by pneumoperitoneum, a routine surgical procedure that nevertheless presents a host of physiological challenges. In patients undergoing elective laparoscopic cholecystectomy we assessed the effects of induction of anesthesia, positive pressure ventilation, pneumoperitoneum, and head-up tilt on ICA blood flow. These changes in blood flow were then related to continuous non-invasive MAP and CO measurements. We here demonstrate that ICA blood flow declines significantly in association with reduced CO, independently of depth of anesthesia, MAP, and end-tidal carbon dioxide ($ETCO_2$). CO is an independent regulator of human cerebral blood flow.

Methods

Eligibility criteria

We recruited healthy (American Society of Anesthesiologists' Physical status (ASA) ≤2), non-obese (body mass index ≤32 kg/m^2) adults (≥18 years old) scheduled for day case laparoscopic cholecystectomy. All eligible patients in the study period (January 10th to March 10th, 2018) were invited to participate. All patients gave written, informed consent to participate. Our procedures conformed to the Declaration of Helsinki, and the Regional Ethics Committee (ref.no: 2017/1064) and the Institutional Data Protection Officer (ref.no: 2017/163) approved the study protocol and procedures.

Patients accepted as day cases are generally healthy, but quite a few take chronic medication for e.g. idiopathic hypertension, hypothyroidism, or diabetes mellitus type II. To obtain a representative population such patients were included if they reported complying with their medication and if their arterial blood pressure and blood sugar measurements were within normal limits on the day of surgery. Patients with known cerebrovascular disease were not included. No formal statistical power calculation was conducted. A sample size of ≥15 patients was considered adequate based on our previous experience with measurements of ICA blood flow in healthy humans. The study was by design a non-randomized, prospective, observational study.

Anesthesia procedure

Our study was purely observational. All anesthetic and surgical procedures followed the unit's protocols and were performed by the unit's personnel. Patients were premedicated 30–60 minutes before operation with *per os* paracetamol 15 mg kg^{-1}, diclofenac 50–100 mg, dexamethasone 8–16 mg and oxycodone depot formulation 5–10 mg. After 2–3 minutes pre-

oxygenation with 100% oxygen, anesthesia was induced with remifentanil and propofol target controlled infusion based on patient age and ideal body weight. Appropriate conditions for endotracheal intubation were achieved with remifentanil; neuromuscular blockade was not used. Anesthesia was maintained with fentanyl 3–5 mcg kg^{-1} and infusions of remifentanil and propofol at the discretion of the anesthetist. Metoclopramide 10 mg and ondansetron 4 mg were given intravenously towards the end of surgery to prevent postoperative nausea and vomiting. Intermittent doses of ephedrine (10 mg) and phenylephrine (100 mcg) or a phenylephrine infusion were used when appropriate to uphold MAP.

Patients were ventilated by volume regulated pressure control ventilation with 40% oxygen in air, tidal volumes 5–6 ml kg^{-1} of ideal body weight, inspiratory to expiratory ratio 1:2 and PEEP 6–8 cm H_2O, targeting maximal airway pressures of 20–24 cm H_2O. Initial respiratory rate was 12 breaths per minute. Respiratory rate and tidal volume were adjusted as necessary to preserve eucapnia. Standard anesthesia monitoring included oscillometric arterial blood pressure (systolic, diastolic, mean) every five minutes, pulse oximetry, heart rate (HR), three-lead electrocardiogram, and capnography. A bispectral index was used to monitor depth of anesthesia. After carbon dioxide insufflation the intraperitoneal pressure was kept at 11–14 mmHg throughout the procedure. A few minutes after induction of pneumoperitoneum the patients were tilted head-up by 10–20 degrees.

Recordings

Mean ICA blood velocity was measured by Doppler ultrasound (8 MHz probe, insonation angle 60°, Mylab Alpha, Esaote, Adcare, Høvik, Norway), approximately 2 cm above the bifurcation of the common carotid artery to avoid turbulent flow.[11] Non-invasive finger arterial pressure was recorded continuously from the middle left finger (Finometer® finger pulse contour

monitor, Finapres Medical Systems, Enschede, The Netherlands) positioned at heart level, and MAP was calculated. The finger arterial blood pressure curve was calibrated and reconstructed against brachial arterial blood pressure using an upper arm cuff before the recordings[22]. SV and CO estimates were calculated beat to beat from the finger arterial blood pressure curve using the Modelflow algorithm[22 23]. Previous work have demonstrated good correspondence between SV calculated by this algorithm and SV measured by Doppler ultrasound during normovolemia and central hypovolemia, the algorithm being particularly accurate in following variations in stroke volume[24 25]. During cardiac surgery, CO estimated by this method corresponded well with pulmonary artery thermodilution CO measurements[26].

Measurements of mean ICA blood velocity were recorded for 10–14 cardiac cycles, 4–6 times in each of the following states: 1) Awake patient fully monitored at the operating table, 2) Approximately two minutes after induction of anesthesia and endotracheal intubation, 3) Approximately one minute after induction of pneumoperitoneum, with the patient in the horizontal position, and 4) Approximately one minute after head-up tilt, i.e., reverse Trendelenburg position. The median ICA velocity value (of the 4–6 means obtained over 10-14 cardiac cycles at each state) was used in the subsequent analyses. The ICA diameter at the site of insonation was obtained in each state before recording velocity. ICA beat volume was calculated from the median ICA velocity and vessel diameter. ICA blood flow was calculated from ICA beat volume multiplied by the median HR in that state. HR, MAP, SV, CO, SVR, $ETCO_2$, peak airway pressure, PEEP, respiratory rate and tidal volume were recorded concurrently with ICA velocity recordings (approximately 2-minute recordings) by obtaining pictures of the anesthesia and pulse contour monitor screens every 3rd second with the use of an iPad. Median values were calculated for each state. Cardiac index, SV index, and SVR index

were calculated, thus adjusting for the patients' body surface area. $ETCO_2$ in awake patients was sampled from the facemask during preoxygenation; during the other states $ETCO_2$ was sampled from the endotracheal tube.

Statistical analysis

Reported values are medians with 95% CI calculated by Hodges-Lehmann's estimate, unless otherwise noted. The Friedman test for four related samples was used to test the difference across the four states. The Wilcoxon matched-pairs signed-rank test against a two-sided alternative was used to test differences between states for our primary outcome variable, ICA blood flow (StatXact, Cytel Studio 10, Cytel Inc., USA). For this test the level of significance was Bonferroni corrected and set at $p<0.01$. For ease of comparison with other work, the percentage changes in ICA blood flow, cardiac index, MAP and HR between states were also calculated for each subject; medians and 95% CI of the percentage change were calculated. The ICA blood flow response to changes in cardiorespiratory variables due to anesthesia, pneumoperitoneum and head-up tilt was modelled using linear mixed-effects multiple regression (Fit Model platform, Personality Standard least squares, Method REML, SAS-JMP 12 software for Windows, SAS Institute, Cary, NC, USA). The aim of the multivariable analysis was to identify the cardiovascular or respiratory variable(s) that could predict a change in ICA blood flow, while controlling for confounders such as the use of vasopressors and for the correlation between observations from the same subject (repeated measures design). ICA blood flow was the response variable. HR, SV index, cardiac index, MAP and $ETCO_2$ were continuous predictors (fixed effects). The use of vasopressors at each time point (dichotomous variable: Yes/No) was entered as a categorical predictor (covariate, fixed effect). Subject identity was entered as a random effect to account for the correlation between repeated

observations from the same subject. The restricted maximum likelihood method[27] was used for the estimation of fixed effects coefficients and variance component estimates for random effects. The covariance structure used was the Variance Component structure. A pre-determined forward variable sequence was followed, initially entering MAP, then cardiac index and finally $ETCO_2$ and the use of vasopressors in the model. If cardiac index turned out to be a significant predictor, substitution with HR and SV index was attempted. Inspection of the residual plots revealed no deviations from the assumptions of normality and homoscedasticity. The statistical significance level was set at $p<0.05$.

Results

Seventeen patients, four males and thirteen females, aged 45.5 years (range 23 to 76), body mass index 28.4 (range 21.1 to 31.5), ASA physical status I or II were recruited. The patients' comorbidities included diabetes mellitus type II (2/17), hypercholesterolemia (2/17), idiopathic hypertension (6/17), bipolar disorder (1/17) and asthma (1/17). One female was excluded from analysis due to an unexpected observation of a possible ICA stenosis. In four of the remaining sixteen patients we were not allowed sufficient time to obtain measurements during pneumoperitoneum in the horizontal position; these patients provided only partial data. All collected data were analyzed and no outliers were observed.

Propofol infusion rates [median (quartiles)] were 7.1 (5.9 to 7.9), 6.3 (5.8 to 7.6), and 6.1 (5.8 to 7.1) mg kg^{-1} h^{-1} after anesthesia induction, pneumoperitoneum, and head-up tilt, respectively. Corresponding remifentanil infusion rates were 0.28 (0.16 to 0.41), 0.30 (0.25 to 0.36), and 0.30 (0.24 to 0.39) mcg kg^{-1} min^{-1}. Ephedrine was given alone (8/16 patients) or in combination with phenylephrine (2/16 patients) to restore MAP after induction of anesthesia and head-up tilt. Median (quartiles) total doses of ephedrine (10 mg) and/or phenylephrine (0.1 mg) was 1 (0 to 2). Measurements of ICA blood velocity were done only after any administered vasopressors had taken effect and MAP was restored.

Table 1 presents absolute values of cerebrovascular, cardiovascular, and respiratory variables at each time point. Figure 1 summarizes group mean ICA flow and velocity, ICA diameter, cardiac index, SV index, HR, MAP, SVR index and $ETCO_2$ in awake patients and after anesthesia, pneumoperitoneum and tilt.

Effects of anesthesia

Induction of anesthesia and tracheal intubation resulted in an 18% reduction in cardiac index (–28% to –9%; p=0.001) and a 30% reduction in MAP (–37% to –24%; p<0.001) compared to the awake state. The decline in cardiac index resulted from a fall in HR (p=0.002); SV index remained unaltered, likely due to a marked decline in SVR index (Figure 1).

ICA diameter declined (p<0.010) on induction of anesthesia (Table 1), while ICA beat volume was reduced by 27% (–38% to –20%; p<0.001) and ICA blood flow was reduced by 37% (–45% to –31%; p<0.001).

Effects of pneumoperitoneum

Induction of pneumoperitoneum with the patient in the horizontal position induced a marked increase in SVR index (p<0.001) and a fall in SV index (p<0.005, Figure 1), causing cardiac index to decrease by a further 16% (–22% to –11%; p=0.001). Compared to measurements after anesthesia induction, HR and MAP remained unaltered. ICA beat volume decreased by an additional 16% (–22% to –14%; p=0.026) upon insufflation of pneumoperitoneum, causing ICA blood flow to fall by an additional 15% (–29% to –7%; p=0.026). The depth of anesthesia (bispectral index, infusion rates of propofol and remifentanil) did not change after induction of anesthesia, and $ETCO_2$ was kept unchanged by ventilator adjustments.

Effects of head-up tilt

Positioning the patient in the reverse Trendelenburg position did not induce further changes in ICA blood flow or ICA beat volume. Also cardiac index remained unaltered, as SV index declined marginally (p=0.024) but HR increased (+15%, p=0.003) and regained pre-anesthetic values. SVR index, MAP, and $ETCO_2$ did not change (Table 1).

Combined effects of anesthesia, pneumoperitoneum and tilt

Overall, compared to the awake state, ICA blood flow declined by 48% (–55% to –43%, $p<0.001$), ICA beat volume by 47% (–54% to –42%, $p<0.001$), and cardiac index by 36% (–41% to –32%, $p<0.001$) (Figure 1). The Friedman test confirmed that ICA blood flow was significantly different among the states ($p<0.001$).

Mixed effects model

A linear mixed-effects model explained 88% of the variance in ICA blood flow (Adjusted R^2= 0.88; p=0.001). Cardiac index and MAP contributed significantly to ICA blood flow variance (Figure 2). $ETCO_2$ and the use of vasopressors did not contribute and were therefore removed from the model. A drop of 1 l min^{-1} m^{-2} in cardiac index predicted a drop of 88 ml min^{-1} in ICA blood flow ($p<0.001$), whereas a drop of 10 mmHg in MAP predicted a drop of 26 ml min^{-1} in ICA blood flow ($p<0.001$). Of the total random variance, 75% was attributed to variability between subjects. When SV index and HR were introduced as predictors instead of cardiac index, a reduction of 10 ml m^{-2} in SV index predicted a 64 ml min^{-1} reduction in ICA blood flow ($p<0.001$), a reduction of 10 beats/min in HR predicted a reduction of 63 ml min^{-1} in ICA blood flow ($p<0.001$), and a reduction of 10 mmHg in MAP predicted a reduction of 21 ml min^{-1} in ICA blood flow ($p<0.001$).

Discussion

We here demonstrate that in ASA I–II patients undergoing elective laparoscopic surgery, internal carotid artery (ICA) blood flow declined by 48% from the awake state to the setting with anesthesia, pneumoperitoneum and head-up tilt. Though reduced cerebral metabolism due to anesthesia likely contributed, we found that cardiac index and MAP were major predictors of the ICA blood flow response. These findings contrast the classical cerebral autoregulation view and introduce cardiac output as an independent effector of cerebral blood flow during laparoscopic surgery.

Induction of pneumoperitoneum decreased cardiac index (–16%) and ICA blood flow (–15%) despite unaltered MAP, $ETCO_2$, bispectral index readings, and infusion rates of anesthetic agents. The observed effect of cardiac index on human cerebral blood flow during general anesthesia is in line with our findings in awake healthy volunteers[18], who experienced a 15% reduction in ICA blood flow during a 30% acute cardiac index reduction, despite preserved MAP. These results may have important implications for treatment strategies.

Several previous studies have reported on the relation between cerebral perfusion and acute changes in CO in awake healthy volunteers[16 18-20 28], as reviewed.[21] However, most of these studies measured cerebral blood velocities rather than flow. The novelty of the present study lies in assessing ICA diameter as well as ICA blood velocity at each study condition, thus preventing changes in ICA diameter[1 29 30] from affecting the results. This method enabled us to estimate the effect of a drop in cardiac index and MAP on cerebral blood flow during general anesthesia in a surgical population.

Several factors interacted to decrease cardiac index, and thus cerebral flow, during laparoscopic cholecystectomy (Figure 1). Induction of anesthesia and mechanical ventilation reduced cardiac index (–18%) by reducing HR, while SV index was maintained by longer filling times and reduced SVR index. Reduced venous return due to positive-pressure ventilation likely contributed to reduce cardiac index.[31] Pneumoperitoneum decreased cardiac index further (–16%) through a marked drop in SV index, although HR returned to preanesthetic levels. Sympathetic stimulation and release of hormones such as renin-aldosterone, vasopressin and catecholamines induced by insufflation of the peritoneum[2 32] probably caused the 21% SVR increase, which maintained MAP despite the decrease in cardiac index.

Increases in SVR as large as 60%, and 30–40% increases in MAP, have been reported upon induction of pneumoperitoneum during nitrous oxide and isoflurane anaesthesia.[3] Reported effects of pneumoperitoneum on cardiac index vary however, likely due to differing anesthetic protocols. Cardiac index measured by transesophageal echocardiography did not change upon pneumoperitoneum during sevoflurane anesthesia despite large increases in SVR and MAP,[33] while other studies found 15–20% reductions in cardiac index upon pneumoperitoneum during intravenous[34] or inhalation anesthesia.[3] Cerebral blood flow may thus be variably affected by pneumoperitoneum.

Our non-invasive study design did not allow us to distinguish the effect of reduced cardiac index on ICA blood flow from possible effects of increased cerebral vascular resistance. Vasopressin induces powerful vasoconstriction in isolated human cerebral arteries.[35] Cerebral vasoconstriction mediated by hormone release and by direct sympathetic activation on the cerebral circulation might have contributed to the fall in ICA blood flow during pneumoperitoneum.

Targeting a MAP >65 mmHg and preserving eucapnia is a commonly used strategy to preserve cerebral blood flow in a clinical setting, based on the concept of a MAP plateau where autoregulation is supposed to maintain flow. Lassen's classical curve was however composed from mean values of 11 subject groups in 7 studies,[12] and a more pressure-passive relationship between cerebral blood flow and MAP has been indicated.[1 36] Rapid fluctuations in MAP of 10–20 mmHg were associated with fluctuations in cerebral arterial blood velocity,[13 14] and cerebral autoregulation seems to buffer hypotension less effectively than hypertensive challenges.[1] Though cerebral autoregulation was thought to remain intact during propofol–remifentanil anesthesia,[37-42] these studies extrapolated cerebral blood flow from velocity recordings and did not control for concomitant cardiovascular changes. In the present study, the initial fall in MAP probably effected the marked drop in ICA blood flow upon induction of anesthesia, though neurovascular coupling and reduced cardiac index contributed. MAP was subsequently kept stable with a fluid bolus and intermittent doses of vasopressors if needed. The continuing decline in ICA blood flow during surgery thus was unlikely to be due to reduced MAP.

Reduced cerebral blood flow during propofol anesthesia has been attributed to reductions in cerebral metabolism,[43 44] i.e., neurovascular coupling.[1] In anesthetized healthy volunteers examined with positron emission tomography, target concentrations of propofol up to 2.5 mcg ml^{-1} resulted in a 54% reduction in cerebral glucose metabolic rate and a 47% reduction in total cerebral blood flow.[43] That study reported unchanged MAP and $PaCO_2$ during propofol anesthesia, but HR declined and CO was not measured. In the present study, reduced cerebral metabolism probably was an important contributor to the large reduction in ICA blood flow (–37%) following induction of anesthesia, though this effect could not be separated from

concurrent effects of reduced MAP and cardiac index. Throughout surgery, bispectral index was unchanged; thus other mechanisms than reduced cerebral metabolism must have acted to further reduce ICA blood flow.

Carbon dioxide is a powerful regulator of cerebral blood flow. Laparoscopic surgery is associated with reductions in total lung volume, functional residual capacity and lung compliance,[5 45] and peritoneal insufflation with carbon dioxide increases $PaCO_2$. Increased minute ventilation is needed to prevent hypercapnia and avoid impaired cerebral autoregulation.[1] In the present study, $ETCO_2$ was kept stable after induction of anesthesia by altering ventilator settings; consequently $ETCO_2$ did not statistically affect cerebral blood flow.

The reverse Trendelenburg position did not further decrease cardiac index or ICA blood flow compared to the horizontal position. Both surgical stimulation and ephedrine used to preserve MAP likely contributed to increase cardiac contractility and heart rate, and thus to uphold cardiac index during tilt. The surgical protocol in the present study, i.e., inducing pneumoperitoneum with the patient in the horizontal position, might have contributed to hemodynamic stability by preventing large reductions in venous return.[46] A previous study where pneumoperitoneum was induced after 10 minutes in the reverse Trendelenburg position reported a 50% decline in cardiac index.[3]

This study was performed in day-surgery patients without known cardiovascular or cerebrovascular pathology apart from controlled idiopathic hypertension. Our findings were uniform, substantial, and statistically significant even in a small study sample. The large total reduction observed in ICA blood flow (48%) had no apparent clinical consequences for our patients, but similar changes could predispose fragile patients to cerebral ischemia during

laparoscopic procedures. Marked cardiovascular changes during laparoscopic cholecystectomy, though no immediate adverse events, were observed in patients with severe cardiovascular disease (ASA III– IV).[47] Studies of ASA I–II patients showed smaller effects.[33] [48] A multifaceted approach to managing cerebral flow during surgery is warranted.[21] Optimizing CO in addition to preserving MAP, tailoring doses of intravenous anesthetic agents, and maintaining eucapnia may alleviate reduced cerebral perfusion in patients prone to hemodynamic decompensation.

Strengths and limitations

A strength of our study is that internal carotid artery blood flow was measured, whereas previous studies reported only cerebral blood velocities and assumed arterial diameter to be constant. We found the decrease in ICA blood flow to be partly due to decreased ICA velocity and partly to a decrease in ICA diameter (Table 1). Reduced vessel diameter may have resulted from reduced MAP after induction of anesthesia; experimental lowering of MAP by 20% using lower body negative pressure has been shown to induce a 5% decline in ICA diameter.[30] ICA should not be considered a rigid vessel in studies of cerebral perfusion.

$ETCO_2$ monitoring may underestimate $PaCO_2$ during laparoscopic surgery due to an increase in alveolar-arterial partial pressure difference of carbon dioxide. The marked reduction in cardiac index in the present study may have contributed to $PaCO_2$ underestimation due to reduced lung perfusion. $ETCO_2$ in the awake state could not be compared with values during anesthesia, pneumoperitoneum and tilt, as the former was sampled from the humidifier filter connected to a facemask with high-flow oxygen while the latter were sampled from the filter connected to the endotracheal tube. As we could not quantify the reduction in cerebral

metabolism, the contribution of cardiac index and MAP to ICA blood flow changes upon induction of anesthesia may be overestimated in the regression analysis.

Conclusion

In day-surgery patients undergoing laparoscopic cholecystectomy under total intravenous anesthesia, internal carotid artery (ICA) blood flow declined markedly following anesthesia, positive pressure ventilation, and pneumoperitoneum. Notably, reduced ICA blood flow was independently associated with reduced cardiac output, despite unchanged MAP, depth of anesthesia, and $ETCO_2$. Our findings imply that non-invasive cardiac output monitoring could be of use in the operating theatre, to better individualize treatment of perioperative cardiovascular perturbations. Laparoscopic surgery is considered minimally invasive, but studies of its effects on cardiac output, cerebral perfusion, and long-term patient-reported outcomes are warranted, especially in fragile patients predisposed to adverse cerebrovascular events.

Details of authors contributions

Concept of the study: S.S. Designed the study: S.S, M.E, M.S. Recruited patients, performed ultrasound measurements, collected and organized data: M.S. Performed statistical analyses: M.S. and S.S. Drafted manuscript and tables: M.S. Created figures: M.S, S.S. Evaluated ongoing analyses, reviewed several revisions of the manuscript, and approved the final version for submission: All authors.

References

1. Willie CK, Tzeng YC, Fisher JA, Ainslie PN: Integrative regulation of human brain blood flow. *J Physiol* 2014; 592(5):841-59
2. O'Leary E, Hubbard K, Tormey W, Cunningham AJ: Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. *Br J Anaesth* 1996; 76(5):640-4
3. Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML: Hemodynamic changes during laparoscopic cholecystectomy. *Anesth Analg* 1993; 76(5):1067-71
4. Bablekos GD, Michaelides SA, Analitis A, Charalabopoulos KA: Effects of laparoscopic cholecystectomy on lung function: A systematic review. *World J Gastroenterol* 2014; 20(46):17603-17.
5. Andersson LE, Baath M, Thorne A, Aspelin P, Odeberg-Wernerman S: Effect of carbon dioxide pneumoperitoneum on development of atelectasis during anesthesia, examined by spiral computed tomography. *Anesthesiology* 2005; 102(2):293-9
6. Gutt CN, Oniu T, Mehrabi A, Schemmer P, Kashfi A, Kraus T, Buchler M W: Circulatory and respiratory complications of carbon dioxide insufflation. *Dig Surg* 2004; 21(2):95-105
7. Berger D, Moller PW, Weber A, Bloch A, Bloechlinger S, Haenggi M, Sondergaard S, Jakob SM, Magder S, Takala J: Effect of PEEP, blood volume, and inspiratory hold maneuvers on venous return. *Am J Physiol Heart Circ Physiol* 2016; 311(3):H794-806
8. Del Pozzi AT, Schwartz CE, Tewari D, Medow MS, Stewart JM: Reduced cerebral blood flow with orthostasis precedes hypocapnic hyperpnea, sympathetic activation, and postural tachycardia syndrome. *Hypertension* 2014; 63(6):1302-8
9. Brothers RM, Lucas RA, Zhu YS, Crandall CG, Zhang R: Cerebral vasomotor reactivity: steady-state versus transient changes in carbon dioxide tension. *Expl Physiol* 2014; 99(11):1499-510
10. Peebles K, Celi L, McGrattan K, Murrell C, Thomas K, Ainslie PN: Human cerebrovascular and ventilatory CO2 reactivity to end-tidal, arterial and internal jugular vein PCO2. *J Physiol* 2007; 584: 347-57
11. Willie CK, Macleod DB, Shaw AD, Smith KJ, Tzeng YC, Eves ND, Ikeda K, Graham J, Lewis N C, Day T A, Ainslie PN: Regional brain blood flow in man during acute changes in arterial blood gases. *J Physiol* 2012; 590(Pt 14):3261-75
12. Lassen NA: Cerebral Blood Flow and Oxygen Consumption in Man. *Physiol Rev* 1959; 39(2):183-238
13. Tan CO: Defining the characteristic relationship between arterial pressure and cerebral flow. *J Appl Physiol* 2012; 113:1194-200
14. Tzeng YC, Ainslie, PN: Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur J Appl Physiol* 2014; 114(3):545-59
15. Hamner JW, Cohen MA, Mukai S, Lipsitz LA, Taylor JA: Spectral indices of human cerebral blood flow control: responses to augmented blood pressure oscillations. *J Physiol* 2004; 559:965-73
16. Ogoh S, Brothers RM, Barnes Q, Eubank WL, Hawkins MN, Purkayastha S, O-Yurvati A, Raven PB: The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J Physiol* 2005; 569(2):697-704
17. Kim DH, Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M: Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: a study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery* 2003; 53(5):1044-51; discussion 51-2

18. Skytioti M, Sovik S, Elstad M: Internal carotid artery blood flow in healthy awake subjects is reduced by simulated hypovolemia and noninvasive mechanical ventilation. *Physiol rep* 2016; 4(19)
19. van Lieshout JJ, Pott F, Madsen PL, van Goudoever J, Secher NH. Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* 2001; 32(7):1546-51
20. Brown CM, Dutsch M, Hecht MJ, Neundorfer B, Hilz MJ: Assessment of cerebrovascular and cardiovascular responses to lower body negative pressure as a test of cerebral autoregulation. *J Neurol Sci* 2003; 208(1-2):71-8
21. Meng L, Hou W, Chui J, Han R, Gelb AW: Cardiac Output and Cerebral Blood Flow: The Integrated Regulation of Brain Perfusion in Adult Humans. *Anesthesiology* 2015; 123(5):1198-208
22. Bogert LW, van Lieshout JJ: Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp Physiol* 2005; 90(4):437-46
23. Bogert LW, Wesseling KH, Schraa O, van Lieshout EJ, De Mol BAJM, van Goudoever J, Westerhof BE, van Lieshout JJ: Pulse contour cardiac output derived from non-invasive arterial pressure in cardiovascular disease. *Anaesthesia* 2010; 65(11):1119-25
24. Holme NL, Rein EB, Elstad M: Cardiac stroke volume variability measured non-invasively by three methods for detection of central hypovolemia in healthy humans. *Eur J Appl Physiol* 2016; 116(11-12):2187-96
25. van Lieshout JJ, Toska K, van Lieshout EJ, Eriksen M, Walloe L, Wesseling KH: Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *Eur J Appl Physiol* 2003; 90(1-2):131-7
26. Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH: A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87(2):212-22
27. Searle SR, Casella G, McCulloch CE: Maximum Likelihood (ML) and Restricted Maximum Likelihood (REML). Variance Components: John Wiley & Sons, Inc. 2008; p. 232-57
28. Levine BD, Giller CA, Lane LD, Buckey JC, Blomqvist CG: Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation* 1994; 90(1):298-306
29. Ogoh S, Sato K, Okazaki K, Miyamoto T, Hirasawa A, Sadamoto T, Shibasaki M: Blood flow in internal carotid and vertebral arteries during graded lower body negative pressure in humans. *Exp Physiol* 2015; 100(3):259-66
30. Lewis NC, Smith KJ, Bain AR, Wildfong KW, Numan T, Ainslie PN: Impact of transient hypotension on regional cerebral blood flow in humans. *Clin Sci* 2015; 129(2):169-78
31. Skytioti M, Sovik S, Elstad M: Respiratory pump maintains cardiac stroke volume during hypovolemia in young healthy volunteers. *J Appl Pysiol* 2018; 124(5):1319-1325
32. Walder AD, Aitkenhead AR: Role of vasopressin in the haemodynamic response to laparoscopic cholecystectomy. *Br J Anaesth* 1997; 78(3):264-6
33. Joshi GP, Hein HA, Mascarenhas WL, Ramsay MA, Bayer O, Klotz P: Continuous transesophageal echo-Doppler assessment of hemodynamic function during laparoscopic cholecystectomy. *J Clin Anesth* 2005; 17(2):117-21
34. Galizia G, Prizio G, Lieto E, Castellano P, Pelosio L, Imperatore V, Ferrara A, Pignatelli C: Hemodynamic and pulmonary changes during open, carbon dioxide pneumoperitoneum and abdominal wall-lifting cholecystectomy. A prospective, randomized study. *Surg Endosc* 2001; 15(5):477-83

35. Martin de Aguilera E, Vila JM, Irurzun A, Martinez MC, Martinez Cuesta MA, Lluch S: Endothelium-independent contractions of human cerebral arteries in response to vasopressin. *Stroke* 1990; 21(12):1689-93
36. Numan T, Bain AR, Hoiland RL, Smirl JD, Lewis NC, Ainslie PN: Static autoregulation in humans: a review and reanalysis. *Med Eng Phys* 2014; 36(11):1487-1495
37. Engelhard K, Werner C, Mollenberg O, Kochs E: Effects of remifentanil/propofol in comparison with isoflurane on dynamic cerebrovascular autoregulation in humans. *Acta Anaesthesiol Scand* 2001; 45(8):971-6
38. Lagace A, Karsli C, Luginbuehl I, Bissonnette B: The effect of remifentanil on cerebral blood flow velocity in children anesthetized with propofol. *Paed Anaesth* 2004; 14(10):861-5
39. Harrison JM, Girling KJ, Mahajan R: Effects of propofol and nitrous oxide on middle cerebral artery flow velocity and cerebral autoregulation. *Anaesthesia* 2002; 57(1):27-32
40. Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW: Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *Anesthesiology* 1995;83(1):66-76
41. McCulloch TJ, Visco E, Lam AM: Graded hypercapnia and cerebral autoregulation during sevoflurane or propofol anesthesia. *Anesthesiology* 2000; 93(5):1205-9
42. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB: Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. *Br J Anaest* 2006; 97(3):333-9
43. Schlunzen L, Juul N, Hansen KV, Cold GE: Regional cerebral blood flow and glucose metabolism during propofol anaesthesia in healthy subjects studied with positron emission tomography. *Acta Anaesthesiol Scand* 2012; 56(2):248-55
44. Song XX, Yu BW: Anesthetic effects of propofol in the healthy human brain: functional imaging evidence. *J Anesth* 2015; 29(2):279-88
45. Loring SH, Behazin N, Novero A, Novack V, Jones SB, O'Donnell CR, Talmor DS: Respiratory mechanical effects of surgical pneumoperitoneum in humans. *J Appl Physiol* 2014; 117(9):1074-9
46. Joshi GP: Complications of laparoscopy. *Anesthesiol clin of North America* 2001; 19(1):89-105
47. Hein HA, Joshi GP, Ramsay MA, Fox LG, Gawey BJ, Hellman CL, Arnold JC: Hemodynamic changes during laparoscopic cholecystectomy in patients with severe cardiac disease. *J Clin Anesth* 1997; 9(4):261-5
48. Cunningham AJ, Turner J, Rosenbaum S, Rafferty T: Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy. *Br J Anaesth* 1993; 70(6):621-5

.

Figure legends

1. **Cerebrovascular and cardiovascular changes during laparoscopic cholecystectomy** in 16 healthy day-surgery patients in propofol–remifentanil anesthesia. Values measured at four time points: 1) awake, 2) after anesthesia induction and intubation, 3) after pneumoperitoneum, and 4) after head-up tilt. *ICA*: internal carotid artery; non-invasive finger pulse contour estimated *MAP*: mean arterial pressure; *SV index*: stroke volume normalized to body surface area, *HR*: heart rate; *SVR index*: systemic vascular resistance normalized to body surface area; $ETCO_2$: End-tidal carbon dioxide sampled from facemask (awake state) or endotracheal tube. Data are means with 95% confidence bars.

2. **Concomitant effects of cardiac index and blood pressure on internal carotid artery (ICA) blood flow**. Upper panels: Individual lines of fit for each of 16 patients. Lower panels: Predicted ICA blood flow response to changes in cardiac index and mean arterial blood pressure (*MAP*) by mixed-model multiple regression. Measurements taken at four time points in 16 patients undergoing day-surgery laparoscopic cholecystectomy.

Table 1 Cerebrovascular, cardiovascular and respiratory variables at four different time points during laparoscopic cholecystectomy in 16 ASA I–II patients

ICA: internal carotid artery. Finger pulse contour estimated (Finometer®) MAP: mean arterial pressure; HR: heart rate; SV: stroke volume, SVR: systemic vascular resistance; P_{max}: peak airway pressure; PEEP: positive end expiratory pressure. §Sampled from humidifier filter on facemask when awake, else from endotracheal tube. Data are medians with 95% CI calculated by Hodges Lehmann's estimate. *n=12

	Awake	After induction of anaesthesia	After pneumo-peritoneum*	After Head-up tilt
ICA blood flow (ml min^{-1})	350 (273–410)	213 (175–249)	178 (127–208)	171 (134–205)
ICA beat volume (ml)	5.2 (4.0–5.7)	3.6 (2.9–3.9)	2.8 (2.0–3.3)	2.5 (2.0–3.1)
ICA diameter (mm)	5.9 (5.2–6.2)	5.6 (5.1–5.9)	5.3 (4.8–5.6)	5.5 (5.0–5.7)
MAP (mmHg)	102 (91–108)	72 (65–76)	70 (63–75)	74 (66–78)
Cardiac index (l min^{-1} m^{-2})	3.2 (2.7–3.5)	2.8 (2.3–3.1)	2.3 (1.9–2.5)	2.1 (1.8–2.3)
SV index (ml m^{-2})	46.2 (37.7–51.1)	47.5 (39.3–50.7)	37.1 (29.4–41.0)	31.7 (27.1–37.2)
HR (beats min^{-1})	70 (63–75)	60 (55–65)	65 (65–70)	69 (63–73)
SVR index (dyn s cm^{-5} m^{-2})	2609 (2342–3208)	2051 (1732–2423)	2522 (2267–3102)	2770 (2294–3469)
P_{max} (cm H_2O)		17 (16–17)	19 (18–19)	19 (18–19)
Tidal volume (ml)		410 (375–435)	380 (355–405)	406 (370–430)
Respiratory rate (breaths min^{-1})		12 (12–13)	12 (12–13)	13 (12–14)
§End-tidal CO_2 (mmHg)	32 (29–35)	38 (36–40)	38 (35–38)	38 (36–39)
Bispectral Index	94 (94–95)	33 (27–37)	35 (32–37)	32 (28–36)

Figure legends

1. **Cerebrovascular and cardiovascular changes during laparoscopic cholecystectomy** in 16 healthy day-surgery patients in propofol–remifentanil anesthesia. Values measured at four time points: 1) awake, 2) after anesthesia induction and intubation, 3) after pneumoperitoneum, and 4) after head-up tilt. *ICA*: internal carotid artery; non-invasive finger pulse contour estimated *MAP*: mean arterial pressure; *SV index*: stroke volume normalized to body surface area, *HR*: heart rate; *SVR index*: systemic vascular resistance normalized to body surface area; $ETCO_2$: End-tidal carbon dioxide sampled from facemask (awake state) or endotracheal tube. Data are means with 95% confidence bars.

2. **Concomitant effects of cardiac index and blood pressure on internal carotid artery (ICA) blood flow**. Upper panels: Individual lines of fit for each of 16 patients. Lower panels: Predicted ICA blood flow response to changes in cardiac index and mean arterial blood pressure (*MAP*) by mixed-model multiple regression. Measurements taken at four time points in 16 patients undergoing day-surgery laparoscopic cholecystectomy.

Figure1 Updated