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The influence of gradually increasing the concentration of desflurane on cerebral perfusion pressure in rabbit

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Abstract

Background: In nearly all cases of general anaesthesia with a volatile agent, the anaesthetic concentration has to be increased. Since the anaesthetic affects both the factors determining intracranial homeostasis and the systemic circulation, it is crucial that cerebral perfusion pressure (CPP) is protected. The aim of the present study was to assess the influence of gradually increased concentrations of desflurane on the cerebral and systemic circulations based on CPP, mean arterial pressure (MAP), intracranial pressure (ICP) and their correlations.

Methods: The study was carried out on 25 rabbits of the same gender (male) randomly assigned to two groups: control (n = 10) and group I (n = 15). Over three 15-minute periods, the animals were exposed to increase concentrations of desflurane so as to achieve 1/3, 2/3 and 1 MAC Minimal Alveolar Concentration (3, 6, 9 vol%) of the effective end-tidal concentration of desflurane (Et) at the end of each period, respectively.

Results: Intragroup analysis of CPP changes demonstrated decreases in its successive values from minute 18, compared with baseline values. The mean values of ICP did not differ throughout the experiment. From minute 19 on, all successive values of MAP decreased compared with baseline values. A weak correlation (r = –0.2179) was found between ICP and CPP and a strong correlation between MAP and CPP (r = 0.98829). Moreover, there was a strong correlation between $Et_{desflurane}$ vs. CPP (r = –0.8769) and MAP (r = –0.8224) and a weak correlation versus ICP (r = 0.15755).

Conclusions: A decrease in CPP induced by desflurane was associated with a decrease in MAP but not an increase in ICP. The depressive effect of desflurane on the cerebral and systemic circulations is a consequence of its effector site concentration.

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Key words: anaesthetics, volatile, desflurane; intracranial pressure; mean arterial pressure; cerebral perfusion pressure

Desflurane is the most rapidly absorbed and eliminated volatile anaesthetic due to it having the lowest blood/gas (0.45) and tissue/blood partition coefficient [1]. In practice, this property enables good control of anaesthesia and quick recovery without the effect of secondary drowsiness caused by drug redistribution from the adipose tissue [2–4]. The cardiovascular effects of desflurane manifest themselves mostly as a dose-dependent increase in heart rate and a reduction in arterial pressure, resulting mainly from dilatation of the vascular bed with the resultant decrease in peripheral resistance, and from negative inotropic action, albeit to a lesser extent [1, 5–9]. As in the peripheral circulation, desflurane dilates the cerebral vessels, which results in increased cerebral blood volume (CBV) likely to lead to increases in intracranial pressure (ICP) [6, 10, 11]. The factors determining intracranial homeostasis include cerebral blood flow (CBF), cerebral metabolic rate (CMR), autoregulation and reactivity of the cerebral vessels to $PaCO_2$. The structural and functional integrity of the central nervous system (CNS) is provided by CMR which, under normal conditions, is strictly associated with CBF. The driving force of CBF is the cerebral perfusion pressure (CPP), i.e. the difference between MAP and ICP.

Desflurane modulates the mechanisms determining intracranial homeostasis. Moreover, its effects on the cardiovascular system are significant and can have an additional

adverse impact leading to a critical decrease in systemic arterial pressure. During general anaesthesia, especially its induction but also its maintenance, the concentration of a hypnotic has to be increased, depending on the type and stage of surgery. Considering its influence on the factors determining intracranial homeostasis and on the systemic circulation, it is crucial that CPP is protected.

The aim of the study was to assess the influence of gradually increased concentrations of desflurane on the cerebral and systemic circulations based on CPP, MAP, ICP and their correlations.

METHODS

The study design was developed in accordance with the guidelines of the Directive 2010/63/UE of the European Parliament and of the European Council of September 22, 2010 and approved by the local Ethics Committee on Animal Research of the Medical University of Gdańsk.

The study was carried out on 25 rabbits of the same gender (male) randomly assigned to two groups: control (n = 10) and group I (n = 15).

Forty-five minutes before the experiment, all the animals received intramuscularly 0.2 mg kg^{-1} of midazolam, 0.75 mg kg^{-1} of dehydrobenzperidol and 0.03 mg kg^{-1} fentanyl. The experiment was commenced with cannulation of the marginal ear veins, which enabled continuous infusions of 5 mL kg h^{-1} of Ringer`s solution and 2.5 mg kg h^{-1} of propofol. Subsequently, the auricular artery was cannulated and connected with a Statham transducer (zeroed at the level of the external auditory foramen) and a Stoelting kit for continuous monitoring of MAP. Once the sufficient depth of general anaesthesia was achieved, the trachea was exposed under infiltration anaesthesia with 1% lidocaine in the dorsal recumbent position and incised; after the insertion of an endotracheal tube and administration of 0.1 mg kg^{-1} of IV vecuronium, pulmonary ventilation was started with an infant ventilator (MK2; Loosco, Amsterdam), maintaining $EtCO_2$ within the range of 39–41 mm Hg.

Subsequently, the animals were placed in a natural position and their heads fixed in a stereotactic frame. Under full aseptic conditions and infiltration anaesthesia with 1% lidocaine the soft tissues were separated; after microtrepanation, a microsensor ICP transducer (Codman) was stereotactically inserted into the white matter of the frontal lobe. A neuro monitor interface control unit (Codman) and the microsensor ICP transducer, combined with the 8000 monitoring system (Simomnsen&Weell) were used for continuous recording of ICP. The proper functioning of the devices was verified assessing the pressure increases in the abdominal and thoracic cavity resulting from mechanical compressions. The body temperature of animals was maintained using the thermoregulatory EST system (Soelting) composed of a thermostat, a warming mattress and a temperature sensor introduced to the rectum. The electrocardiographs from three extremity leads and the heart rate were observed using the 8000 monitoring system; SpO_2 was monitored by means of a veterinary pulse oximeter lingual sensor (Nonin). The ventilation parameters and the concentration of desflurane were assessed using a Vamos anaesthetic gas analyser (Dräger).

First, all the conditions essential for the proper course of the experiment were observed; after a 15-minute stabilisation period, the main part of the experiment was initiated. Over three 15-minute periods, the animals were exposed to increased concentrations of desflurane administered via a Sigma Elite vaporiser (Penlon), so as to achieve the effective end-tidal concentration of 1/3, 2/3 and 1 MAC (3, 6, 9 vol%) at the end of each period, respectively [12]. The $Et_{desflurane}$ changes throughout the experiment were presented in Figure 1.

The concentrations of blood haemoglobin and glucose were determined half-way through the experiment using Hemocue analysers (Hemocue AB).

After completing the experiment, the animals were euthanized with a lethal dose of thiopental (500 mg). The cessation of heart electrical activity meant the moment of death and discontinuation of ventilation.

Statistical analysis was performed using STATISTICA software for WINDOWS 7.1 (StatSoft Inc. Tulsa, USA). The distribution of data was assessed using the Shapiro-Wilk test. In cases of a non-normal distribution, the analysis of intra- and intergroup comparisons was based on the Friedman, Kruskal-Wallis and U Mann-Whitney tests. The intra- and intergroup comparisons of normal distribution data was performed using the Fisher and Dunnett tests after verification of variance homogeneity with the Levene test. The strength of correlations between CPP versus ICP

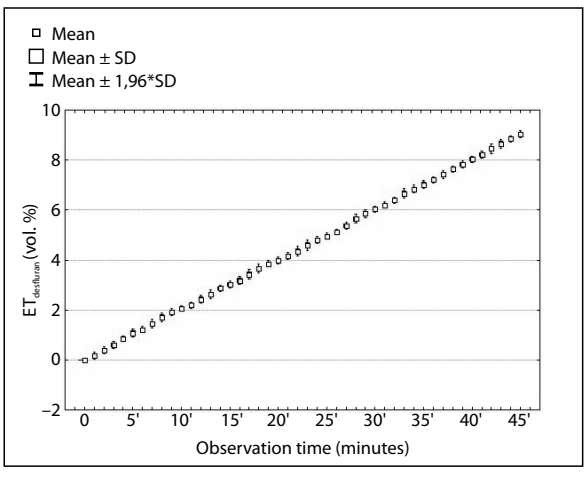

Figure 1. Mean end-tidal concentrations of desflurane ($Et_{desflurane}$) during the experiment (vol%)

and MAP and between $Et_{desflurane}$ versus CPP, ICP and MAP was determined using the Pearson correlation coefficient. Numerical data were presented as a mean ± SD. $P < 0.05$ was considered statistically significant.

To obtain reliable results, it is necessary to maintain the same conditions throughout the experiment.

In order to assess CPP, the ICP sensor has to be inserted into the cerebral nervous tissue; according to clinical practice, this should not affect the intracranial pressure-volume relationship (albeit theoretically such effects are possible). To exclude the influence of the ICP sensor and propofol infusion on the parameters studied, a control group was used.

RESULTS

The mean body mass of the study animals was 3.88 ± 0.13 kg, 3.87 ± 0.16 kg in the control group and group I, respectively.

As mentioned earlier, to exclude the impact of the ICP sensor and propofol infusions, the control group was used. Analysis of the results did not demonstrate significant differences in CPP, ICP and MAP in the control group. Therefore, the effects of the ICP sensor and propofol infusions on the course of the experiment and results may be excluded. The results are listed in Figures 2, 3 and 4.

Analysis of $EtCO_2$, SpO_2 and core temperature in the individual groups revealed their comparable effects on intracranial homeostasis (Tables 1–3).

There were no intergroup differences in the concentrations of blood haemoglobin and glucose determined half-way through the experiment; their mean values were as follows: 149.8 ± 7.5 and 150.8 ± 4.8 g L^{-1} for haemoglobin and 148.1 ± 4.1 and 146.9 ± 73 mg dL^{-1} for glucose in the control group and group I, respectively.

Comparative analysis of mean CPP, ICP and MAP at point 0 in the control group and group I did not show statistically significant differences, which evidences the fact that the conditions at the beginning of the main experiment part were comparable in both groups.

The mean values of CPP during the observation period are presented in Figure 5. Intragroup analysis demonstrated a decrease of all successive values of CPP from minute 18 compared with baseline values.

The mean values of ICP during the observation period were listed in Figure 6. Intragroup analysis did not reveal significant changes in the mean values of ICP.

The mean values of MAP are presented in Figure 7. Intragroup analysis showed a reduction in all successive MAP values from minute 19 compared with baseline values.

Analysis of ICP and CPP changes in group I demonstrated a low correlation between these parameters (r = –0.2179); otherwise, the correlation between MAP and CPP was found to be strong (r = 0.98829).

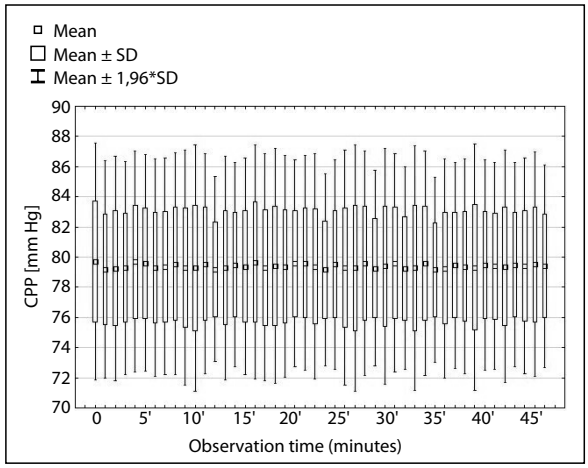

Figure 2. Mean CPP in the control group at the individual stages of the experiment

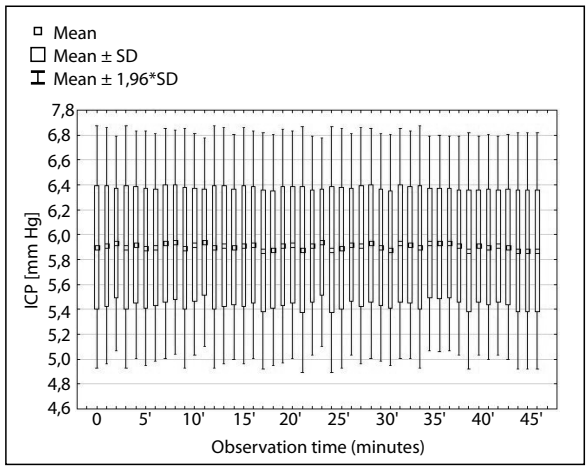

Figure 3. Mean ICP in the control group at the individual stages of the experiment

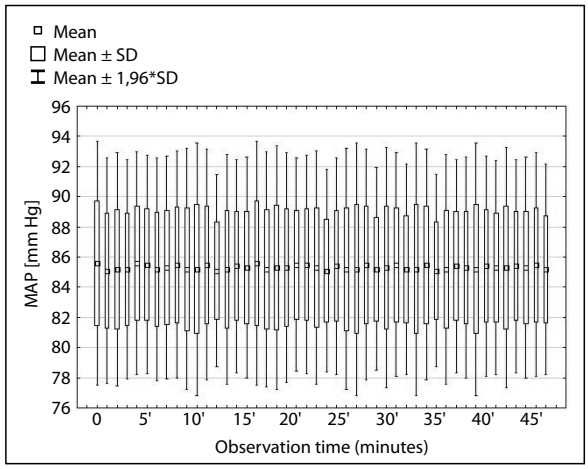

Figure 4. Mean MAP in the control group at the individual stages of the experiment

Table 1. Mean $EtCO_2$ in the study groups

Observation time	Control		Group I	
	Mean	SD	Mean	SD
0	39.30000	0.674949	39.00000	0.755929
5′	39.50000	0.849837	39.40000	0.736788
10′	39.30000	0.823273	39.13333	0.833809
15′	39.40000	0.699206	39.46667	0.743223
20′	39.20000	0.632456	39.00000	0.534522
25′	39.60000	0.699206	39.46667	0.639940
30′	39.10000	0.875595	39.73333	0.703732
35′	39.40000	0.966092	39.20000	0.414039
40′	39.30000	0.948683	39.06667	0.961150
45′	39.30000	0.674949	39.20000	0.560612

Table 2. Mean SpO_2 in the study groups

Observation time	Control		Group I	
	Mean	SD	Mean	SD
0	97.20000	1.032796	96.93333	0.798809
5′	97.80000	1.549193	97.53333	1.060099
10′	97.80000	1.549193	97.40000	0.985611
15′	97.80000	1.549193	97.33333	0.975900
20′	97.30000	0.674949	97.33333	0.975900
25′	97.60000	0.699206	97.46667	0.990430
30′	97.80000	0.788811	97.46667	0.990430
35′	97.70000	0.823273	97.40000	0.985611
40′	97.20000	1.032796	97.93333	1.387015
45′	97.60000	0.966092	97.86667	1.355764

Table 3. Mean values of core temperature in the study groups

Observation time	Control		Group I	
	Mean	SD	Mean	SD
0	38.05333	0.250333	38.03333	0.191485
5′	38.06667	0.231969	38.02667	0.198086
10′	38.06667	0.231969	38.02000	0.207709
15′	38.08000	0.217781	38.02667	0.198086
20′	38.06667	0.231969	38.02667	0.198086
25′	38.05333	0.250333	38.03333	0.191485
30′	38.06667	0.231969	38.02667	0.198086
35′	38.06667	0.231969	38.02000	0.207709
40′	38.08000	0.217781	38.02667	0.198086
45′	38.06667	0.231969	38.02667	0.198086

There was a strong correlation between $Et_{desflurane}$ versus CPP ($r = –0.8769$) and MAP ($r = –0.8224$) and a poor correlation versus ICP ($r = 0.15755$).

DISCUSSION

Induction is the key stage of general anaesthesia as the anaesthetics used, their doses and synergism of individual

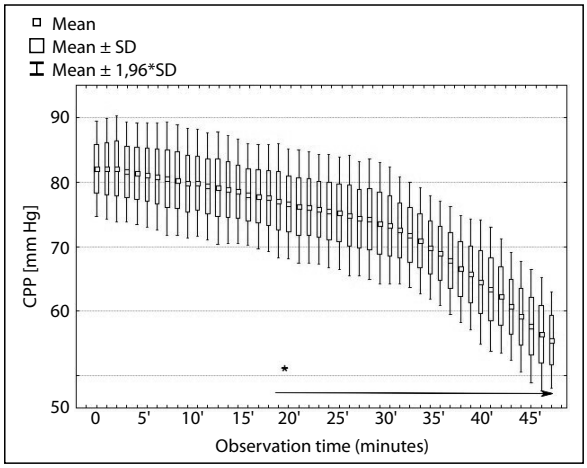

Figure 5. Changes in mean CPP in group I at the individual stages of the experiment (*→ $P < 0.05$ for all successive values compared with baseline)

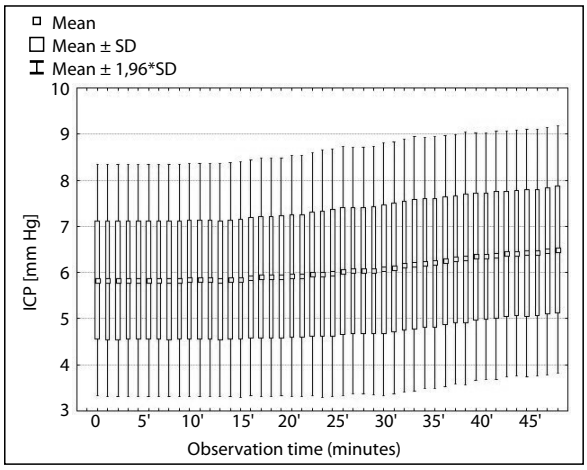

Figure 6. Mean ICP in group I at the individual stages of the experiment

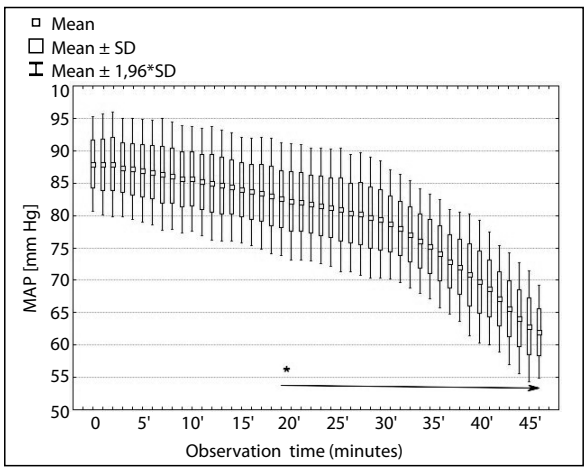

Figure 7. Mean MAP in group I at the individual stages of the experiment. (*→ $P < 0.05$ for all successive values compared with baseline)

drug groups depress both the cardiovascular system and CNS, which significantly impairs the internal balance of the body while the standard monitoring available in operating theatres does not enable quick assessment of volatile anaesthetic effects on the parameters of intracranial homeostasis. Moreover, during the surgery itself the anaesthesia has to be frequently deepened by increasing the concentration of a volatile anaesthetic.

The concentrations of desflurane used during our experiment impaired the stability of the systemic and cerebral circulation.

CPP, determined by MAP and ICP, is the driving force of CBF. This phenomenon, essential for the provision of normal CNS functioning and is autoregulated under physiological conditions, which minimises the adverse consequences of fluctuations of circulatory and respiratory parameters [13–15].

An increase in the inhalational anaesthetic concentration in the respiratory mixture above 1/3 MAC reduced CPP. Of note is the fact that the highest decrease in CPP was observed in the third period of the experiment at over 2/3 MAC while the absolute values of CPP noted then were below 60mmHg, which is considered safe. The available literature contains only a few clinical studies directly assessing the effect of desflurane on CPP [16–18]. The findings of the study analysing the effect of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on ICP and CPP in children are comparable with our results. However, it should be stressed that the study population included patients with intracranial pathology [16].

A similar study was carried out in adults undergoing craniotomy for supratentorial brain tumours. The study assessed the effects of 1.0 MAC isoflurane and desflurane on ICP and CPP and arterio-jugular differences of oxygen ($AVDO_2$). The results demonstrated a decrease in CPP both for isoflurane and desflurane [18]. The findings of both studies directly correlate with the results of our observations, allowing one to assume that they can be cautiously transferred into everyday clinical practice. In one of the studies presented earlier, nitrous oxide was used in the respiratory mixture, which could have affected the final result of observations. However, taking into consideration that N_2O is commonly used (also documented in relatively new studies [19]), this observation may be valuable for practicing anaesthesiologists.

ICP, whose value depends on the balance between the nervous tissue, cerebrospinal fluid and blood contained inside the cranial cavity, remains constant under physiological conditions. All of the factors affecting this balance can lead to severe CNS dysfunctions.

The analysis performed by us regarding changes in ICP during the experiment did not show differences compared with baseline values. Although an upward trend cannot go unnoticed, it should be stressed that ICP remained within normal values throughout the observation period. In the

studies mentioned earlier, the results of direct measurements of ICP remained unchanged [18] or showed an increasing trend [16], still remaining within the upper normal limits, which is consistent with our findings. A low correlation of changes in $ET_{desflurane}$ and ICP seems to be an additional argument confirming this thesis.

Several studies have assessed the effect of desflurane on intracranial homeostasis using CBF [20–24] and lumbar cerebral fluid pressure (LCSFP) [25–28] measurements.

A study analysing the effects of 1.1 MAC desflurane in patients with intracranial proliferative processes has demonstrated an increase in LCSEP [25]. In the study, the volatile anaesthetic was used in the oxygen-air mixture. According to another study in which a slightly higher end-tidal concentration of desflurane (1.2 MAC) was used, LCSEP did not increase [26]. The selection of patients, the technique of measurement and moderate hyperventilation used in both studies were similar. The differences in findings are likely to result from the technological advances as the studies were carried out more than 20 years apart. The study performed under normocapnic conditions has revealed, at most, an increasing LCSEP trend caused by analogous concentrations of desflurane [28]. Assuming that under suitable conditions increases in LCSEP correspond to increases in ICP, the findings reported are comparable with our results.

The assessment of CBF changes in the context of ICP changes is based on the assumption (for physiological conditions) that an increase in cerebral flow causes an increase in CBV, which, in turn, leads to an increase in ICP. However, due to direct effects of inhalational anaesthetics on the smooth muscle layer of blood vessels causing their dilatation, impaired autoregulation of cerebral circulation and reduced cerebral metabolism, the interpretation of results is ambiguous [29,30]. Nevertheless, it seems that the desflurane-induced changes in CBF are a result of decreased flow due to reduced CMR and increased flow due to vascular bed dilatation. It is known that most of the CBV is located in the venous part of cerebral vascular bed; moreover, inhalational anaesthetics affect the regional redistribution of CBF to the subcortical regions and posterior cranial cavity [29].

The study assessing the effects of desflurane and isoflurane on CBF using ^{133}Xe has not demonstrated the differences in CBF at 1.5 MAC as compared with 1.0 MAC under hypocapnia; otherwise, in normocapnia, CBF increased [21]. In a study, in which the Kety-Schmidt method was used, CBF decreased compared with the baseline value at 1 MAC of desflurane both in normo- and hypocapnia; in hypercapnia, CBF increases were rapid. According to still another study, $CMRO_2$ and CMR_{glc} decreased, irrespective of $PaCO_2$, while significant CBF increases did not correspond with low CMR in the hypoventilation phase, which evidences the reactivity of cerebral vessels to $PaCO_2$ [23].

The results of some other studies have demonstrated that the mechanism of autoregulation is impaired at 1 MAC desflurane and completely eliminated above 1.5 MAC [14]. Likewise, the results of experiments in animal models [20, 31–34] are not explicit. According to studies on pigs, ICP and CBF increased after the use of desflurane under normocapnic conditions. In cases of decreasing $PaCO_2$ below the lower normal limit, the effect of desflurane was practically irrelevant [20, 32]. Moreover, studies on dogs undergoing anaesthesia with 0.5–1.0–1.5 MAC desflurane have not revealed its effects on ICP both in normo- and hypocapnia [34, 35]. The differences in results are likely to be associated with the different species studied and the different methods used for CBF measurements.

A tendency to ICP increases seems to be common to the vast majority of studies, irrespective of the methodology and techniques used, as well as the selection of study groups. Therefore, the thesis may be put forward that desflurane in concentrations up to 1MAC has minimum effects on ICP, which is consistent with our findings.

MAP, the basic parameter responsible for organ perfusion, depends on numerous factors. The changes in heart rate, myocardial contractility, pre- and afterload and peripheral resistance modify MAP. Under physiological conditions, there are many mechanisms to keep MAP within normal limits thus to maintain systemic homeostasis. General anaesthesia, especially when volatile agents are administered, can affect the individual components of arterial pressure and its mean value.

Our observations revealed a continuous trend of MAP to decrease; a significant decrease was observed after exceeding 2/3 MAC, as compared with baseline values. Of note is the fact that during the final stage of our experiment at the assumed level of $ET_{desflurane}$, the extent of MAP depression was the highest. The above is confirmed by a strong correlation between these parameters in our study. Transient increases in circulatory parameters due to increased concentrations of desflurane in the respiratory mixture, described in literature, result from sympathetic stimulation [36–39]. In the clinical trial, desflurane administered in the concentrations rapidly increasing to 0.5, 1.0 and 1.5 MAC caused a transient, several-minute increase in heart rate and MAP; subsequently MAP values decreased to values lower than the baseline values while the heart rate remained increased. This tendency was more and more pronounced at each successive increase in the concentration of desflurane [38]. Other analyses have confirmed the above phenomenon with their authors suggesting the use of low doses of opioids, clonidine or β-blockers to prevent it [40]. Numerous experimental animal studies have not disclosed the effects of desflurane on the circulatory system, irrespective of the animal species [41–44]. Studies by Pac-Soo *et al.* [41, 42]

carried out on rabbits have not documented a transient increase in MAP and heart rate during desflurane anaesthesia, including a concentration above 1.0MAC. This finding is consistent with our results as no transient MAP increase was noted at each concentration of desflurane. However, it should be emphasised that in our experiment, the animals received fentanyl, dehydrobenzperidol and midazolam in addition to propofol, which could have affected the results.

From the point of view of anaesthetic practice, it is important to determine which of the parameters studied has the strongest effect on CPP decreases that are potentially dangerous for intracranial homeostasis. For this purpose, the correlations between CPP and the parameters affecting its value, i.e. ICP and MAP were analysed. Our findings demonstrated a weak correlation between changes in desflurane concentration and ICP and a strong correlation between CPP and MAP, as well as a high level of correlation between these parameters and $ET_{desflurane}$. Of note is the fact that the highest decreases in CPP and MAP were observed at desflurane concentrations above 2/3 MAC, and that their values were not within the reference limits.

Only few clinical studies refer directly to the above correlations. Fraga *et al.* [18] have not demonstrated the differences in ICP compared with baseline values. Otherwise, MAP and CPP decreased significantly below 1.0 MAC and remained at the same level until the end of a 30-minute observation. The above-mentioned observations show that desflurane-induced CPP decreases depend on MAP. In another study involving patients with internal hydrocephalus, ICP increases and MAP decreases leading to critical decreases in CPP were found at 0.5 and 1.0 MAC [16]. The above-mentioned results are consistent with our observations, which prove that MAP affects CPP decreases while ICP remains unaltered.

The assumed experimental model imposes certain limitations of interpretation, especially for everyday clinical practice. Although the observations of the control group suggest that the agents used, propofol in particular, did not affect the results, there is no absolute certainty. Propofol in the dose used and administered in a continuous infusion does not affect the elements determining intracranial homeostasis [45]. It is difficult to imagine that the supply of this anaesthetic is discontinued and the main part of experiment commenced when we are sure that propofol is not longer in the animal body. Due to species differences implying the extent of structural and functional complexity of the CNS, as well as the remaining organs and organ systems, the results should be interpreted with caution. The differences in absolute values of MAC concentrations seem to confirm this thesis [46]. Despite the reservations described above, it is evident that our observations are consistent with the results reported by other authors of experimental and clinical studies.

In everyday anaesthetic practice, we frequently deal with the stages of surgery requiring the deepening of anaesthesia. In such cases, desflurane is found to be superior to other available volatile anaesthetics, due to its properties. However, the question remains whether the benefit resulting from anaesthesia control dose not adversely affect the CNS and the elements determining its structural and functional integrity. The key conclusion of our study, that the perfusion pressure determining the CNS balance during desflurane anaesthesia depends on MAP, is essential for anaesthesiologists. With a wide range of pharmacological agents and other methods enabling one to increase the pressure in the systemic circulation, CPP can be maintained within the limits providing proper perfusion of the CNS.

CONCLUSIONS

1. An increase in the effective concentration of desflurane up to 1 MAC induces a decrease in CPP.
2. Desflurane in effective concentrations up to 1 MAC does not affect ICP.
3. 1 MAC desflurane depresses the systemic circulation, which is expressed as a reduction in MAP.
4. A desflurane-induced decrease in CPP is associated with a decrease in MAP but not an increase in ICP.
5. The depressive effect of desflurane on the cerebral and systemic circulation is a consequence of its effector site concentration.

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2. Conflict of interest: none.

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