

Effect of age on intraoperative cerebrovascular autoregulation and near-infrared spectroscopy-derived cerebral oxygenation

C. S. Burkhardt^{1†}, A. Rossi^{2†}, S. Dell-Kuster¹, M. Gamberini¹, A. Möckli¹, M. Siegemund¹, M. Czosnyka³, S. P. Strebel¹ and L. A. Steiner^{1,2*}

¹ Department of Anaesthesia and Intensive Care Medicine, University Hospital Basel, Switzerland

² Department of Anaesthesia, University Hospital Centre and University of Lausanne, Switzerland

³ Department of Clinical Neurosciences, Neurosurgery Unit, University of Cambridge, UK

* Corresponding author: Service d'Anesthésie, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, BH10, CH-1011 Lausanne, Switzerland. E-mail: luzius.steiner@chuv.ch

Editor's key points

- The authors evaluated whether, in the elderly, intraoperative cerebral autoregulation and oxygenation were affected.
- The lowered cerebral autoregulation in the elderly was not considered clinically significant.
- Cerebral oxygenation was not associated with the advanced age.
- The study did not support the hypothesis that the brain in the elderly is more vulnerable to the systemic changes.

Background. Age is an important risk factor for perioperative cerebral complications such as stroke, postoperative cognitive dysfunction, and delirium. We explored the hypothesis that intraoperative cerebrovascular autoregulation is less efficient and brain tissue oxygenation lower in elderly patients, thus, increasing the vulnerability of elderly brains to systemic insults such as hypotension.

Methods. We monitored intraoperative cerebral perfusion in 50 patients aged 18–40 and 77 patients >65 yr at two Swiss university hospitals. Mean arterial pressure (MAP) was measured continuously using a plethysmographic method. An index of cerebrovascular autoregulation (Mx) was calculated based on changes in transcranial Doppler flow velocity due to changes in MAP. Cerebral oxygenation was assessed by the tissue oxygenation index (TOI) using near-infrared spectroscopy. End-tidal CO₂, O₂, and sevoflurane concentrations and peripheral oxygen saturation were recorded continuously. Standardized anaesthesia was administered in all patients (thiopental, sevoflurane, fentanyl, atracurium).

Results. Autoregulation was less efficient in patients aged >65 yr [by 0.10 (SE 0.04; P=0.020)] in a multivariable linear regression analysis. This difference was not attributable to differences in MAP, end-tidal CO₂, or higher doses of sevoflurane. TOI was not significantly associated with age, sevoflurane dose, or Mx but increased with increasing flow velocity [by 0.09 (SE 0.04; P=0.028)] and increasing MAP [by 0.11 (SE 0.05; P=0.043)].

Conclusions. Our results do not support the hypothesis that older patients' brains are more vulnerable to systemic insults. The difference of autoregulation between the two groups was small and most likely clinically insignificant.

Keywords: age groups; anaesthesia; cerebrovascular circulation

Accepted for publication: 2 June 2011

When confronted with perioperative cerebral complications such as stroke, delirium, or postoperative cognitive dysfunction (POCD), often intraoperative hypotension, insufficient intraoperative cerebral perfusion, or both are assumed. However, the data on associations between intraoperative hypotension, stroke, delirium, and POCD are contradictory. A recent review reports that only 9% of perioperative strokes can be attributed to hypoperfusion.¹ Gustafson and colleagues² reported that intraoperative hypotension was associated with postoperative delirium in patients undergoing repair

of hip fractures, whereas Marcantonio and colleagues³ found intraoperative hypotension not to be associated with postoperative delirium. Moller and colleagues⁴ were not able to demonstrate a role of perioperative hypotension in the development of POCD. However, in cardiac surgery, hypotension has been shown to be associated with POCD,⁵ and intraoperative cerebral desaturation has been linked to POCD in cardiac⁶ and non-cardiac surgery.⁷ In contrast, age has clearly been shown to be an important risk factor for all the perioperative cerebral complications discussed above.^{1 8 9}

[†]These authors contributed equally to this work.

Cerebrovascular autoregulation is a key defence mechanism of the brain against hypo- and hyperperfusion. There are only few data on the effects of age on cerebrovascular autoregulation in volunteers, again with controversial results.^{10 11} To the best of our knowledge, there are no data comparing intraoperative cerebrovascular autoregulation in anaesthetized patients of different age groups. If autoregulation fails, the brain will compensate the reduction in cerebral blood flow by increasing oxygen extraction. Near-infrared spectroscopy (NIRS) allows us to non-invasively measure brain tissue oxygenation, a surrogate marker of the cerebral oxygen extraction fraction.¹² Hence, to some extent, it is possible to non-invasively characterize the vulnerability of the cerebral perfusion to systemic insults such as hypotension or hypoxia by monitoring autoregulation and cerebral oxygenation.

We explored the hypothesis that cerebrovascular pressure autoregulation during anaesthesia is less efficient and that cerebral oxygenation is lower in elderly than in younger patients. Furthermore, we addressed the question whether such a difference could be attributed to anaesthetic management, i.e. differences in mean arterial pressure (MAP), end-tidal CO₂ (E_tCO₂), or the dose of volatile anaesthetic that is administered during the procedure.

Methods

The study was approved by the Regional Ethical Committees of Basel and Lausanne, and all patients gave written informed consent before participation. The study is registered with www.clinicaltrials.gov (NCT00512200).

Patients aged 18–40 or >65 yr and undergoing elective major surgery were eligible for inclusion. Two groups of patients with a non-overlapping range of age were chosen deliberately in order to compare young patients with a presumed normal cerebrovascular pressure autoregulation to elderly patients with a potentially less efficient autoregulation. Exclusion criteria were cardiac surgery, neurosurgery, carotid endarterectomy, any cranial or other surgery precluding the use of NIRS or transcranial Doppler (TCD), a history of cerebrovascular disease or any intracranial pathology, a preoperative Mini-Mental Score <24, and long-term psychiatric medication. Some of the elderly patients also participated in a trial exploring the pathophysiology of POCD. All patients received a standardized anaesthetic regimen consisting of thiopental for induction (3–5 mg kg⁻¹), sevoflurane, fentanyl, and atracurium. All other aspects of anaesthetic management including dosing of sevoflurane and fentanyl and arterial pressure or E_tCO₂ targets were left to the discretion of the anaesthesiologist in charge of the patient. The clinician was not aware of the perfusion monitoring data. No BIS monitoring was used, as this is not standard procedure at either institution.

MAP was measured continuously using a plethysmographic device (Finometer Model-2, Finapres Medical Systems B.V., Amsterdam, The Netherlands). As the position of the finger on which the measurement is performed may

be above or below the right atrium, a correction factor obtained by comparing MAP with that measured by a standard arterial pressure cuff at the beginning of the procedure was added or subtracted as appropriate. After induction of anaesthesia, bilateral TCD probes (MultiDop T; Compumedics DWL, Singen, Germany) were fixed to the head of the patients with a head rack and adjusted until a clear signal from the middle cerebral artery was obtained. Bilaterally, the optodes for the NIRS device (NIRO-200, Hamamatsu Photonics, Solothurn, Switzerland) were applied to the forehead of the patient and covered with an opaque fabric to avoid interference of ambient light with our measurements. The tissue oxygenation index (TOI) was used as a marker of cerebral oxygenation. All other variables (E_tCO₂, E_tO₂, E_tSevoflurane, peripheral oxygen saturation, and oesophageal or rectal temperature) were downloaded continuously from the anaesthesia machine [Datex-Ohmeda ADU AS3, GE Medical Systems (Schweiz) AG Glattbrugg, Switzerland].

Data collection and analysis

For data collection and analysis, ICM⁺ software was used.¹³ Waveforms were sampled from the analogue output of the MAP and TCD monitors at 30 Hz and digitized (12 bits) using an analogue-to-digital converter (DT 2814, Data Translation, Marlborough, CA, USA). Using time-wave integration, mean values for MAP and mean flow velocity (FVm) were calculated every 10 s. Data from all other monitors were sampled at 1 Hz. Cerebrovascular pressure autoregulation was characterized by the index Mx¹⁴ which was calculated every 60 s as the moving linear correlation coefficient between the last 30 consecutive values of MAP and FVm, that is, a 5 min moving time-window was used. Data from both hemispheres were averaged. This method has been validated against other methods used to determine autoregulation.^{15–18} Its strength is the possibility to use spontaneous fluctuations in MAP to characterize autoregulation rather than inducing changes in MAP pharmacologically or through manoeuvres such as compression of the carotid artery or bilateral thigh cuffs, which are not suitable for the intraoperative setting. Furthermore, it allows a quantitative statement regarding efficiency of autoregulation. Higher values of Mx denote less efficient autoregulation. As we excluded patients with a history of cerebrovascular disease, in patients in whom only a unilateral Doppler signal was available, data from this hemisphere were used instead of the averaged value from both hemispheres. Induction and emergence were excluded from analysis, as artifacts due to manipulations during intubation and the highly variable arterial CO₂ during induction and emergence preclude collection of interpretable data. During surgery, electrical cautery accounts for most artifacts. These are easily recognizable and were removed and also any other artifacts offline after completion of the data recording. Mx has a relatively low signal-to-noise ratio. Therefore, to ensure a valid measurement, data sets were excluded if after artifact removal, Mx data were not available for at least 25 min. For analysis of

the effects of sevoflurane on autoregulation, we calculated the age-corrected minimum alveolar concentration (MAC) for each patient based on the formula developed by Mapleson¹⁹ and used this to transform the measured $E'_{\text{Sevoflurane}}$ concentration to an age-corrected MAC equivalent. For all patients, we calculated the maximal intraoperative cerebral desaturation as the maximal difference between the initial TOI values and the lowest intraoperative 1 min average value of TOI in either hemisphere.

Statistics

As our primary endpoint was autoregulation, we calculated the sample size based on normocapnic volunteer data¹⁸ and the assumption that a difference in $M_x > 0.15$ between the two groups is clinically significant. This assumption is based on data from healthy volunteers demonstrating an interhemispheric difference of M_x [mean (standard deviation, *SD*)] of 0.07 (0.07).²⁰ Two groups of at least 32 patients each result in a power of 90% ($\alpha=0.05$). To allow for insufficient M_x data, that is, < 25 min, due to artifacts or inability to obtain a valid Doppler signal, we decided to recruit at least 50 patients for each group. At the time we finished recruiting, patients aged 18–40, data from 77 elderly patients were available. Data from all elderly patients were included. Summary statistics are given as mean (*SD*) or median [interquartile range (IQR)] as appropriate.

The difference in autoregulation between elderly and young people was modelled using a linear regression analysis adjusted for gender, MAP, E'_{CO_2} , and the age-corrected

MAC equivalents of sevoflurane. The difference in TOI between the age groups was also modelled using linear regression analysis adjusted for gender, MAP, FVm, E'_{CO_2} , E'_{O_2} , and the age-corrected MAC equivalents of sevoflurane. The model assumptions of both linear regression models were checked by plotting the standardized residuals and by using the Breusch–Pagen test for heteroscedasticity. The model excluding influencing observations has been compared with the full model.

The numbers of cerebral desaturations in both age categories were compared using Fisher's exact test. Data are reported as means (*SD*) unless otherwise indicated.

Results

After excluding data sets with an insufficient duration of valid autoregulation measurements, 42 data sets of the 50 patients aged 18–40 yr and 62 data sets of the 77 patients aged 65 yr or older remained. In two younger and 16 older patients, TCD data from only one hemisphere were available. The patient characteristics are shown in Table 1.

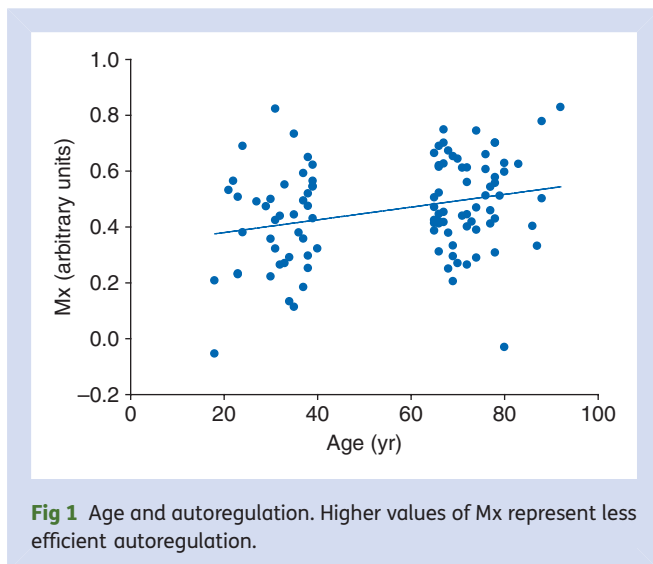
In a multiple regression analysis including age, gender, MAP, E'_{CO_2} , and MAC equivalents of sevoflurane, only age had a significant effect on M_x (Table 2, Fig. 1). This changed only minimally after excluding the three most influencing observations. One important factor that may alter autoregulation is the presence of hypertension (Table 1). There were no untreated hypertensive patients in our groups. M_x was slightly higher in patients with hypertension, but the difference did not reach statistical significance (0.450

Table 1 Patient characteristics. E' , end-tidal; $F_{\text{I}\text{O}_2}$, fraction of inspired O_2 ; FVm, mean flow velocity; MAC, minimum alveolar concentration; MAP, mean arterial pressure; M_x , index of cerebrovascular autoregulation; Sp_{O_2} , peripheral oxygen saturation; TOI, tissue oxygenation index. Data are presented as median (range), or mean (*SD*) except sevoflurane concentrations which are median (IQR)

	All patients	Patients ≤ 40 yr	Patients ≥ 65 yr
<i>n</i> (%)	104	42 (40)	62 (60)
Age (yr)		34 (18–40)	72 (65–92)
Females (%)	45 (43%)	24 (57%)	21 (34%)
Hypertension (<i>n</i>)	36	2	34
Diabetes mellitus (<i>n</i>)	5	0	5
$F_{\text{I}\text{O}_2}$	0.55 (0.06)	0.56 (0.07)	0.55 (0.05)
Sp_{O_2} (%)	98 (93–100)	98 (93–100)	98 (97–100)
E'_{O_2}	0.49 (0.06)	0.49 (0.07)	0.49 (0.04)
E'_{CO_2}	4.6 (0.3)	4.8 (0.3)	4.6 (0.3)
$E'_{\text{Sevoflurane}}$ (%)	1.82 (0.26)	1.94 (0.21)	1.75 (0.27)
Sevoflurane MAC equivalents	1.10 (0.99–1.24)	1.01 (0.95–1.10)	1.19 (1.09–1.32)
Heart rate (beats min^{-1})	68 (12)	71 (14)	66 (10)
MAP (mm Hg)	76 (11)	76 (13)	75 (10)
FVm (cm s^{-1})	43 (16)	47 (14)	41 (17)
M_x	0.462 (0.174)	0.412 (0.181)	0.500 (0.163)
TOI (%)	67.9 (5.8)	69.5 (5.7)	66.8 (5.7)
Desaturation (%)	6 (4–12)	6 (2–12)	7 (4–14)
Desaturation $> 13\%$ [<i>n</i> (%)]	23 (22)	7 (17)	16 (26)
Desaturation $> 20\%$ [<i>n</i> (%)]	11 (11)	1 (2)	10 (16)
Body temperature ($^{\circ}\text{C}$)	35.9 (0.5)	36.0 (0.4)	35.8 (0.5)

Table 2 Univariate and multivariable analysis of autoregulation ($n=104$). E' , end-tidal; MAC, minimum alveolar concentration; MAP, mean arterial pressure

Covariates	Univariate analysis		Multivariable analysis	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Age (elderly vs young)	0.08 (0.02; 0.15)	0.015	0.10 (0.02; 0.18)	0.020
Gender (female vs male)	-0.06 (-0.13; 0.01)	0.098	-0.04 (-0.11; 0.03)	0.287
MAP (per 1 mm Hg increase)	-0.00 (-0.01; 0.00)	0.061	-0.00 (-0.01; 0.00)	0.055
E'_{CO_2} (per 1 kPa increase)	0.00 (-0.10; 0.11)	0.937	0.05 (-0.05; 0.16)	0.309
MAC equivalent (per 1 unit increase)	0.04 (-0.17; 0.24)	0.730	-0.08 (-0.30; 0.14)	0.454



vs 0.462; $P=0.31$). Intraoperative MAP was similar in patients with and without hypertension: 75 (10) and 75 (12) mm Hg, respectively.

The regression model investigating TOI shows that FVm and MAP influenced cerebral oxygenation but not age or autoregulation (Table 3, Fig. 2). We found intraoperative desaturations, that is, TOI values lower than baseline in younger and older patients (Table 1). While desaturations to at least -13% of baseline were observed more frequently in the older patients, this difference did not reach statistical significance. However, older patients show significantly more desaturations to 20% or more below baseline than younger patients ($P=0.047$).

Discussion

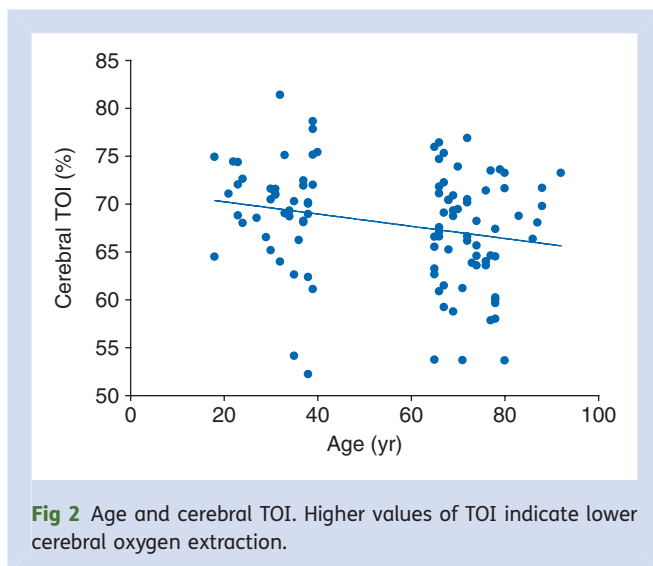
We found significantly less effective cerebrovascular autoregulation in older compared with younger patients undergoing elective surgery under sevoflurane-based anaesthesia. We also found lower values for cerebral oxygenation measured by NIRS in the older group of patients. However, this difference was not due to age but rather FVm and MAP.

The most important question is whether the difference in autoregulation we found is clinically relevant. While our

protocol was not designed to answer this question, some inferences from volunteer data may be made. In healthy volunteers, the difference in Mx between the left and the right hemispheres was 0.07 (0.07).²⁰ In our patients, we found similar differences of Mx between the two hemispheres: 0.01 (0.08) in the younger and 0.01 (0.09) in the older patients. As all these data were collected in patients without known intracerebral or cerebrovascular pathology, this could also imply that an interindividual difference of Mx in the range of 2 sds of the interhemispherical differences cited above, that is, 0.18 is normal. This would suggest that despite statistical significance, the difference in Mx we found between younger and older patients (0.09) is clinically not relevant. In contrast, the Mx values we found intraoperatively are considerably higher in the younger [Mx: 0.41 (0.18) at 4.8 kPa of E'_{CO_2}] and older patients [Mx: 0.50 (0.16) at 4.6 kPa of E'_{CO_2}] than in awake healthy volunteers [Mx: 0.21 (0.16) at 5.8 kPa of E'_{CO_2}].¹⁸ This suggests that under sevoflurane-based anaesthesia, cerebral perfusion in the older and in the younger patients may be more vulnerable to hypotension than in awake volunteers. Ideally, we would have collected data on Mx in all our patients before induction of anaesthesia. However, such a measurement would have to be made before induction of anaesthesia and requires ~1 h, which is unfortunately not compatible with the surgical scheduling at our institutions. Alternatively, measurements could have been repeated several days or perhaps even weeks after surgery to avoid effects of analgesic and other drugs. In both instances, the data would be difficult to interpret as it is unlikely that the same arterial pressure, and particularly the same E'_{CO_2} , is present during measurements performed intraoperatively and before or after operation. Autoregulation is strongly influenced by vascular tone.²¹ The arterial partial pressure of CO_2 (Pa_{CO_2}) affects vascular tone in the segments of the cerebral vascular bed that are responsible for autoregulation. Increases in Pa_{CO_2} not only narrow the plateau of the autoregulatory curve,²¹ but also the rate at which the cerebral resistance vessels react to changes in MAP is decreased,²² and Mx is increased,¹⁸ suggesting less efficient autoregulation. The opposite effects occur with decreases in Pa_{CO_2} . To address the problem of the interaction between Pa_{CO_2} and autoregulation, we again decided to rely on data obtained from healthy volunteers by the Cambridge group.¹⁸ The Mx

Table 3 Univariate and multivariable analysis of cerebral tissue oxygenation ($n=104$). E_t , end-tidal; FVm, mean flow velocity; MAC, minimum alveolar concentration; MAP, mean arterial pressure; Mx, index of cerebrovascular autoregulation

Covariates	Univariate analysis		Multivariable analysis	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Age (elderly vs young)	-2.73 (-5.00; -0.46)	0.019	-1.86 (-4.64; 0.92)	0.186
Gender (female vs male)	0.88 (-1.42; 3.18)	0.448	-0.02 (-2.39; 2.36)	0.989
MAP (per 1 mm Hg increase)	0.11 (0.01; 0.21)	0.036	0.11 (0.00; 0.21)	0.043
E_{CO_2} (per 1 kPa increase)	4.24 (0.91; 7.57)	0.013	1.65 (-2.04; 5.34)	0.376
E_{O_2} (per 1 kPa increase)	0.06 (-0.14; 0.26)	0.563	0.09 (-0.11; 0.29)	0.358
FVm (per 1 $cm\ s^{-1}$ increase)	0.11 (0.04; 0.18)	0.003	0.09 (0.01; 0.16)	0.028
Mx (per 1 unit increase)	-0.63 (-7.21; 5.95)	0.850	0.12 (-6.76; 6.99)	0.973
MAC equivalent (per 1 unit increase)	-2.42 (-9.16; 4.32)	0.478	0.41 (-7.00; 7.82)	0.913



values we measured were higher than those of healthy normocapnic volunteers,¹⁸ suggesting less efficient autoregulation both in the younger and older patients in comparison with awake volunteers.¹⁸ Moreover, in our data, E_{CO_2} was lower (4.6 kPa) than in the volunteer study cited above (5.8 kPa).¹⁸ At comparable E_{CO_2} , the difference between volunteers and our patients would be even larger for the reasons outlined above. One possible explanation for the difference in Mx between volunteers and patients is an effect of sevoflurane. Mx is an index of dynamic autoregulation, and while static autoregulation seems to be quite robust even with higher sevoflurane concentrations than we used,²³ it has been previously shown that dynamic autoregulation is impaired by sevoflurane at lower concentrations and also in the range of concentrations present in our patients.²⁴ Apart from sevoflurane, hypertension could shift the autoregulatory curve to the right and have an impact on Mx. Pre-existing hypertension was not associated with higher values of Mx [mean difference between no hypertension and hypertension: -0.04 (95% CI -0.11; 0.03; $P=0.31$)]. While there are sufficient data to make an effect of a pre-

existing hypertension on our results unlikely, only five patients (5%, all belonging to the older age category) were diabetics and an analysis of the effect of this condition, which has been shown earlier to interfere with autoregulation,²⁵ is not possible with our data. However, there are many factors, our protocol did not control for, that could have an impact on autoregulation such as concomitant medication.

The small significant difference in TOI between younger and older patients as indicated by univariate analysis was not confirmed by the multivariable analysis. However, there were significant associations with FVm and MAP. The significant association with FVm is not surprising. TOI is a surrogate marker of oxygen extraction, and in our patients, oxygen extraction will most likely depend exclusively on delivery, that is, cerebral blood flow (CBF) or its surrogate marker FVm. In our patients, E_{O_2} was adequate and cerebral metabolic rate of oxygen was reduced due to the volatile anaesthetic, making an increased demand or insufficient O_2 transport highly unlikely. The association of TOI with MAP we found in our patients is interesting, as it supports an impairment of autoregulation as discussed above and, hence, vulnerability to hypotension; for younger and older patients alike. In our patients, boluses of ephedrine and phenylephrine and infusions of norepinephrine were used as deemed necessary by the anaesthesiologist in charge of clinical management. The effects of vasopressors on cerebral oxygenation are controversial. Earlier work failed to show an effect of norepinephrine²⁶ or ephedrine²⁷ on cerebral haemodynamics in awake healthy volunteers. Recently, it has been suggested that in awake healthy volunteers, norepinephrine may decrease FVm and cerebral oxygenation.²⁸ However, the results of that study could also be explained by variations in P_{aCO_2} rather than norepinephrine alone.²⁹ Phenylephrine but not ephedrine has also been shown to decrease cerebral oxygenation.³⁰ Unfortunately, no CO_2 data are reported in that publication. In all experiments investigating changes in CBF or FVm induced by drugs, MAP, or other interventions such as hypothermia, the control of P_{aCO_2} is crucial. With normal cerebrovascular CO_2 reactivity in the range of 15–20% kPa^{-1} ,³¹ even small

differences in P_{aCO_2} may lead to changes in CBF and FVm that are larger than the effects of the intervention in question. Since we averaged our data over the duration of the surgical procedure, it is not possible to analyse the effect of the vasopressors that were used on cerebral oxygenation. As with Mx, a comparison with an awake TOI value would have been interesting. However, our patients were premedicated with benzodiazepines, and due to organizational limitations, we were unable to obtain values before premedication. Intraoperative cerebral desaturations, that is, decreases in TOI, occurred in younger and older patients. The threshold at which desaturations become clinically relevant is controversial. One group showed that a change of -13% is relevant when EEG data are analysed;³² another group found a threshold of -20% to be associated with clinical changes.³³ Both studies were performed in patients undergoing carotid endarterectomy. Interestingly, we could not identify clear causes for the desaturations in most of our patients. Only in three patients who had TOI desaturations $>20\%$, this happened concomitantly with a hypotensive episode. One of these three patients was younger than 40 yr and had short-lived decreases in MAP to <50 mm Hg. More data are needed to explore the pathophysiology of intraoperative desaturations and to define their clinical relevance and relevant thresholds for patients undergoing general surgery.

Limitations

Our study has several limitations. We decided not to use BIS monitoring for our study. This monitor is not part of standard monitoring at our institutions, and in many patients, it would have been impossible to correctly place the sensors for TCD, NIRS, and BIS monitoring due to the limited amount of space on the forehead. Had we used BIS monitoring, many patients would probably have received lower doses of sevoflurane. However, it is not clear, whether this would have influenced our results.

Our data were averaged over the complete duration of the procedure. This precludes any statement on short-term changes in autoregulation. However, the method we used is not suitable to investigate short-term changes in autoregulatory efficiency. It depends on a minimal duration of ~ 25 min over which measurements have to be averaged. A further drawback of our method is the inability to discriminate between worsening of autoregulation and intraoperative arousal of the patient. Such an event would be characterized by an increase in FVm and most likely an increase in MAP, which with our method would result in an increase in Mx. However, in view of the rather high sevoflurane concentrations that were used and the fact that we averaged our data over longer periods, we assume that the relatively high values we report are not due to intraoperative arousal but represent autoregulation.

All our patients were haemodynamically reasonably stable and the variability of E'_{CO_2} and $E'_{Sevoflurane}$ was limited as well. This precludes extrapolation of our results to patients

with marked intraoperative instability. Finally, our results cannot be extrapolated to patients anaesthetized with other volatile agents or propofol.

In summary, despite the fact that our data show statistically significant differences in cerebral autoregulation between younger and older patients under sevoflurane-based anaesthesia, these differences are small and of questionable clinical significance. The cerebral TOI was not significantly influenced by age. These data suggest that there is no fundamental difference in intraoperative cerebral perfusion between younger and older patients that could explain the effect of age on the risk for perioperative cerebral complications.

Acknowledgement

Allison Dwileski's help in preparation of this manuscript is gratefully acknowledged.

Conflict of interest

ICM⁺ (www.neurosurg.cam.ac.uk/icmplus) software is licensed by Cambridge Enterprise Ltd, University of Cambridge, UK. M.C. has a financial interest in a fraction of licensing fee. L.A.S. has received an unrestricted research grant from Abbott AG, Baar, Switzerland.

Funding

M.C. was supported by the National Institute of Health Research Biomedical Research Centre, Cambridge University Hospital Foundation Trust-Neurosciences Theme. Swiss National Science Foundation (SNSF) Grant Number 32003B_121956; Department of Anaesthesia and Intensive Care Medicine, University Hospital Basel, Switzerland; Department of Anaesthesia, University Hospital Centre Lausanne, Switzerland.

References

- Selim M. Perioperative stroke. *N Engl J Med* 2007; **356**: 706–13
- Gustafson Y, Berggren D, Brannstrom B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc* 1988; **36**: 525–30
- Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. *Am J Med* 1998; **105**: 380–4
- Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; **351**: 857–61
- Gottesman RF, Hillis AE, Grega MA, et al. Early postoperative cognitive dysfunction and blood pressure during coronary artery bypass graft operation. *Arch Neurol* 2007; **64**: 1111–4
- Yao FS, Tseng CC, Ho CY, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2004; **18**: 552–8
- Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major

- abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg* 2005; **101**: 740–7
- 8 Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008; **108**: 18–30
 - 9 Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; **104**: 21–6
 - 10 Carey BJ, Panerai RB, Potter JF. Effect of aging on dynamic cerebral autoregulation during head-up tilt. *Stroke* 2003; **34**: 1871–5
 - 11 Wollner L, McCarthy ST, Soper ND, Macy DJ. Failure of cerebral autoregulation as a cause of brain dysfunction in the elderly. *Br Med J* 1979; **1**: 1117–8
 - 12 Geisen G. Is near-infrared spectroscopy living up to its promises? *Semin Fetal Neonatal Med* 2006; **11**: 498–502
 - 13 Smielewski P, Czosnyka M, Steiner L, Belestri M, Piechnik S, Pickard JD. ICM+: software for on-line analysis of bedside monitoring data after severe head trauma. *Acta Neurochir Suppl* 2005; **95**: 43–9
 - 14 Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996; **27**: 1829–34
 - 15 Lang EW, Mehdorn HM, Dorsch NW, Czosnyka M. Continuous monitoring of cerebrovascular autoregulation: a validation study. *J Neurol Neurosurg Psychiatry* 2002; **72**: 583–6
 - 16 Reinhard M, Roth M, Muller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. *Stroke* 2003; **34**: 2138–44
 - 17 Czosnyka M, Smielewski P, Lavinio A, Pickard JD, Panerai R. An assessment of dynamic autoregulation from spontaneous fluctuations of cerebral blood flow velocity: a comparison of two models, index of autoregulation and mean flow index. *Anesth Analg* 2008; **106**: 234–9
 - 18 Piechnik SK, Yang X, Czosnyka M, et al. The continuous assessment of cerebrovascular reactivity: a validation of the method in healthy volunteers. *Anesth Analg* 1999; **89**: 944–9
 - 19 Mapleson WW. Effect of age on MAC in humans: a meta-analysis. *Br J Anaesth* 1996; **76**: 179–85
 - 20 Schmidt EA, Piechnik SK, Smielewski P, Raabe A, Matta BF, Czosnyka M. Symmetry of cerebral hemodynamic indices derived from bilateral transcranial Doppler. *J Neuroimaging* 2003; **13**: 248–54
 - 21 Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2**: 161–92
 - 22 Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989; **20**: 45–52
 - 23 Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. *Br J Anaesth* 1997; **79**: 469–72
 - 24 Ogawa Y, Iwasaki K, Shibata S, Kato J, Ogawa S, Oi Y. The effect of sevoflurane on dynamic cerebral blood flow autoregulation assessed by spectral and transfer function analysis. *Anesth Analg* 2006; **102**: 552–9
 - 25 Kim YS, Immink RV, Stok WJ, Karemaker JM, Secher NH, van Lieshout JJ. Dynamic cerebral autoregulatory capacity is affected early in type 2 diabetes. *Clin Sci (Lond)* 2008; **115**: 255–62
 - 26 Moppett IK, Sherman RW, Wild MJ, Latter JA, Mahajan RP. Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: transcranial Doppler study in healthy volunteers. *Br J Anaesth* 2008; **100**: 240–4
 - 27 Moppett IK, Wild MJ, Sherman RW, Latter JA, Miller K, Mahajan RP. Effects of ephedrine, dobutamine and dopexamine on cerebral haemodynamics: transcranial Doppler studies in healthy volunteers. *Br J Anaesth* 2004; **92**: 39–44
 - 28 Brassard P, Seifert T, Secher NH. Is cerebral oxygenation negatively affected by infusion of norepinephrine in healthy subjects? *Br J Anaesth* 2009; **102**: 800–5
 - 29 Moppett IK. Sympathetic activity and cerebral oxygenation. *Br J Anaesth* 2009; **103**: 769; author reply 769–70
 - 30 Nissen P, Brassard P, Jorgensen TB, Secher NH. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anaesthesia-induced hypotension. *Neurocrit Care* 2010; **12**: 17–23
 - 31 Ide K, Eliasziw M, Poulin MJ. Relationship between middle cerebral artery blood velocity and end-tidal PCO₂ in the hypocapnic–hypercapnic range in humans. *J Appl Physiol* 2003; **95**: 129–37
 - 32 Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke* 2006; **37**: 2720–5
 - 33 Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. *Anesthesiology* 2007; **107**: 563–9