SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Evaluation of the effects of different anesthetics on systemic and cerebral circulation, cerebral autoregulation and carbon dioxide reactivity

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EVALUATION OF THE EFFECTS OF DIFFERENT ANESTHETICS ON SYSTEMIC AND CEREBRAL CIRCULATION, CEREBRAL AUTOREGULATION AND CARBON DIOXIDE REACTIVITY

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The Examination (online format) takes place at 11:00 AM, December 9, 2021.

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Publicity is guaranteed during the online Defense. If you are willing to participate, please send an e-mail to juhasz.marianna@med.unideb.hu before 16:00 PM, December 8, 2021. Due to technical reasons later sign-ups are not possible and you will not be able to join the online.

INTRODUCTION

General anesthesia may be induced and maintained using different anesthetics depending on complete inhalation, combined balanced, or total intravenous anesthesia. All anesthetics affect the functioning of the whole body, mainly the circulation and modifying the perfusion of various organs. From a neuroanesthetic perspective, changes in cerebral circulation are of paramount importance.

Cerebral blood flow is basically determined by three factors: arterial blood pressure, cerebrovascular resistance, and intracranial pressure. These factors interact with each other and dominate their effect in different areas of the brain (arteries, arterioles, capillaries, veins). All three factors can be altered by certain pathological conditions (arrhythmia, sepsis, intracranial hypertension) and certain chronic diseases that affect the blood vessels of the brain (eg hypertension, diabetes mellitus), or by therapeutic intervention and medication.

Cerebral autoregulation and vasomotor response provide continuous cerebral blood flow under adverse conditions. In addition to cardiac output, heart rate, and peripheral vascular resistance, arterial blood pressure is also determined by the elasticity of the body's peripheral arterial vasculature of the body. The increase in peripheral artery stiffness are not the same as the increase in peripheral vascular resistance. Elastic peripheral arteries support continuous cerebral blood flow. Different medications can have an effect on arterial stiffness, including anesthetics. The ideal anesthetic does not change cerebral autoregulation and vasomotor response and does not incrase arterial stiffness. The effects of anesthetics on cerebral circulation and the simultaneous modification of arterial stiffness have not been studied.

REGULATION OF CEREBRAL PERFUSION

Regulation of blood flow is complex, the elements of which interact with each other, but are also influenced by a number of other factors, such as: certain vasodilators (carbon dioxide, nitrous oxide), drugs (acetazolamide, papaverine, antihypertensives), etc.
The most important components of cerebral blood flow:

1. Metabolic: provides a balance between cerebral metabolism (demand) and cerebral blood flow (supply), which provides oxygen and glucose transport. The metabolic mechanism probably the most contributes to autoregulation in the microvasculature.

2. Miogenic: change in transmural pressure results in constriction or dilation of cerebral blood vessels. The diameter of the arterioles narrows when blood pressure increases and vice versa, maintaining a steady cerebral blood flow (CBF) (Bayliss effect) by altering cerebral vascular resistance (CVR).

3. Neurogenic: the cerebral resistance vessels and capillaries have extensive innervation through the interaction between brainstem vasomotor centers and sympathetic nerve fibers. Vasomotor center of the brainstem mainly affects the global flow of blood to the brain. Hypoxic-induced dilation in the internal carotid artery and the reduction in perfusion in the periferal artery are provided by brainsteam, i.e. the changes in the blood distribution of the body. Regional cerebral blood flow changes proportionately on the basis of changes in neural activity and metabolic demand. It is the neurovascular coupling, that given by the interaction between cerebral arterioles, capillaries, and axons of surrounding neurons. In certain diseases, neurovascular coupling is impaired, such as hypertension, ischemic stroke.

4. Endothelial regulation: Nitric oxide (NO) released by parasympathetic fibers by excitatory glutaminergic impulses causes dilatation of vascular smooth muscle. ATP, prostaglandins produced by neurons and astrocytes, vasoactive substances produced by GABAergic interneurons, perivascular potassium and calcium ions released by astrocytes also modulate vascular tone. The endothelium also transmits vasoactive substances at the cortical level area in response to neuronal activity. This interaction ensures that changes in cerebral blood flow are proportional to neuronal activity.

CEREBRAL VASOREACTIVITY

Cerebral arteries and arterioles dilate when elevated levels of arterial carbon dioxide and low levels of $PaCO_2$ levels cause cerebral vasoconstriction. According to the hypothesis, diffusing CO_2 changes the pH in the extracellular space and in vascular smooth muscle cells. When the value of $PaCO_2$ changes by 1 mmHg, leads to a change in CBF by 1- 6%. The cerebral vascular response to the change in CO_2 develops rapidly, within 2 minutes.

Acute changes in $PaCO_2$ modify cerebral autoregulatory. When $PaCO_2$ does not exceed 40 mmHg, autoregulation is intact, cerebral blood flow is continuous. In severe hypercapnia, above 60 mmHg PCO_2, the cerebral vessels do not narrow, as beyond the upper range of autoregulation, the cerebral vessels are already completely dilated.

Hypocapnia broadens the plateau of cerebral autoregulation of the MAP in both directions. Blood pressure affects cerebral vasoreactivity, elevated $PaCO_2$ levels can cause minimal vasodilation when blood pressure is low.

Cerebral autoregulation

Cerebral autoregulation (CA) ensures that cerebral blood flow (CBF) remains relatively constant over a wide range of cerebral perfusion pressure (CPP) and mean arterial pressure (MAP). Outside the range of autoregulation, cerebral hypo- or hyperperfusion occurs. At first in 1959 Lassen published the cerebral autoregulation curve. Lassen presented the MAP–CBF curve, which showed a constant CBF for MAP values between 50 and 150 mmHg. The classic static autoregulation curve shows a plateau of cerebral blood flow versus mean arterial pressure in the MAP range of about 50 mmHg to approximately 170 mmHg.

STATIC AUTOREGULATION

Static autoregulation reflects the slow response of cerebral vascular resistance to changes in mean arterial pressure. Static CA, sometimes referred to as steady-state CA, are autoregulatory responses to steady-state changes in ABP or ICP, providing information about the range of CPP in which CA is active. This curve shows a characteristic shape of a monotonically increasing CBF with CPP and a distinct CBF plateau in a range of CPP where autoregulation is intact and vessel constriction can compensate for increased pressure. Significant hypotension-induced vasodilation is not sufficient to maintain adequate CBF.

Measured CBF and MAP values determine cerebral vascular resistance (CVR):

$$CVR = MAP/CBF$$

An index of static CA could be defined on the basis of the slope of changes in CVR. This index has been variably named the static autoregulation index (SARI).

$$sARI = \%\Delta CVR / \%MAP$$

where %CVR is the change in CVR (in percent of its baseline value) and %MAP is the change in MAP (also expressed in percent of its baseline value). If CBF follows MAP passively, SARI=0. On the contrary, if the change of CVR fully compensates for the change in MAP, there is no change in CBF and SARI=1. Autoregulation is abnormal if the sARI value is less than 0.4.

Cerebral perfusion pressure can replace the MAP value:

$$CPP= MAP – ICP$$

$$CVR = CPP / CBF$$

$$sARI = \%\Delta CVR / \%\Delta CPP$$

DYNAMIC CEREBRAL AUTOREGULATION

Aaslid's leg cuff method is a well validated technique to measure dynamic cerebral autoregulation from 1980. In the method large pneumatic cuffs placed around both thighs are inflated 50 mmHg above systolic pressure for ≥3 minutes and then suddenly released, a sharp drop in MAP of about 20 mmHg is usually observed, lasting 6-7 seconds before returning to its original level. A simultaneous drop in cerebral blood flow velocity (CBFV), usually estimated with Doppler ultrasound, accompanies the decrease in ABP. The mathematical model fits the change in cerebral vascular resistance and determines the dynamic rate of regulation (dROR). The normal dROR is 20%/s.

SYSTEMIC CIRCULATION AND ARTERIAL STIFFNESS

The mean blood pressure values depend on three parameters: stroke volume (SV), heart rate (HR) and systemic vascular resistance (SVR). Mean arterial pressure tends to remain unchanged in the arterial system, from the ascending aorta to peripheral arteries.

$$MAP = SV \times HR \times SVR$$

Very different blood pressure levels can correspond to the same mean arterial pressure value. Accurate analysis of cardiovascular hemodynamics cannot ignore that blood pressure has two distinct but interdependent components: MAP and a pulsatile component, defined as pulse pressure (PP), which represents the fluctuation of pressure values around the mean value of arterial pressure.

Large arteries have a "buffer" function, have the task of damping the pulsatile output of the left ventricle and of changing the rhythmic, intermittent and discontinuous activity of the cardiac pump. Arterial stiffness describes the rigidity of the arterial wall.

Arterial stiffness is different from vascular resistance. While an increase in systemic vascular resistance causes an increase in both systolic and diastolic blood pressure, increased arterial stiffness is accompanied by a decrease in the buffer function of the aorta on cardiac output. This causes an increase in systolic blood pressure values and a decrease in diastolic blood pressure and, therefore, an increase in pulse pressure.

When stroke volume and aortic valve closure occur, a large amount of blood remains "stored" in the aorta and large elastic arteries, to be released afterward (Windkessel effect) so that proper pressure values are maintained in diastole as well.

The elastic properties of the aortic and large arteries can be altered by stress and drugs. Therefore anesthetics can modify arterial stiffness. If the narcotic increases the stiffness of the arteries, it may result in deterioration of the organs, the brain microcirculation.

THE PRINCIPLE OF APPLANATION TONOMETRY

Applanation tonometry is the gold standard for the noninvasive evaluation of arterial stiffness. The essence of the procedure: the radial artery pressure wave and amplitude were recorded noninvasively with a pencil-type probe over the left radial artery or carotid artery. The system software generates an average peripheral and corresponding central waveform, which then subject to further analysis, calculates the pressure values in the ascending aorta, i.e. the central pressure.

Two pressure peaks characterise the systolic part of the central waveform. The first peak results from left cardiac ventricle ejection, and the second one results from wave reflections from the periphery. The difference between these two peaks represents the degree of increase in central arterial pressure due to wave reflection. The augmentation pressure is the absolute increase of the pulse pressure due to the reflected wave, and the augmentation index is the measure of the contribution of the wave reflection to the arterial pressure waveform. The augmentation index is expressed as a percentage of the pulse pressure. The amplitude and timing of the reflected wave ultimately depend on the stiffness of the small vessels and large arteries, representing a measurement of the systemic arterial stiffness.
SphygmoCor (AtCor Medical, Sydney, Australia) was used for our study.

THE PRINCIPLE OF TRANSCRANIAL DOPPLER

TCD ultrasonography is based on the principle of the Doppler effect. According to this principle, ultrasound waves emitted from the Doppler probe are transmitted through the skull and reflected by moving red blood cells within the intracerebral vessels.

Through the transtemporal acoustic window, the major branch of the circle of Willis should be assessed. Cerebral autoregulation is based on the fundamental assumption that changes in CBFV represent changes in volumetric CBF, that is, by assuming that the diameter of the basal cerebral arteries does not change significantly. The constriction of the cerebral arterioles is associated with increased pulsatility index (PI) and resistance index (RI) and decreases the CBF.

In our study the Rimed Digilite ultrasound machine (Rimed Ltd., Israel) was used. CBFV of the cerebri media artery was measured through the temporal acoustic window.

PROPERTIES OF THE ANESTHETICS USED IN OUR STUDIES

INHALATIONAL ANESTHETIC, SEVOFLURANE

Sevoflurane altered neurotransmission by strongly increasing GABAergic inhibition while decreasing glutamatergic NMDA activity.

Sevoflurane increases CBF and decreases $CMRO_2$ and CVR in a dose-dependent manner but less potent cerebral vasodilator than other volatile anesthetics. It has no effect on cerebrospinal fluid production and resorption. This “weak” cerebral vasodilatory effect may explain why preserved cerebral vessels respond to changes in perfusion pressure. Sevoflurane is an appropriate anesthetic in neurosurgery anesthesia because intracranial pressure does not increase even during 1.5 MAC sevoflurane anesthesia.

With sevoflurane, cerebral autoregulation preserved at lower concentrations, but at higher concentrations it provides luxury perfusion by vasodilation and impaired autoregulation with hypercapnia.

2 MAC sevoflurane anesthesia generally results in a shortening of the autoregulatory plateau and deteriorates the autoregulatory response to hypotension, and the age of patients does not have an effect on autoregulation.

The effect of sevoflurane on hemodynamic and vascular parameters is insignificant but increases increasing dose. By interrupting anesthesia, blood pressure returns in a shortamount of time.

1,5 MAC sevoflurane preserves preload but attenuates cardiac contractility, reduces afterload. Sevoflurane has fewer depressant effects on cardiac function (left ventricular stroke work index, stroke volume index) than eqivalent enflurane.

Sevoflurane has no effect on sinoatrial node function, it does not sensitize the myocardium to the arrhythmogenic effects of catecholamines but can lead to prolongation of the QTc interval.

INTRAVENOUS ANESTHETIC, PROPOFOL

Propofol enhances the function of the GABA receptor, the most abundant fast inhibitory neurotransmitter receptor in the CNS. Under propofol anesthesia, cerebral blood flow decreases, cerebral vascular resistance increases, cerebral oxygen consumption decreases, which is associated with a decrease in neuronal activity in the EEG.

During low dose propofol anesthesia mean cerebral perfusion pressure decreases, but remains within the ranges of autoregulation. Even very high dose propofol ((200 micrograms.kg-1.min-1) preserves cerebral autoregulation.

Propofol induces dose-dependent vasodilation and hypotension in the clinical setting by stimulating the release of nitric oxide (NO) and decreasing cardiac output. Protein kinase C mediated Ca^{2+} sensitization plays an important role in vascular smooth muscle contraction. Propofol has a negative inotropic effect and decreases peripheral resistance. Heart rate decreases as baroreflex decreases.

Propofol is administered by perfusor during total intravenous anesthesia.

TOTAL INTRAVENOUS ANESTHESIA, TARGET-CONTROLLED INFUSION

Total intravenous anaesthesia (TIVA) can be defined as a technique of general anesthesia using a combination of agents administered axclusively intravenously route and in the absence of all inhalational agents.

There is a mathematical relationship between an administered dose of a venous drug and the resulting observed changes in plasma concentration. This relationship allows mathematical pharmacokinetic models to be constructed that can then be used to facilitate the calculation of dosing regimens and to guide pharmacotherapeutic management.

Computer-assisted target controlled infusion has been developed to rapidly achieve and maintain the effect site concentration of intravenous anesthetics. Target controlled infusions (TCI) of propofol allow anesthetists to target constant blood concentrations.
TCI systems have two models for propofol with the Asena PK system, the choice is between the Marsh and Schnider adult models.

The Schnider model predicted much faster effect site equilibration in the blood than the Marsh model. This model takes into account total body weight, age, height, and lean body mass of the patient, avoiding over and undershoot in plasma concentration.

GOALS

The goal of our studies was to determine the effect of the most commonly used anesthetics, propofol and sevoflurane, on the systemic and cerebral circulation at normocapnia after induction of anesthesia and at decreasing arterial carbon dioxide values during anesthesia.

We aimed to answer the following study questions in the first study:

- What is the effect of anesthesia induction and achievement of steady state sevoflurane anesthesia on systemic hemodynamics and cerebral blood flow?

- Is cerebral autoregulation maintained under normocapnic steady state of 1 MAC sevoflurane anesthesia?

- What are the cerebral and systemic hemodynamic effects of induced hypocapnia at 1 MAC sevoflurane?

We aimed to answer the following study questions int he second study:

- What are the cerebral and systemic hemodynamic effects of 4 μg / ml effect site concentration propofol, is there any correlation between the effects?

- Is cerebral autoregulation maintained at normocapnic steady state 4 μg / ml effect site concentration propofol anesthesia?

- What are the cerebral and systemic hemodynamic effects of induced hypocapnia at 4 μg / ml effect site concentration propofol anesthesia?

METHODS

SEVOFLURANE

STUDY POPULATION

After approval of the local Ethics Committee (DEOEC RKEB/IKEB 3584–2012;), written informed consent was obtained from 35 ASA I-II patients scheduled for varicectomy and inguinal hernial repair surgery. The study was registered at http://www.clinicaltrials.gov, identifier: NCT02054143, retrospectively registered. Exclusion criteria were age <18 years or> 60 years,

severe cardiovascular disease, severe carotid artery stenosis, cerebrovascular disease, smoking, diabetes mellitus, hypertension, renal disease, hyperlipidemia, left ventricular hypertrophy and severe alteration of the preoperative pulmonary

function, characterized as FEV1 <70% and FEV1/FVC ≤70% of the predicted value.

STUDY PROTOCOL

Preoperative measurements were recorded one hour before anesthetic induction in a supine position in a quiet environment. The patients were then premedicated with 7.5 mg of midazolam orally 60 min before entering the operating room.

Anesthesia was induced with a combination of 2 mg.kg− 1 propofol and 2 μg.kg− 1 fentanyl. Intubation was facilitated by administration of 0.6 mg.kg− 1 rocuronium. Fentanyl and rocuronium were repeated as needed. Anesthesia was maintained with sevoflurane in 40% oxygen. Sevoflurane concentration was titrated to a target Bispectral Index (BIS) between 40 and 60 (Covidien, Dublin, Ireland) and it was aimed at 1 MAC. Neuromuscular block was monitored with acceleromyography (TOF Watch SX, NV Organon, Oss, The Netherlands).

Standard monitoring included five-lead ECG, NIBP, core temperature in the tympanic membrane, and pulse oximetry. Normothermia was maintained with a forced air system (Bair Hugger 750, 3 M, Eden Prairie, MN, USA). Patients were ventilated using volume-controlled square-wave flow pattern ventilation with 6–8 ml.kg− 1 TV, 5 cmH2O PEEP, 2 L.min− 1 fresh

gas flow and with a respiratory rate adjusted to reach and maintain 40 mmHg $EtCO_2$ (Draeger Primus anesthesia workstation, Draeger Lübeck, Germany).
After induction of general anesthesia and intubation, the lungs were ventilated in a supine position for 20 min as described above. At this stage, hemodynamic, transcranial Doppler, applanation tonometry and ventilatory parameters were simultaneously recorded.

PROPOFOL

STUDY POPULATION

After approval of the local Ethics Committee (DERKEB/IKEB 4100-2014), written informed consent was obtained from 30 patients with physical status I-II of American Society of Anesthesiologists (ASA) scheduled for elective varicectomy, inguinal hernioplasty, or breast surgery under general anesthesia.

This was a case series study. Exclusion criteria were severe cardiovascular disease, severe carotid artery stenosis, cerebrovascular disease, smoking, diabetes mellitus, renal disease, hyperlipidemia and left ventricular hypertrophy. The study was registered at http://www.clinicaltrials.gov, identifier: NCT02203097, registration date: July 29. 2014.

STUDY PROTOCOL

Patients were premedicated with 100 mg diclofenac orally 60 minutes before anesthetic induction. Preoperative measurements were recorded one hour before anesthetic induction in a supine position in a quiet environment.

Anesthesia was induced with a combination of 2 μg.kg-1sufentanil bolus and propofol. Anesthesia was maintained using the TCI method according to the Schnider model, effect site concen-tration: 4 μg.ml-1. The Alaris Asena PK^{TM} (Cardinal Health, Alaris Products, Basingstoke, UK) TCI system was used for propofol administration. Intubation was facilitated by administration of 0.6 mg.kg-1rocuronium. Neuromuscular block was monitored with acceleromyograph (TOF Watch SX, NV Organon, Oss, the Netherlands). Standard monitoring included five lead ECG, NIBP, BIS, and pulse oximetry. Normothermia was maintained with a forced air system (Bair Hugger 750, 3M, Eden Prairie, MN, USA). The patients were ventilated using volume-controlled square-wave flow pattern ventilation with 6-8 ml.kg-1Tidal Volume

(TV), 5 cmH_2O PEEP, 2 L.min-1fresh gas flow and with a minute volume adjusted to reach and maintain 40 mmHg end-tidal carbon dioxide ($EtCO_2$) (Draeger Primus anesthesia workstation, Draeger Lübeck, Germany).

After induction of general anesthesia and intubation, the lungs were ventilated in a supine position for 20 minutes to reach $EtCO_2$ of 40 mmHg. At this stage, hemodynamic, transcranial Doppler, applanation tonometry, and ventilatory parameters (TV and breathing frequency) were recorded simultaneously. In the second phase of the study minute ventilation (respiratory rate and tidal volume) was changed to reach and maintain 35 mmHg $EtCO_2$. After a 5-minute stabilization period all measurements were repeated. At the next stage of measurement series, the ventilator settings were changed to reach and maintain 30 mmHg $EtCO_2$. After a 5-minute stabilization period, applanation tonometry and transcranial Doppler measurements were repeated.

During each measurement, peripheral oxygen saturation (SpO_2), heart rate, systolic and diastolic blood pressure, mean blood flow velocities and pulsatility indices in the middle cerebral artery, systolic and diastolic aortic pressure, aortic pulse pressure, peripheral pulse pressure, augmentation pressure, augmentation index normalized to actual heart rate (Alx @ HR), duration of ejection, and operation index were recorded.

STATISTICAL METHODS

Before starting the sevoflurane study, a power analysis was performed to calculate the necessary number of patients to be included. We hypothesized that sevoflurane will not affect cerebral CO_2-reactivity at 1 MAC (primary end point). Based on our previous study performed among non-anesthetized individuals, we found that hyperventilation lasting for 1 min results in a decrease in PCO_2 by 7 mmhHg, accompanied by a decrease 26.7 cm/s in mean blood flow velocity of the middle cerebral artery. Consequently, we calculated that a 1 mmHg decrease in PCO_2 results in a 3.84 cm/s change in blood flow velocity. As per protocol we intended to decrease CO_2 by 10 mmHg in 2 steps, we calculated with a 38.4 cm/s (30 cm/s standard deviation) change, with a power of 0.9 and with an alpha of 0.01. Our power calculation indicated that 12 patients need to be included to test our hypothesis. As both registration methods may be operator-dependent, for the sake of clarity we decided to include 30 patients. The normality of the distribution of the data was tested by the Shapiro–Wilks test. Thereafter, differences were analyzed with Repeated Measures Analysis of Variance (ANOVA) with

Bonferroni post hoc correction. Values of $p < 0.05$ were accepted as statistically significant. Data are presented as mean (SD). MedCalc Statistical Software version 18.2.1. (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis.

Before our second study, the normality of the data distribution was tested using the Shapiro-Wilks test. Differences were analyzed with Repeated Measures Analysis of Variance (ANOVA) with Bonferroni posthoc correction. Values of $p < 0.05$ were accepted as statistically significant. Data are presented as mean (SD). MedCalcStatistical Software version 18.2.1. (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis. Spearman correlation analysis was used to assess the correlation between %-changes in MCAV and MAP values during induction.

Before starting the study, a power analysis was performed to calculate the necessary number of patients to be included. Our primary endpoint hypothesis was that propofol would not affect cerebral CO_2-reactivity. Based on a previous study, we assumed that hyperventilation lasting 1minute results in a decrease in PCO_2 by 7 mmHg, accompanied by a 26.7 cm.s-1 decrease in the middle cerebral artery mean blood flow velocity, which corresponds to a 3.84 cm.s-1change in blood flow velocity per 1 mmHg decrease in PCO_2. During our study we planned an overall 10 mmHg decrease (2×5 mmHg) in CO_2, we calculated with a 38.4 cm.s-1 (30cm.s-1standard deviation) change. Using a power of 0.9 and an alpha of 0.01, our calculation indicated that 12 patients need to be included to test our hypothesis. As both registration methods may be operator-dependent, for the sake of clarity, we decided to include 30 patients.

RESULTS

EFFECTS OF SEVOFLURANE ON SYSTEMIC CIRCULATION AND CEREBRAL AUTOREGULATION, CARBON DIOXIDE REACTIVITY

Demographic data

Twenty-nine patients aged 19 to 58 years (mean 37), 17 female, 12 male were enrolled. 7 patients underwent inguinal hiatal repair surgery, while 22 underwent varicetomy. One patient was excluded due to an inappropriate temporal window for TCD.

Respiratory parameters and anesthetic depth during the procedure

During the course of the study, ventilatory settings were changed at different stages of the study to reach and maintain different levels of $EtCO_2$ (40, 35 and 30 mmHg respectively). Consequently, there were significant differences in the values of tidal volumes and respiratory rates. BIS values were stable during the entire procedure, indicating that the appropriate depth of anesthesia has not been previously studied.

At $EtCO_2$ 40 mmHg, the tidal volume was 516 ±64 ml, $EtCO_2$ 35 mmHg 550 ±63 ml ‡‡‡ and $EtCO_2$ 30 mmHg 570± 88 ml ‡‡‡

‡ : significant difference compared to $EtCO_2$ 40 mmHg values, ‡‡‡: $p < 0.001$, values are given as mean ± SD.

We measured a significant difference compared to $EtCO_2$ 40 mmHg the respiratory rate at $EtCO_2$ 35 mmHg and at $EtCO_2$ 30 mmHg, there was also a significant difference compared to at $EtCO_2$ 35 mm Hg in both at $EtCO_2$ 40 mm Hg and at $EtCO_2$ 30 mm Hg.

Respiratory rate at $EtCO_2$ 40 mmHg: 9 ±2/ min †††, $EtCO_2$ 35 mmHg: 12 ± 13/min ‡‡‡ $EtCO_2$ 30 mmHg: 15 ± 3/ min ‡‡‡, ††† ‡: significant difference compared to at $EtCO_2$ 40 mmHg,

†: significant difference compared to $EtCO_2$ 35 mmHg ‡‡‡, †††: $p<0.001$, values are given as mean ± SD.

BIS values indicated an adequate and unchanged anesthesia depth throughout the procedure. $EtCO_2$ 40 mmHg: 42 ± 2, $EtCO_2$ 35 mmHg: 42 ± 1, $EtCO_2$ 30 mmHg: 42 ± 2. $p = 0.75$, the values are given as mean ± SD.

Hemodynamic parameters

There were significant differences neither in systolic blood pressure values, nor in heart rate during the course of the study. On the contrary, there were significant differences in diastolic blood pressure: preoperative values were significantly higher than values measured at any other time point.

Heart rate and systolic blood pressure values did not change significantly. The preoperative heart rate was 67 ± 10 / min, at $EtCO_2$ 40 mm Hg 70 ± 12 / min, at $EtCO_2$ 35 mm Hg 67 ± 11, at $EtCO_2$ 30 mm Hg 69 ± 12 $p = 0.38$, values are given as mean ± SD.

The preoperative systolic blood pressure was 109 ± 29 mm Hg, at $EtCO_2$ 40 mm Hg 106 ± 8 mm Hg, at $EtCO_2$ 35 mm Hg 108 ± 9 mm Hg, at $EtCO_2$ 30 mm Hg 108 ± 9 mm Hg p = 0.46, values are given as mean ± SD.

Diastolic blood pressure values were significantly lower compared to the preoperative value. Preoperative diastolic blood pressure value 81 ± 9 mm Hg, at $EtCO_2$ 40 mm Hg 65 ± 10 mm Hg ***, at $EtCO_2$ 35 mm Hg 67 ± 10 mm Hg ***, at $EtCO_2$ 30 mm Hg 66 ± 11 mm Hg ***
*: significant deviation from preoperative value. ***: p <0.001, values are given as mean ± SD.

Results of applanation tonometry measurements

Mean arterial pressure decreased significantly during induction of anesthesia, reaching a steady state and remained stable during the entire course of the study. In parallel, aortic and peripheral pulse pressures both increased during the induction phase as did the augmentation index. All parameters remained unchanged during the next phases of the study.

The preoperative MAP value was 91.667 (86.667 - 95.417) mmHg, at $EtCO_2$ 40 mm Hg 78,000 (73.667-85.583) mmHg*, at $EtCO_2$ 35 mm Hg 80.667 (75.833-87.333) mmHg *, at $EtCO_2$ 30 mmHg 80,000 (74.917-89.167) mmHg *.
*: significant difference compared to preoperative value, p <0.05, median and CI values.

The preoperative peripheral pulse pressure was 35,000 (30,000-40,000) mmHg at $EtCO_2$ 40 mmHg 40,000 (35,000-46,250) mmHg *, at $EtCO_2$ 35 mmHg 41,000 (36,000-44,250) mmHg *, at $EtCO_2$ 30 mmHg 39,000 (36,750-43,000) Hgmm *.
*: significant difference compared to preoperative value, p <0.05, median and CI values.

The preoperative aortic pulse pressure was 24 (21,75-29,25) mmHg, at $EtCO_2$ 40 mmHg 28 (26-35) mmHg *, at $EtCO_2$ 35 mmHg 30 (27,75-32,25) mmHg*, at $EtCO_2$ 30 mmHg 29 (26,75-34)) mmHg *.
*: significant difference compared to preoperative value, p <0.05, median and CI values.

The preoperatively measured augmentation index was 14 (1-20,25), at $EtCO_2$ 40 mm Hg 18 (5-25,5) *, at $EtCO_2$ 35 mm Hg 15 (7-21,5) *, at $EtCO_2$ 30 mm Hg 16 (7,25-26) *.
*: significant difference compared to the preoperative value, $p < 0.05$, median and CI values.

Transcranial Doppler Sonography Parameters

Preoperative values of mean blood flow velocity of the middle cerebral artery values were not significantly different from the values measured at steady state sevoflurane stage under normocapnic conditions ($EtCO_2$ 40 mmHg). However, the values of mean blood flow velocity values measured during $EtCO_2$ 35 and 30 mmHg were significantly different from each other, as well as from preoperative and values measured at $EtCO_2$ 40 mmHg.

The preoperative value of the velocity measured in the middle cerebral artery was 60 (56-67) cm/sec ‡‡‡, at $EtCO_2$ 40 mm Hg 57 (47,75-62) cm/sec ‡‡‡, at $EtCO_2$ 35 mm Hg $EtCO_2$ 42 (36-49,25) cm/sec ** †††, at 30 mmHg 31 (27- 36) cm/sec *** ††† ‡‡‡. *: significant difference from preoperative value, †: difference from $EtCO_2$ 40 mm Hg, ‡: difference from $EtCO_2$ 35 mm Hg ** $p < 0.01$, *** $p < 0.001$, ‡‡‡ $p < 0.001$, ††† $p < 0.001$ median and CI values.

Pulsatility index values did not change during the induction phase and reached the steady state, however they significantly increased along with the decreased $EtCO_2$ values. There was a strong significant correlation between Vmean and $EtCO_2$ values
($p < 0.001$, Pearson's $r = 0.79$).

The preoperative value of the pulsatility index was 0.84 (0.78-0.925) ‡‡‡, at $EtCO_2$ 40 mm Hg 0.76 (0.7-0.837) ‡‡‡, at $EtCO_2$ 35 mm Hg 0.92 (0.79-1.085) * ‡‡‡, at $EtCO_2$ 30 mm Hg 1,08 (0.917-1,265) *** ††† ‡‡‡. *: significant difference from preoperative value, * $p < 0.05$, *** $p < 0.001$, †: difference from $EtCO_2$ 40 mmHg, ‡: difference from $EtCO_2$ 35 mmHg, ‡‡‡ $p < 0.001$, ††† $p < 0.001$, median and CI values.

We evaluated the percent change between mean arterial pressure and mean blood flow velocity of the middle cerebral artery before anesthetic induction and 20 min after the anesthesia was induced and a steady state of sevoflurane anesthesia was reached at normocapnic PCO_2 (40 mmHg). There was a significant linear relationship between the two parameters, indicating preserved static autoregulation of the cerebral circulation

at normocapnic steady state of sevoflurane anesthesia.

EFFECTS OF PROPOFOL ON SYSTEMIC CIRCULATION AND CEREBRAL AUTOREGULATION, CARBON DIOXIDE REACTIVITY

Demographic data

Twenty-seven patients, aged 38 ± 9 years, 15 females, 12 males were enrolled. Their average height was 171.8 ± 10 cm, weight: 74.4 ± 20 kg, Body Mass Index (BMI): 24.8 ±5 kg.m-2. There were 9 patients with inguinal hiatal repair surgeries, 10 with breast surgeries, and 8 with varicectomies. Three patients were excluded due to inappropriate temporal window for transcranial Doppler.

Respiratory parameters during the procedure

During the study the ventilator settings were changed at different stages in order to reach and maintain different levels of $EtCO_2$ (40, 35, and 30 mmHg, respectively). Consequently, we observed significant differences in the values of tidal volumens and respiratory rates.

The tidal volume measured at $EtCO_2$ 40 mm Hg was 460 ± 99 ml, at $EtCO_2$ 35 mm Hg was 530 ± 124 ml *, and at $EtCO_2$ 30 mm Hg was 505 ± 95 ml *. *: significant difference compared to $EtCO_2$ 40 mmHg, values are given as mean ± SD,* $p < 0.001$.

The respiration rate is 8.7 ± 1.1 / min at $EtCO_2$ 40 mm Hg, 11.8 ± 1.3 / min * at $EtCO_2$ 35 mm Hg, and 13.6 ± 1.7 / min * at $EtCO_2$ 30 mm Hg. *: significant difference compared to $EtCO_2$ 40 mmHg, values are given as mean ± SD, * $p < 0.001$.

Systemic hemodynamic values

Systolic blood pressure decreased significantly during anesthetic induction and remained unchanged throughout the study. Diastolic blood pressure values showed a similar pattern. On the contrary, no statistically significant changes have been observed in heart rate during anesthetic induction.

The preoperative value of systolic blood pressure was 124.8 ± 13.4 mm Hg, at $EtCO_2$ 40 mm Hg 99.2 ± 10.4 mm Hg *, at $EtCO_2$ 35 mm Hg 97.7 ± 9.8 mm Hg *, at $EtCO_2$ 30 mm Hg 99.1

± 10.2 mm Hg *. *: significant difference compared to the preoperative value, the values are given as mean ± SD, * p = 0.001.

The preoperative value of diastolic blood pressure was 81.2 ± 11.5 mm Hg, at $EtCO_2$ 40 mm Hg 57.2 ± 8.7 mm Hg *, at $EtCO_2$ 35 mm Hg 58.6 ± 8.9 mm Hg *, at $EtCO_2$ 30 mm Hg 58.5 ± 9.2 mm Hg *. *: significant difference from the preoperative value, mean ± SD, * p <0.001.

The preoperative value of heart rate was 68 ± 9.9 / min, at $EtCO_2$ 40 mm Hg 62 ± 9.4 / min, at $EtCO_2$ 35 mm Hg 60.3 ± 9.3 / min *, at $EtCO_2$ 30 mm Hg 58.7 ± 8.2 / min *. *: significant difference from the preoperative value, the values are given as mean ± SD, * p = 0.05.

Applanation Tonometry Parameters

Mean arterial pressure decreased significantly during induction of anesthesia and reached the steady state and remained stable during the entire study. In contrast to this, the aortic and peripheral pulse pressures did not change significantly during induction and reaching the target concentration of propofol, and in the phases of the study (changes in PCO_2). A significant decrease in augmentation index was observed during the inuction of anesthesia and reaching the steady state with propofol but it remained unchanged during the CO_2-reactivity phases of the study.

The preoperative mean arterial pressure was 96.667 (88.75-101.083) mmHg, at $EtCO_2$ 40 mmHg, 68.667 (65.667-76.250) mmHg *, at $EtCO_2$ 35 mmHg 71.333 (66.333-78) mmHg *, at $EtCO_2$ 30 mmHg 73 (66.583-77.25) mmHg *. *: significant difference compared to the preoperative value, p <0.05, median and CI values.

The preoperative value of peripheral pulse pressure was 46 (40,5-54,75) Hgmm at $EtCO_2$ 40 mm Hg, 43 (35-47,75) mmHg, at $EtCO_2$ 35 mm Hg 38 (35,250-45,75) mmHg, at $EtCO_2$ 30 mm Hg 40 (37-45) mmHg . p <0.05, median and CI values.

The preoperative aortic pulse pressure was 32 (28,25-38,75) mmHg, at $EtCO_2$ 40 mmHg 31 (26-33,75) mmHg, at $EtCO_2$ 35 mmHg 29 (24,25-32,75) mmHg, at $EtCO_2$ 30 mmHg 30 (25,25-32) mmHg. p <0.05, median and CI values.

The preoperative measured augmentation index was 11.741 (12.769-2.457), at $EtCO_2$ 40 mm Hg 6.185 (10.745-2.068) *, at $EtCO_2$ 35 mm Hg 5.333 (10.038-1.932) *, at $EtCO_2$ 30 mm Hg 4.185 (10.525-2.026) *. *: significant difference from preoperative value, p = 0.05, median and CI values.

Transcranial Doppler Sonography Parameters

Preoperative middle cerebral artery means that blood flow velocity values decreased significantly during induction of anesthesia under normocapnic conditions ($EtCO_2$ 40 mmHg). Mean blood flow velocity values decreased significantly further at $EtCO_2$ 35 and 30 mmHg. Pulsatility index values increased significantly during induction phase and they significantly increased along with the decreased $EtCO_2$ values. There was a strong significant correlation between the mean and $EtCO_2$ values ($p < 0.001$, Pearson's $r = 0.79$).

The preoperative value of the blood flow velocity measured in the middle cerebral artery was 58.704 (11.993-2.308) cm / sec ‡‡‡, at $EtCO_2$ 40 mm Hg 37.037 (8.088-1.557) cm / sec *** ‡‡‡, at $EtCO_2$ 35 mm Hg $EtCO_2$ 28.481 (6.309-1.214) cm / sec *** †††, at 30 mmHg 23.593 (4.774-0.919) cm / sec *** ††† ‡‡‡. *: significant deviation from preoperative value, †: deviation from $EtCO_2$ 40 mmHg, †: deviation from $EtCO_2$ 35 mmHg, ***: p <0.001, ‡‡‡: p <0.001, †††: p <0.001 median and CI values.

The preoperative value of the pulsatility index was 0.93 (0.85-1.045) ‡‡‡, at $EtCO_2$ 40 mm Hg 1.29 (1.135-1.5) *** ‡‡‡, at $EtCO_2$ 35 mm Hg 1.55 (1.320-1.805) ** ‡‡‡, at $EtCO_2$ 30 mm Hg 1.810 (1.490-2.098) ** †† ‡‡. *: significant deviation from preoperative value, **: p <0.01, ***: p <0.001, †: deviation from $EtCO_2$ 40 mmHg, ‡: deviation from $EtCO_2$ 35 mmHg, ‡‡‡: p <0.001, ‡‡: p <0.01 †††: p <0.001, ††: p <0.01, median and CI values.

We assessed the percentage change between the mean arterial pressure and the mean blood flow velocity of the middle cerebral artery before anesthetic induction and 20 minutes after anesthesia was induced and a steady state of propofol anesthesia was reached at normocapnic PCO_2 (40 mmHg). At this normocapnic state, a significant linear relationship was found between the percent change of mean arterial blood pressure and mean blood flow velocity, indicating preserved static cerebral autoregulation.

DISCUSSION

The extensive vascular system of the brain is exposed to continuous mechanical forces generated by the pulsation of the heart. Permanently elevated central and periferal arterial stiffness and increased pulsatility can profoundly affect cerebral perfusion, cause lacunar infarcts, cerebral microbleeds, and white matter hyperintensities. The effects of many anesthetics on systemic vascular resistance and cardiac output have been investigated. It is important to know the effect of anesthetics on pulse pressure too, whereas aortic stiffness has a proven effect on cerebral function.

Priya Palta et al. published their results in 2019, which were based on> 20 years of collected data. Central arterial stiffening and pressure pulsatility are plausible microvascular contributors to cognitive aging, the central arterial hemodynamics were associated with structural brain damage and poorer cognitive performance among older adults.

Söderström was the first to study the changes in arterial stiffness during anesthesia in 2002. He analyzed how nitrous oxide and fentanyl drugs may affect the arterial stiffness. According to his results, both fentanyl and nitrous oxide decreased MAP but had opposite effects on the augmentation pressure, nitrous oxide increased both the aortic and radial artery augmentation index. The effect of propofol and sevoflurane on arterial stiffness has not been studied

Our aim was to assess the interaction between the systemic and cerebrovascular effects of sevoflurane and propofol.

Previous reports indicated that sevoflurane between 0.5 and 1.0 MAC has minimal direct vasodilatory effect on the brain arteries and has no systemic hemodynamic effects (cardiac contractility and/or peripheral vascular resistance) at the most frequently used 1 MAC sevoflurane. In the present study, during the induction phase, the combination of propofol fentanyl-rocuronium and the addition of sevoflurane resulted in a decrease in mean arterial pressure (mainly due to a decrease in the diastolic pressure) and an increase in aortic and pulse pressure. However during the later phases of anesthesia, however no significant changes occurred in any of the hemodynamic parameters (mean arterial pressure, aortic pressure, pulse pressure and augmentation index), indicating that there were no systemic effects of sevoflurane. It is conceivable that the peripheral vasodilation observed during the induction phase can be mainly ascribed to the use of propofol.

We found that reaching the stady state under sevoflurane anesthesia resulted in a decrease in mean arterial pressure leading to non significant change in the cerebral blood flow velocity.

Cerebral autoregulation is defined as the inherent ability of the brain circulation to maintain a constant cerebral blood flow during changes in cerebral perfusion pressure. In line with this, we checked the relationship between %-changes in MAP and cerebral blood flow velocity values and found a linear relationship between the two factors, indicating preserved autoregulation. While the mean arterial pressure decreased, the cerebral blood flow velocity remained unchanged during the induction phase and reaching the steady state. The pulsatility index (representing the vascular resistance of the cerebral arterioles) decreased significantly during this period, allowing unchanged cerebral blood flow during the decrease of MAP.

The reactivity carbon-dioxide in the cerebral circulation is defined as the change in cerebral blood flow velocity per mmHg change in PCO_2. In previous volunteer studies, forced hyperventilation lasting for 60 s has been demonstrated that results in a 38% percent decrease in mean flood flow velocity of the middle cerebral artery compared to the resting blood flow velocity. The accepted normal values for CO_2-reactivity are 2–5 cm/s/mmHg. In the present study a decrease of PCO_2 from 40 mmHg to 35 mmHg resulted in an average decrease in mean blood flow velocity of 4 cm/s/mmHg, while at 30 mmHg PCO_2 resulted in a decrease of 8 cm/s/mmHg. These values correspond to previous observations and indicate preserved CO_2-reactivity during sevoflurane anesthesia at MAC 1 concentrations.

During 1 MAC sevoflurane anesthesia although arterial stiffness increases after induction, which could create an unfavorable condition for cerebral microcirculation, cerebral autoregulation and vasomotor reactivity are preserved.

Propofol has been used commonly for the induction and maintenance of general anesthesia since 1980. Several studies have investigated the cause of the hypotensive effect of propofol. According to their results hypotension is caused by a propofol-mediated decrease in sympathetic activity including a decrease in systemic vascular resistance and a decrease in cardiac output due to a combination of venous and arterial vasodilation, impaired baroreflex mechanism and depression of myocardial contractility. Propofol decreases myocardial oxygen consumption and creates a favorable condition for the balance of myocardial oxygen supply/ demand.

The results of studies investigating the hypotensive effect of propofol are controversial.

In a 1989 study isolated hepatic portal veins and aorta taken from rats were used to investigate the direct action of the intravenous anaesthetic propofol. The result suggested that the hypotension may be due to the direct vasodilator action on the veins and arterioles. The concentrations required to produce a hypotension effect on the veins were significantly lower than those required to produce similar changes in the isolated artery preparation. Venous

compliance of the forearm was significantly increased during propofol administration, this may be the explanation for hypotension during propofol anesthesia in humans which seems to be related to its direct effects on venous smooth muscle tone. The effects of propofol anesthesia on vascular resistance of the forearm and compliance of the forearm vein are similar to the effects of sympathetic denervation by stellate ganglion blockade. According to an animal study from 2011 the perivascular adipose tissue enhances the relaxation effect induced by propofol in the rat aorta through both endothelium-dependent and endothelium-independent pathways.

In a 2015 study, the effects of propofol on preload dependency were investigated in septic shock patients. A significant decrease in the arterial blood pressure was observed due to angiotasis and decreased venous return. The results indicated that obvious vasodilatation was induced in patients with preload dependency after propofol infusion, propofol increased preload dependency in patients with septic shock with fluid nonresponsiveness.

Propofol decreases systemic blood pressure and cardiac output by approximately 30% and 40%, respectively. A more recent study by De Wit et al. demonstrated that within the clinically administered dose range, cardiac output is not influenced by propofol, its main effect on the blood pressure exerted by decreasing the tone of the vessels venous capacitance. Goodchild and Serrao reported on similar experimental observations: normal plasma concentrations of propofol do not have a negative inotropic effect but may cause relaxation of the veins and increased capacitance without a direct effect on the arteries and arterioles at the periphery. A similar observation was published by Muzi et al. in humans.

In our propofol study, every patient received 500 ml of crystalloid infusion before surgery to limit the effect of preoperative fluid intake restriction.

In our study, we have also demonstrated an unchanged central aortic blood pressure and peripheral pulse pressure. A significant decrease in the augmentation index and mean arterial pressure has been observed during the induction of anesthesia, which justified a reduction in the stiffness of the peripheral arteries.

The mechanisms proposed to understand the effect of propofol on cerebral circulation include the following components:

a) systemic hypotension challenging cerebral autoregulation by decreasing cerebral perfusion pressure,

b) the direct effect of propofol on the metabolism of cerebral tissue.

The interaction between these factors is mutual. It is possible that there is a balance between autoregulatory arteriolar vasodilation (as a consequence of decreased cerebral perfusion pressure) and arteriolar vasoconstriction (as a consequence of decreased $CMRO_2$) during

propofol anesthesia. In previous studies propofol was observed to decrease the metabolic rate of the cerebral tissue. One of the most important factors is the decrease in the local CO_2 production as a consequence of the decreased metabolism. Along with the decrease in local CO_2 production, there is a vasoconstriction of the resistance arterioles occurs. Based on the physiological mechanism of flow-metabolism coupling, if the metabolism of the cerebral tissue decreases, a vasoconstriction of the corresponding cerebral arterioles occurs in order to decrease the unnecessary hyperperfusion of the brain tissue. Therefore the effect of propofol on cerebral circulation is a complex process: during propofol administration, global (and regional) cerebral blood flow decreases and it is counterbalanced by decreased $CMRO_2$, ensuring preservation of brain tissue metabolism.

Propofol has been shown that low doses (4-6mg.kg-1.h-1) do not alter cerebral vasoreactivity. According to these previous observations, in the present study, graded hypocapnia resulted in a 2 cm.s-1/1 mmHg change in the cerebral blood flow velocity in the middle cerebral artery accompanied by an increased pulsatility index, indicating preserved hypocapnic vasoreactivity during propofol anesthesia.

NEW RESULTS

Our study is the first non-experimental observation referring to this effect of sevoflurane and propofol in humans using noninvasive systemic hemodynamic monitoring in paralell with cerebral flow monitoring. We examined the relationship between arterial stiffness and cerebral vasoreactivity, autoregulation.

According to the results of our studies:

- During the induction phase of 1 MAC sevoflurane narcosis, there is a decrease in mean arterial pressure (mainly due to the decrease in the diastolic pressure) and an increase in aortic and pulse pressure and in the augmentation index. During the later phases of anesthesia, no significant changes occur in any of the hemodynamic parameters (mean arterial pressure, aortic pressure, pulse pressure and augmentation index).

- During 1MAC sevoflurane narcosis, while the arterial stiffness increases, the cerebral vasoreactivity and autoregulation response are unchanged.

- During propofol anesthesia, which is maintained using the Target-Controlled Infusion (TCI) method according to the Schnider model with an effect site propofol concentration of 4 μg.mL $^{-1}$, the systemic mean arterial pressure significantly decreased during anesthetic induction and remained unchanged during the entire study period.

- Propofol does not significantly change central aortic and peripherial pulse pressure significantly during anesthetic induction and maintenance, while the augmentation index as a marker of arterial stiffness decreased significantly during the anesthetic induction and remained stable.

- While blood pressure and arterial stiffness decrease, both cerebral autoregulation and cerebral CO_2-reactivity are maintained affected by propofol anesthesia.

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List of publications related to the dissertation

1. **Juhász, M.**, Páll, D., Fülesdi, B., Molnár, L., Végh, T., Molnár, C.: The effect of propofol-sufentanil intravenous anesthesia on systemic and cerebral circulation, cerebral autoregulation and CO2 reactivity: a case-series.
   Brazilian Journal of Anesthesiology (English Edition). [Epub ahead of print], 2021.
   DOI: http://dx.doi.org/10.1016/j.bjane.2021.04.002

   IF: 0.964 (2020)*

2. **Juhász, M.**, Molnár, L., Fülesdi, B., Végh, T., Páll, D., Molnár, C.: Effect of sevoflurane on systemic and cerebral circulation, cerebral autoregulation and CO2 reactivity.
   BMC Anesthesiol. 19 (1), 109-116, 2019.
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List of other publications

3. László, I., Molnár, C., Koszta, G., Végh, T., Fábián, Á., Berhés, M., **Juhász, M.**, Fülesdi, B.: A COVID-19-betegek kórházon belüli újraélesztésének speciális szempontjai.
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