NEUROLOGIA I NEUROCHIRURGIA POLSKA 48 (2014) 181–187

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Original research article

Blood flow velocity in the middle cerebral artery during transnasal endoscopic skull base surgery performed in controlled hypotension

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ARTICLE INFO

Article history:
Received 7 January 2014
Accepted 26 May 2014
Available online 6 June 2014

Keywords:
Cerebral blood flow
Endoscopic surgery
Middle cerebral artery
Hypotension
Transcranial Doppler sonography

ABSTRACT

Background and purpose: To assess blood flow velocity in the middle cerebral artery (MCA) during transnasal endoscopic procedures performed with decreased hemodynamic parameters.
Materials and methods: In 40 patients who underwent endoscopic skull base surgery in controlled hypotension (studied group) and in 13 patients operated without reduction of hemodynamic parameters (control group), blood flow velocity in MCA was assessed with transcranial color Doppler sonography.
Results: Blood flow velocity in MCA remained within the range of age-specific reference values in all patients before operation. It decreased significantly in both groups after induction of anesthesia and then dropped even further in studied group of patients when hemodynamic parameters were reduced; the systolic velocity fell below the normal reference values in 25% of patients, the mean velocity in 50% and the diastolic velocity in 57% of patients. The diastolic velocity was much more heavily influenced by diminished hemodynamic parameters than systolic velocity in the studied group as opposed to the control group where reduction of blood flow velocity pertained equally systolic and diastolic velocity.
Conclusion: During transnasal endoscopic procedures performed in moderate hypotension, in addition to significant drop of blood flow velocity to values well below the normal reference range, a divergent reduction of systolic and diastolic velocity was detected. Since divergent systolic and diastolic velocity may indicate an early phase of cerebral autoregulation compromise, and the decrease of mean blood flow velocity in MCA corresponds with a decrease of cerebral blood flow, further investigations in this field seem warranted.

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http://dx.doi.org/10.1016/j.pjnns.2014.05.006

1. Introduction

During the past decade there has been a substantial movement to develop expanded endonasal approaches to the ventral skull base as well as the methods of reconstruction of the postoperative defects. Precision of surgical manipulations and good overall effect of these procedures can be achieved only if intraoperative bleeding is reduced to a minimum. Besides local application of vasoconstrictors and putting the patient in the reverse Trandelenburg position moderate hypotension with mean arterial pressure (MAP) of about 60 mmHg is nowadays more and more commonly used in some centers as an indispensable component of general anesthesia for extensive endoscopic operations [1]. Survey of the literature as well as the results of our previous study revealed that lowering of arterial pressure alone does not always result in reduced bleeding during operative procedures [2–4]. Inhaled anesthetic agents reduce MAP by dilation of blood vessels which results in tachycardia with consequent increase of bleeding. Thus concomitant reduction of both heart rate (HR) and MAP is considered as a necessary prerequisite for obtaining satisfactory bloodless surgical field.

Mild to moderate controlled hypotension has been used during certain surgical procedures and is generally considered safe in healthy, normotensive subjects. However the tolerance of decreased hemodynamic parameters may vary between healthy individuals and can supposedly be considerably weaker in patients with comorbidities, or elderly people who also may require surgery. Because insufficient brain perfusion is a main hazard of systemic hypotension, the quest of safe and reliable methods of intraoperative brain perfusion monitoring becomes the main concern of the neuroanesthesiologist.

Transcranial color Doppler sonography (TCCS) via temporal bone window enables the assessment of blood flow velocity in the major cerebral arteries, which has been proved to remain in direct proportion to the volume of cerebral blood flow [5–7]. Of all basal cerebral arteries the M1 segment of the middle cerebral artery (MCA) is most suitable for persistent monitoring of blood flow using transcranial Doppler sonography.

The aim of our study was the assessment of changes in blood flow velocity in the MCA during transnasal endoscopic operations performed in moderate controlled hypotension with decreased, stable heart rate.

2. Materials and methods

The study protocol was approved by the Bioethical Committee of Medical University of Bialystok and all participants have signed the informed consent. The studied group consisted of 40 patients (19 females and 21 males in the age ranged 20–58 years, on average 41.5) who underwent endoscopic surgery for various pathologies of the paranasal sinuses and the anterior and middle skull base in hypotensive conditions. Thirteen patients (5 females and 8 males in the age ranged 28–56 years, on average 42.6) underwent surgery to cervical spine pathologies without reduction of their hemodynamic parameters during surgery constituted control group. Patients belonging to the control group were positioned during the surgery in exactly the same way as the patients from the studied group i.e. horizontal supine position. Patients with a history of systemic diseases (hypertension, coronary heart disease, diabetes, chronic respiratory disorders) were excluded from the study, as were those with insufficient acoustic window. Another exclusion criterion was excessive risk of general anesthesia, as assessed with American Society of Anesthesiologists Physical Status Scale (ASA) – grade II and higher.

General anesthesia was performed according to the same protocol in all patients. For induction of anesthesia propofol at a dose of 2 mg/kg i.v. was used followed by cis-atracurium at the intubation dose of 0.1 mg/kg i.v. Aesthesia was maintained with sevoflurane at minimal alveolar concentration (MAC) 0.8 occasionally to 1.5 and remifentanil in continuous intravenous infusion at a rate of 0.1–0.5 μg/kg/min. Heart rate, blood pressure, end-tidal carbon dioxide pressure ($ETCO_2$) and pulse oximeter oxygen saturation (SpO_2) were monitored during the procedure.

The reduction of hemodynamic parameters in the studied group was achieved by gradual increase of the rate of continuous intravenous infusion of remifentanil first, keeping the MAC of sevofluorane stable at the level of 0.8. This resulted in conspicuous decrease of HR with only slight reduction of MAP. When HR dropped close to the lower range of the physiological norm i.e. ca. 60/min and further reduction of MAP was necessary to improve surgical conditions, the MAC of sevofuorane was enhanced. Normocapnia was preserved during the whole operation.

Reduction of HR and MAP was aimed at achieving bloodless surgical field or minor bleeding not interfering with surgical manipulation.

Depending on the extent of the procedure, concomitant intraoperative trauma and individual quality of surgical field (bleeding intensity) as well as required precision of surgical manipulation, low hemodynamic parameters were maintained for 40–90 min.

2.1. *Doppler ultrasonography*

Blood flow velocity in the middle cerebral artery was assessed with transcranial color Doppler imaging using a ''vivid-i'' device (General Electric) and 2.5–3.6 MHz sector transducer 3S-RS according to the methodology described earlier [8]. The measurements were performed by single experienced operator throughout the study. The optimal position, angle and depth of insonation were determined preoperatively for each patient individually and applied during the surgical procedure. Right acoustic window, if present, was used routinely for sampling the M1 sector of the middle cerebral artery. In six patients left window was used and the left MCA was examined. In each patient the assessment of blood flow velocity was performed three times: before operation (P1), just after the induction of anesthesia (P2) and during the surgery at the time when satisfactory bloodless surgical field was achieved due to reduced blood pressure and heart rate (P3).

In the control group the third measurement was taken in normotensive conditions ca. 30–40 min after onset of surgery. Variations of peak systolic velocity (V_{ps}), end-diastolic velocity

(V_{ed}) and mean (V_m) blood velocity were analyzed and compared to the normal reference range [5].

2.2. Statistical analyses

Iman-Devenport variant of nonparametric Friedman test was used to compare the blood flow velocities in the middle cerebral artery between examinations at three time-points. Post hoc comparisons between each pair of time-points were performed using nonparametric Conover test.

Mann–Whitney test was used to compare blood flow velocities in the studied and control groups of patients at three time-points. Analyses were carried out using IBM SPSS Statistics 20.0 software, except for Friedman and Conover test, which were calculated according to appropriate algorithms [9]. Tests' results were considered significant at $p < 0.05$ level.

3. Results

Prior to the operation (P1) in the studied group of patients, the mean arterial pressure oscillated between 76 and 103 mmHg (median 92 mm Hg) and heart rate between 65 and 89/min (median 75/min). After induction of anesthesia (at P2) MAP dropped to 70–83 mmHg (median 80) and HR to 65–90/min (median 74). At the moment when bloodless surgical field was achieved (P3), MAP varied between 60 and 72 mmHg (median 63) whereas heart rate remained within a span of 55–71/min (median 62).

In the control group MAP and HR at P1 and P2 time points were similar to the values of the studied group: 78 and 102 mmHg (median 90 mmHg) and 68 and 84/min (median 76/min) – MAP and HR respectively at P1; 68–86 mmHg (median 82) and 68–92/min (median 74) – MAP and HR respectively at P2. Hemodynamic parameters in these patients were kept stable during entire procedure, thus at P3 time point (ca. 40 min after induction of the anesthesia) they were not much different from the measurements taken at P2 – MAP 70–90 mmHg (median 84) and HR 64–86/min (median 70).

Table 1 – Percentage drop of blood flow velocities between each of the two time-points in both groups of patients.

	Hypotensive group			Control group		
	P1/P2	P2/P3	P1/P3	P1/P2	P2/P3	P1/P3
V_{ps}	20.1	15.2	32.7	24.1	2.3	29.9
V_{ed}	28.2	21.3	45.6	23	4.5	26.6
V_m	29.3	18.4	43.3	25.8	5.5	30.2

V_{ps}, peak systolic velocity; V_{ed}, end diastolic velocity; V_m, mean velocity.
P1, before operation; P2, after induction of aneasthesia; P3, after reduction of hemodynamic parameters (studied group)/30–40 min after induction, in normotension (control group).

Statistical analysis showed highly significant differences in blood flow velocity measurements taken at three time points (Iman–Devenport variant of Friedman test, $p < 0.001$).

At P1 time point i.e. before operation, blood flow velocity (V_{ps}, V_m and V_{ed}) in the middle cerebral artery remained within the range of age-specific reference values in all patients. After induction of anesthesia (at P2 time point) blood flow velocity decreased markedly in most patients. Table 1 shows that in the studied group the most conspicuous drop was that of V_m (on average by 29.3%) followed by the rate of drop in V_{ed} (on average 28.2%) and then V_{ps} (on average 20.0%). It is worth emphasizing that V_{ps} in the middle cerebral artery fell below the minimal value of the normal reference range in three patients (7.5%), V_m in six patients (15%) whereas V_{ed} in eleven patients (27.5%). The differences of blood flow velocities between measurements taken at P1 and P2 were statistically highly significant (Conover test, $p < 0.001$) (Figs. 1–3).

When the satisfactory, bloodless operative conditions were achieved at P3, further substantial reduction of blood flow velocity (V_{ed}, V_m and V_{ps}) was detected in most patients of the studied group. The most considerable further drop was that of V_{ed} (on average 21.3%), followed by V_m (on average 18.4% reduction) and then that of V_{ps} (on average by 15.2%) (Table 1). At that time peak systolic velocity fell below the lower limit of

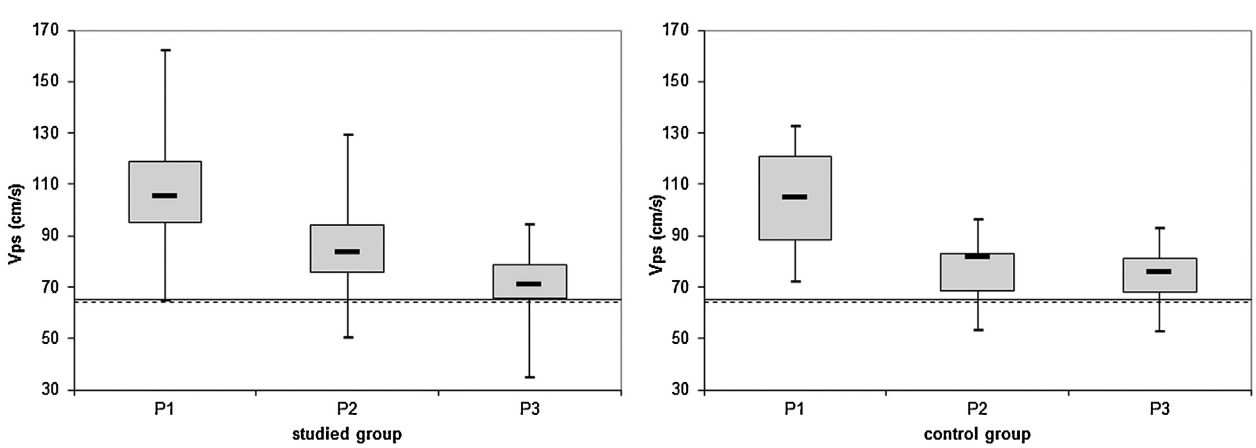

Fig. 1 – Decrease of peak systolic velocity (V_{ps}) in studied (hypotensive) and control group of patients. Solid line – lower limit of normal reference range for patients aged 20–40 years (65 cm/s). Dashed line – lower limit of normal reference range for patients aged 40–60 years (64 cm/s).

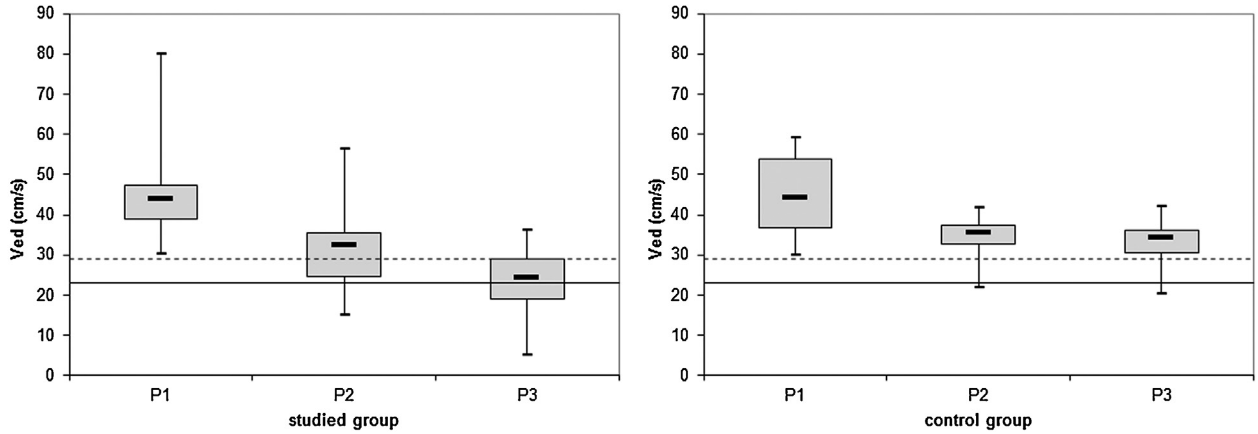

Fig. 2 – Decrease of end diastolic velocity (V_{ed}) in studied (hypotensive) and control group of patients. Solid line – lower limit of normal reference range for patients aged 20–40 years (23 cm/s). Dashed line – lower limit of normal reference range for patients aged 40–60 years (29 cm/s).

normal reference range in ten patients (25%), mean velocity in twenty patients (50%) and end diastolic velocity in as many as twenty-three patients (57.5%). The reduction of the value of blood flow parameters between measurements taken at P2 and P3 proved statistically highly significant (Conover test, $p < 0.001$) (Figs. 1–3).

In all patients satisfactory surgical conditions of the operative field were obtained before their MAP and HR dropped below the values commonly regarded as safe for healthy subjects.

In the control group, at P2 time point (after induction of anesthesia) a decrease of blood flow velocity was also observed in most patients. V_m dropped on average by 25.8%, V_{ed} on average by 23% and V_{ps} by 24.1% (Table 1). The differences of blood flow velocities between measurements taken at P1 and P2 were statistically highly significant (Conover test, $p < 0.001$) (Figs. 1–3).

Just as in the hypotensive group, in the control subjects after induction of anesthesia blood flow velocities dropped below lower limit of normal reference values in few cases: systolic velocity in 1 patient (7.6%), the mean velocity in 2 patients (15.4%) and diastolic velocity in 3 patients (23.1%). After hemodynamic parameters had been stabilized (P3 time point) only a minor further reduction of blood flow velocities was detected in this group of patients: systolic velocity fell additionally on average by 2.3%, diastolic velocity by 4.5% and mean velocity by 5.5% (Table 1). The number of patients whose blood flow velocity dropped below normal reference range did not increase at P3 and remained the same as at P2 time point (Figs. 1–3).

As opposed to hypotensive group, in the control subjects the P1/P3 drop of blood flow velocity pertained equally to systolic and diastolic velocity. In the studied group of patients a divergent reduction of blood flow velocity was observed i.e. diastolic velocity was much more heavily influenced by reduced hemodynamic parameters than systolic velocity (Table 1).

Comparison between groups of patients revealed that systolic blood flow velocity dropped similarly in both groups while diastolic and mean velocity were reduced much more intensely in the studied group (Table 1). The differences in mean and diastolic blood flow velocities at P3 between

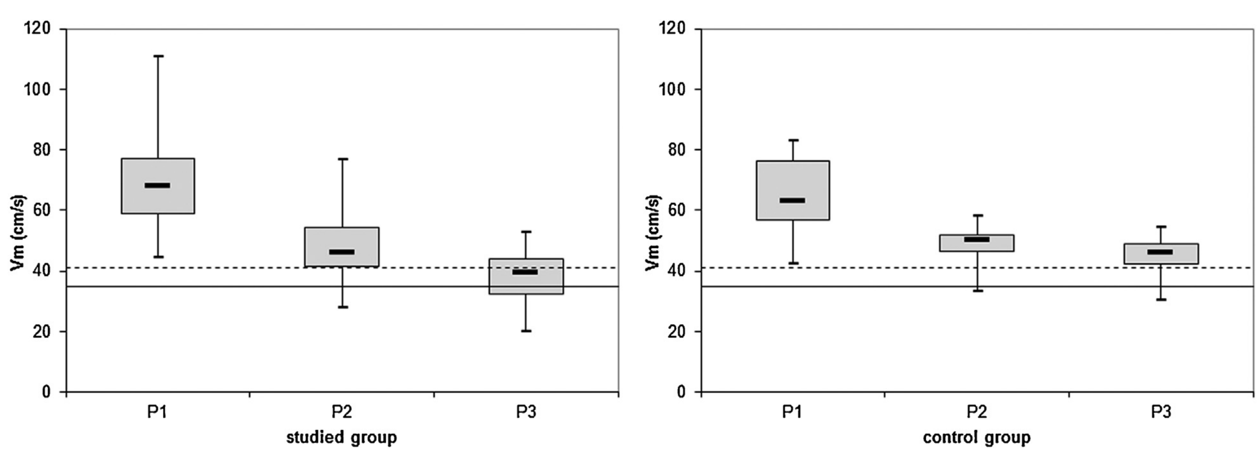

Fig. 3 – Decrease of mean velocity (V_m) in control (hypotensive) and control group of patients. Solid line – lower limit of normal reference range for patients aged 20–40 years (35 cm/s). Dashed line – lower limit of normal reference range for patients aged 40–60 years (41 cm/s).

studied and control group were statistically significant (Mann–Whitney test, $p < 0.05$).

No complications were revealed in any of our patients with standard neurological examination in the postoperative period.

4. Discussion

This study demonstrates that during surgery performed in moderate hypotension with decreased, stable heart rate, blood flow velocity in the major cerebral arteries decreases to values which are below the normal reference range in healthy subjects. Furthermore, this finding can be extrapolated to diminution of cerebral blood flow, at least in the territory supplied by the MCA. For that to be true, the cross-sectional area of the insonated artery needs to remain constant. Liu et al. suggested that large cerebral arteries are involved in cerebral autoregulation [10], while Valdueza et al. and Serrador et al. found constant caliber of the MCA throughout different phases of cerebral autoregulation [11,12]. Certainly the validity of using transcranial Doppler measurement of cerebral blood flow velocity to assess cerebral blood flow still is a concern. However several approaches have been employed to ascertain whether TCD measurements are confounded by potential changes in vascular dimensions and all have concluded that such dimensional changes did not lead to a misleading outcome [13–17]. Moreover, a significant positive correlation has been found by Kirkham et al. [7] between blood flow velocity (CBV) and cerebral blood flow (CBF) values, particularly for the middle cerebral artery. Validation of Doppler sonography as an indicator of cerebral blood flow has been also performed in other reports [18–21] Taking into consideration the findings of the above mentioned studies one can conclude that controlled hypotension may in some patients result in a decrease of cerebral blood flow in the territory supplied by the MCA.

An important problem is why cerebral blood flow decreased in our patients despite their MAP and HR not falling below the lower limits of efficient cerebral autoregulation. A definite answer is not possible based on the data available within our experimental set-up and can only be to some extent speculative. First, it ought to be stressed that the drop in blood flow velocity was not related to the type of surgery because the study group and the control group did not differ with regard to duration of surgical procedure, intraoperative trauma, patient's position and blood loss. Also, in both groups surgical interventions were restricted to areas not involved in regulatory mechanism of cardiac or vascular reflexes. Therefore, it can be assumed that the drop of cerebral blood flow velocity was due to deliberately applied hypotension.

It is the mean blood flow velocity value which has been shown to positively correlate to a highest degree with the volume of flow and this flow velocity decreased significantly in the MCA of our patients after induction of anesthesia (studied and control group) and then during hypotensive conditions (studied group). As the mean blood flow velocity depends on the peak systolic and the end diastolic velocity, it is notable that the decrease of the end diastolic velocity contributed in our patients mostly to the observed decrease of the mean blood flow velocity between points P1 and P3 of the anesthesia/operation. End diastolic velocity is more heavily influenced by the status of the peripheral cerebral circulation than the peak systolic velocity and the arterioles are responsible for the effect of cerebral autoregulation [22,23]. It was proved in animal model that during hypotension in early phase of autoregulatory failure, divergent systolic and diastolic blood flow velocity might be detected [24]. More profoundly decreased end diastolic than peak systolic velocity in studied group may suggest that the peripheral cerebral circulation has failed to respond adequately to the challenge of decreased heart output thus resulting in diminished cerebral blood flow. The divergence of systolic and diastolic blood flow velocities was not evident in the control group.

Cerebral blood flow can be suggested to decrease markedly in our patients in spite of the fact that MAP and HR were maintained within reputedly "safe" limits. In such situation the influence of anesthetics on cerebral autoregulation should be analyzed. Generally all the anesthetics applied in our patients are known not to interfere with cerebral autoregulation in therapeutic doses. This pertains to cis-atracurium, propofol, sevofluran with some exception of remifentanyl which can somewhat decrease cerebral blood flow velocity though in certain regions of the brain actually an increase of blood flow velocity has been found to occur [25–28]. Additionally, several studies have shown that the anesthetic agents are responsible for global whole-brain metabolic reduction [29,30]. The lower metabolic requirements of the anesthetized brain are associated with reduced demand for blood supply. Although induction of anesthesia caused a decrease of sonographically assessed cerebral blood flow velocity (control and studied group), which might be related to diminished hemodynamic parameters, maintenance of anesthesia without further lowering of MAP and HR, did not affect Doppler measurements so intensely, as it was the case in the control group. Thus rather the reduced hemodynamic parameters in patients of studied group and not the applied combination of anesthetic agents, seem to contribute more to the drop of cerebral blood flow during surgical procedures. The reduced metabolic requirements of the brain during general anesthesia may be perceived as a protective mechanism which allows patients to withstand greater reductions in cerebral blood flow.

Also the influence of oxygen in increased concentration can constrict cerebral arterioles, but this effect occurs mainly with 100% oxygen inhalation whereas in our patients a 50% concentration of oxygen was used.

Whatever mechanism evoked the reduction of cerebral blood flow velocity, this phenomenon has been demonstrated in this study to occur when MAP and HR are purposefully reduced during surgery in general anesthesia. Though no anesthesia-related complications have ever been reported in similar groups of patients, nor have occurred in our patients, the problem should not be ignored. Apparently, lack of conspicuous neurological deficits after the performed procedures cannot stand for evidence that cerebral blood flow during the whole operation was sufficient. More careful and detailed examination of these patients would be warranted in order to reveal possible latent neuropsychological disorders like cognitive impairment, depression or anxiety. Such abnormalities have been documented in patients after cardiosurgical procedures carried out in controlled hypotension [31,32].

Our ability to measure only the velocity of blood in one major cerebral artery is an apparent limitation of our study. The problem of relation between cerebral blood flow velocity and the volume of cerebral blood flow has been discussed above and it seems reasonable to conclude that the volume of cerebral blood flow actually decreases with decreased blood flow velocity in the middle cerebral artery. Whether moderately decreased cerebral blood flow can harm the brain depends on current metabolic demand of this organ. Though cerebral metabolism is known to be depressed in general anesthesia, any kind of direct monitoring of cerebral perfusion/metabolism seems justified. Unfortunately most of these methods (such as those based on isotopes, thermodilution, MRI), are either not applicable in an operating theatre, or invasive, such as monitoring of metabolites in the brain parenchyma.

5. Conclusions

Reduction of MAP and HR during transnasal, endoscopic procedures in order to improve surgical field conditions, may result in profound and uneven drop of blood flow velocities in the MCA to values which are well below the normal reference range. Since divergent reduction of systolic and diastolic velocity may indicate an early phase of cerebral autoregulation compromise, and decrease of mean blood flow velocity in the major cerebral arteries corresponds with a decrease of cerebral blood flow, further investigations in this field seem warranted.

Conflict of interest

None declared.

Acknowledgement and financial support

Investigation supported by grants of the Ministry of Science and Education, Warsaw, Poland. Grant No N N403 150139 and NR13 0037 10/2010

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

References

[1] Degoute CS. Controlled hypotension: a guide to drug choice. Drugs 2007;67:1053–76.
[2] Eberhart LHJ, Folz BJ, Wulf H, Geldner G. Intravenous anaesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. Laryngoscope 2003;113:1369–73.
[3] Nair S, Collins M, Hung P, Rees G, Close D, Wormald PJ. The effect of ß-blocker premedication on the surgical field during endoscopic sinus surgery. Laryngoscope 2004;114:1042–6.
[4] Sieśkiewicz A, Drozdowski A, Rogowski M. The assessment of correlation between mean arterial pressure and intraoperative bleeding during endoscopic sinus surgery in patients with low heart rate. Otolaryngol Pol 2010;64:225–8.
[5] Krejza J, Mariak Z, Walecki J, Szydlik P, Lewko J, Ustymowicz A. Transcranial color Doppler imaging of basal cerebral arteries in 182 healthy subjects: age and sex variability and normal reference values for blood flow parameters. Am J Roentgenol 1999;172:213–8.
[6] Krejza J, Szydlik P, Liebeskind D, Kochanowicz J, Bronov O, Mariak Z, et al. Age and sex variability and normal reference values for VMCA/VICA index. Am J Neuroradiol 2005;26:730–5.
[7] Kirkham FJ, Padayachee TS, Parsons S, Seargeant LS, House FR, Gosling RG. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. Ultrasound Med Biol 1986;12:15–21.
[8] Krejza J, Mariak Z, Melhem ER, Bert RJ. A guide to the identification of major cerebral arteries with transcranial color Doppler sonography. Am J Roentgenol 2000;174:1297–303.
[9] Iman RL, Davenport JM. Approximations of the critical region of the Friedman statistic. Commun Stat 1980;18:571–95.
[10] Liu J, Zhu YS, Hill C, Armstrong K, Tarumi T, Hodics T, et al. Cerebral autoregulation of blood velocity and volumetric flow during steady-state changes in arterial pressure. Hypertension 2013;62:973–9.
[11] Valdueza JM, Balzer JO, Villringer A, Vogl TJ, Kutter R, Einhäupl KM. Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. Am J Neuroradiol 1997;18:1929–34.
[12] Serrador JM, Picot PA, Rutt BK, Shoemaker JK, Bondar RL. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. Stroke 2000;31:1672–8.
[13] Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986;17:913–5.
[14] Sorteberg W, Lindegaard KF, Rootwelt K, Dahl A, Russell D, Nyberg-Hansen R, et al. Blood velocity and regional blood flow in defined cerebral artery systems. Acta Neurochir (Wien) 1989;97:47–52.
[15] Dahl A, Russell D, Nyberg-Hansen R, Rootwelt K. A comparison of regional cerebral blood flow and middle cerebral artery blood flow velocities: simultaneous measurements in healthy subjects. J Cereb Blood Flow Metab 1992;12:1049–54.
[16] Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. Stroke 1994;25:793–7.
[17] Clark JM, Skolnick BE, Gelfand R, Farber RE, Stierheim M, Stevens WC, et al. Relationship of 133Xe cerebral blood flow to middle cerebral arterial flow velocity in men at rest. J Cereb Blood Flow Metab 1996;16:1255–62.
[18] Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;20:45–52.
[19] Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. Stroke 1994;25:1985–8.

[20] Smith M. Perioperative uses of transcranial perfusion monitoring. Anesthesiol Clin 2007;25:557–77.
[21] Sorond F, Hollenberg NK, Panych LP, Fisher ND. Brain blood flow and velocity: correlations between magnetic resonance imaging and transcranial Doppler. J Ultrasound Med 2010;29:1017–22.
[22] Krejza J, Mariak Z, Huba M, Wolczynski S, Lewko J. Effect of endogenous estrogen on blood flow through carotid arteries. Stroke 2001;32:30–6.
[23] Ohkuma H, Manabe H, Tanaka M, Suzuki S. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 2000;31:1621–7.
[24] Lewis SB, Wong ML, Bannan PE, Piper IR, Reilly PL. Transcranial Doppler identification of changing autoregulatory thresholds after autoregulatory impairment. Neurosurgery 2001;48(2):369–75.
[25] 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 Anaesth 2006;97:333–9.
[26] 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.
[27] Dragal A, Lam AM. Cerebral autoregulation in anesthesia. Curr Opin Anaesthesiol 2009;22:547–52.
[28] Albera R, Ferrero V, Canale A, De Siena L, Pallavicino F, Poli L. Cochlear blood flow modifications induced by anaesthetic drugs in middle ear surgery: comparison between sevoflurane and propofol. Acta Otolaryngol 2003;123:812–6.
[29] Alkire MT, Pomfrett CJ, Haier RJ, Gianzero MV, Chan CM, Jacobsen BP, et al. Functional brain imaging during anesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism. Anesthesiology 1999;90:701–9.
[30] Alkire MT, Haier RJ, Shah NK, Anderson CT. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. Anesthesiology 1997;86:549–57.
[31] Raja PV, Blumenthal JA, Doraiswamy PM. Cognitive deficits following coronary artery bypass grafting: prevalence, prognosis, and therapeutic strategies. CNS Spectr 2004;9:763–72.
[32] Anastasiadis K, Argiriadou H, Kosmidis MH, Megari K, Antonitsis P, Thomaidou E, et al. Neurocognitive outcome after coronary artery bypass surgery using minimal versus conventional extracorporeal circulation: a randomised controlled pilot study. Heart 2011;97:1082–8.