



# Choosing the optimal method of anaesthesia in anterior resection of the rectum procedures — assessment of the stress reaction based on selected hormonal parameters

Wybór optymalnej metody znieczulenia podczas zabiegów przedniej resekcji odbytnicy — ocena reakcji na stres w oparciu o wybrane parametry hormonalne

Elżbieta Wojarska-Tręda<sup>1</sup>, Krzysztof Olejnik<sup>1</sup>, Zoran Stojcev<sup>2</sup>, Szymon Białka<sup>3</sup>, Hanna Misiołek<sup>3</sup>

<sup>1</sup>Department of Anaesthesiology, Maria Skłodowska-Curie Memorial Cancer Centre, Gliwice Branch, Gliwice, Poland

<sup>2</sup>Department of Oncological Surgery, Medical University of Silesia Katowice, Poland

<sup>3</sup>Department of Anaesthesiology and Intensive Therapy, Medical University of Silesia, Katowice, Poland

## Abstract

**Introduction:** The aim of this study was to compare hormonal stress responses (changes in adrenaline, noradrenaline, and cortisol concentrations) to surgical injury during total intravenous propofol anaesthesia and volatile anaesthesia with sevoflurane in patients subjected to anterior resection of the rectum.

**Material and methods:** The prospective randomised study included 61 patients qualified for anterior resection of the rectum. The subjects were randomised into two groups, based on the type of anaesthesia: 1) Group I (TIVA, n = 31), administered total intravenous propofol anaesthesia, and 2) Group II (VIMA, n = 30), administered volatile induction and maintenance sevoflurane anaesthesia. Serum concentrations of adrenaline, noradrenaline, and cortisol were determined prior to surgery, during assessment of abdominal cavity, after resection of the rectum, and 30 min and one day post-surgery.

**Results:** The two groups did not differ significantly in terms of their haemodynamic parameters: heart rate and arterial blood pressure. Compared to individuals subjected to TIVA, patients from the VIMA group presented with significantly higher concentrations of adrenaline during evaluation of the abdominal organs. No significant intergroup differences were found in terms of intra- and postoperative serum concentrations of noradrenaline and cortisol.

**Conclusions:** TIVA and VIMA induce similar hormonal stress responses during anterior resection of the rectum. The increase in serum adrenaline concentration during evaluation of the abdominal organs in the VIMA group implies that the dose of sevoflurane should be escalated at this time point. (*Endokrynol Pol* 2018; 69 (4): 403–410)

**Key words:** anaesthesia, stress reaction, TIVA, VIMA

## Streszczenie

**Wstęp:** Celem badania było porównanie odpowiedzi stresu hormonalnego (zmiany stężenia adrenaliny, noradrenaliny i kortyzolu) na uraz chirurgiczny podczas całkowitego dożylnego znieczulenia propofolem i wziewnego znieczulenia przy użyciu sewofluranu u pacjentów poddanych przedniej resekcji odbytnicy.

**Materiał i metody:** W prospektywnym randomizowanym badaniu wzięło udział 61 pacjentów zakwalifikowanych do przedniej resekcji odbytnicy. Badanych podzielono losowo na dwie grupy w zależności od rodzaju znieczulenia: grupa I (TIVA, n = 31) — podano całkowite znieczulenie dożylnie propofolem; grupa II (VIMA, n = 30) — podawano wziewną indukcję i utrzymanie znieczulenia z wykorzystaniem sewofluranu. Stężenie adrenaliny, noradrenaliny i kortyzolu w surowicy mierzono przed operacją, podczas oceny narządów jamy brzusznej, po resekcji odbytnicy, 30 minut i dobę po operacji.

**Wyniki:** Obie grupy nie różniły się istotnie pod względem parametrów hemodynamicznych: częstości akcji serca i ciśnienia tętniczego. W porównaniu z osobami poddanymi TIVA pacjenci z grupy VIMA wykazywali znacznie wyższe stężenia adrenaliny podczas oceny narządów jamy brzusznej. Nie stwierdzono istotnych różnic między grupami w zakresie śród- i pooperacyjnych stężeń noradrenaliny i kortyzolu w surowicy.

**Wnioski:** TIVA i VIMA wywołują podobne hormonalne reakcje na stres podczas przedniej resekcji odbytnicy. Wzrost stężenia adrenaliny w surowicy podczas oceny narządów jamy brzusznej w grupie VIMA sugeruje, że w tym momencie należy zwiększyć dawkę sewofluranu. (*Endokrynol Pol* 2018; 69 (4): 403–410)

**Słowa kluczowe:** znieczulenie, reakcja stresowa, TIVA, VIMA



Hanna Misiołek, Department of Anaesthesiology and Intensive Therapy, Medical University of Silesia, 3 Maja 13–15, 41–800 Zabrze, Poland; tel.: +48 501 035 191, fax: +48 32 370 16 17, e-mail: hanna.misiolek@gmail.com

## Introduction

Surgical procedures within the abdominal cavity, including those in the final section of the gastrointestinal tract located in the pelvis minor, require sufficiently strong analgesia and complete neuromuscular blockade. Removing the rectum through the abdominal cavity, i.e. anterior resection, is aimed at achieving radical oncologic results while preserving the working order of the anal sphincter, which is significant for preserving the quality of life and relative homeostasis of the body. The innervation of the rectum requires proper blockade of the sympathetic nervous system and suppressing nociception, so that the surgical intervention does not cause an avalanche of stress and inflammatory responses.

The stress reaction caused by a stimulus surgical trauma is characterised by disruption of the neurohumoral, immunological, and metabolic homeostasis. The response of the body to trauma depends on the scope of the surgical procedure, its duration, intraoperative blood loss, type of anaesthesia, and the severity of postoperative pain.

Catecholamines, in particular, are commonly considered to be connected with the stress reaction. However, we must remember that many other hormones and enzymes, and the nervous, immune and circulatory systems, change their activity in response to a stress stimulus. Moreover, neither neurotransmitters nor hormones work in isolation or cause isolated singular effects.

In the complex mechanism of reactions to a stressor, the activation of two systems: sympathetic-adrenomedullary system (SAM) and hypothalamic-pituitary-adrenocortical axis (HPA) is of fundamental importance. The first system consists of the autonomous sympathetic nervous system and adrenal medulla, and the second consists of the hierarchical neuroendocrine axis.

Within several seconds of the activation of the sympathetic-adrenomedullary system, the plasma concentration of the following catecholamines increases: adrenaline secreted mainly by adrenal glands in response to such stressors as physical exertion, damage to the heart muscle, haemorrhage, emotional tension, and noradrenaline secreted continuously by the synapses of postganglionic sympathetic fibres and maintained on a set, constant level. In a state of homeostasis most of the neurotransmitter is re-captured by the postganglionic cells and metabolised. Only a small part diffuses from the synapses to the capillaries and enters systemic circulation. During a stress reaction, serum concentration of the hormone increases significantly.

The hypothalamic-pituitary-adrenocortical axis (HPA), also known as the stress axis, works with ca. 30 min delay, but its effects last for a long time. This hier-

archical neuroendocrine axis starts in the hypothalamus in the nucleus periventricular posterior cells that secrete corticotropin-releasing hormone (CRH), which stimulates secretion of the adrenocorticotropic hormone (ACTH) by the pituitary gland. ACTH stimulates the secretion of cortisol by adrenal glands [1, 2].

Limiting the stress reaction caused by a surgical procedure and trauma is largely attributed to optimal anaesthesia. Excessive reaction to surgical trauma can cause severe complications, up to multiorgan failure syndrome. The effect of different types of anaesthesia on stress is mostly connected with their influence on the afferent nociceptive signalling from the operative field.

Anaesthesiology commonly uses both intravenous and inhalation anaesthesia [3]. In the case of total intravenous anaesthesia (TIVA), intravenous agents are administered to cause loss of consciousness, ensure analgesia, loss of memory, sympathoadrenergic reflex control and skeletal muscle relaxation. The used opioids, which relax the muscles, are meant to stop the nociceptive impulses from the operative field, allow mechanic ventilation, and provide haemodynamic stabilisation for the patient [4]. General anaesthesia ought to foreseeably and within a limited scope of doses render the patient unconscious, allow fast adjustment of the depth of the anaesthesia to current needs, and not impair the functions of the circulatory system.

Another type of anaesthesia is volatile induction and maintenance anaesthesia (VIMA). Anaesthetic fumes are administered intratracheally into the lungs [5]. They diffuse into the bloodstream and then to other parts of the body. In the brain, anaesthetics interact with the neuronal membrane, and stop and suppress the transmission of stimuli by synapses and by nerve endings of small diameter axons.

## Material and methods

We obtained approval from the Bioethics Committee of the Medical University of Silesia. A total of 85 subjects, who gave their written informed consent, were enrolled into the prospective, randomised study. Out of the initial number, 61 subjects completed the study — with operative risk classified into I-II class according to ASA — they underwent anterior resection of the rectum. The subjects were divided into two groups based on the type of anaesthesia: Group I (TIVA,  $n = 31$ ) — patients were administered total intravenous anaesthesia, Group II (VIMA,  $n = 30$ ) — patients were administered volatile induction and maintenance anaesthesia.

Sixty minutes prior to the procedure, the patients were pre-medicated with midazolam. In Group I (TIVA) general anaesthesia was induced with propofol, with dose set at  $1.5 \text{ mg} \cdot \text{kg}^{-1} \text{ IV}$ , and in Group II (VIMA)

with sevoflurane in doses increasing from 0.6% Vol% to 6 Vol%, with fresh gas flow 6 L·min<sup>-1</sup>. Moreover, while anaesthesia was being induced, subjects from both groups were administered fentanyl at a dose set at 2 µg·kg<sup>-1</sup> IV and atracurium at a dose set at 0.6 mg·kg<sup>-1</sup> IV.

In Group I general anaesthesia was maintained using propofol according to the following schema: 10 mg·kg<sup>-1</sup>·h<sup>-1</sup> for 10 min, then 8 mg·kg<sup>-1</sup>·h<sup>-1</sup> for 10 min, and later 6 mg·kg<sup>-1</sup>·h<sup>-1</sup>. In Group II, we used sevoflurane 2 Vol% with fresh gas flow 2 L·min<sup>-1</sup>, so that the established target MAC value was maintained at 0.8. All patients were ventilated with a mixture of oxygen and air in a 1:1 ratio. In order to ensure analgesia, fentanyl 5 µg·kg<sup>-1</sup>·h<sup>-1</sup> was administered in continual infusion in both groups until the tumour was removed, afterwards the dose was reduced to 3 µg·kg<sup>-1</sup>·h<sup>-1</sup> and finally to 1.2 µg·kg<sup>-1</sup>·h<sup>-1</sup> after the anastomosis was performed. Muscle relaxation was maintained with continual infusion of atracurium, with dose set at 0.3–0.5 mg·kg<sup>-1</sup>·h<sup>-1</sup>, depending on the monitored depth of relaxation.

During the procedure, all patients were monitored with standard intraoperative monitoring with additional bispectral index monitoring (BIS).

At set times (prior to the procedure, during the assessment of the abdominal cavity by the surgeon, after the tumour was removed, 30 min after the patient woke up, and in the first 24 hours after the procedure) we took readings of haemodynamic and ventilation parameters, BIS, serum adrenaline, noradrenaline, and cortisol concentration.

During the duration of anaesthesia we used a uniform method of hydration in both groups, administering 8 ml·kg<sup>-1</sup>·h<sup>-1</sup> of infusion fluids. The crystalloid-to-colloid volume ratio was 4:1.

The supply of the analgesic and the muscle relaxant was stopped after a surgical drain was inserted into the peritoneal cavity.

We monitored the time elapsed from the moment we stopped administering the hypnotic until the BIS indicator reached 90. We assessed the time it took the patients to wake up using the Aldret scale in the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 5<sup>th</sup>, 10<sup>th</sup>, and 20<sup>th</sup> minute after anaesthesia. We recorded the duration of anaesthesia and of the procedure. In the postoperative period, we also determined the severity of pain on the Numerical Rating Scale (NRS) and recorded the side effects: coughing, nausea, and vomiting in the 0 day after the procedure.

### Limitations of the method

During the surgical procedure in general anaesthesia, several factors can affect the plasma concentration of catecholamines: dilution, reabsorption, enzymatic degradation in the liver, and strong surgical stimuli

**Table I. Demographic and clinical characteristics of the study participants**

**Tabela I. Charakterystyka demograficzna i kliniczna uczestników badania**

Variable	TIVA	VIMA
Number of subjects	31	30
Women	18 (58%)	13 (44%)
Men	13 (42%)	17 (56%)
Age (years)	59.4 ± 11.1	56.6 ± 12.8
Body height [m]	1.66 ± 0.08	1.69 ± 0.08
Body weight [kg]	68.3 ± 13.5	72.1 ± 14.9
BMI [kg/m <sup>2</sup> ]	24.7 ± 3.8	25.2 ± 4.2
Coronary artery disease	3 (9.6%)	4 (15.3%)
Arterial hypertension	7 (22.5%)	9 (30%)
Diabetes mellitus	1 (3.3%)	2 (6.6%)
Tobacco smoking	7 (22.5%)	6 (20%)
Duration of anaesthesia [min]	223 ± 68.7	221.8 ± 69.2
Introductory dose of fentanyl [µg·kg <sup>-1</sup> ]	4.5 ± 0.9	4.4 ± 0.7
Maintenance dose of fentanyl [µg·kg <sup>-1</sup> ·h <sup>-1</sup> ]	3.5 ± 1.4	3.4 ± 1.2
Hospitalisation (days)	13.6 ± 6.4	14 ± 8.0

with inadequate depth of anaesthesia with its three constituents. Another limitation of the method can be the inability to standardise the surgical and operative factors, which can affect the severity of the stress reaction.

### Statistical analysis

Normal distribution of the analysed variables was verified using Shapiro-Wilk's test. In the case of quantitative data, depending on the distribution of data either Student's t-test, or U Mann-Whitney's test were used. The analysis of repeated measurements was performed using the ANOVA test for the timing chart, and Tukey's post-hoc test for data with normal distribution, or Friedman's ANOVA and post-hoc tests for data not normally distributed. Qualitative variables were analysed using either the Pearson's chi-square test or Fisher's accuracy test if the expected multiplicities were below 5. Statistical significance was set at  $p < 0.05$ . The calculations were performed using Statistica 6.0 Software.

### Results

The study groups were comparable in demographic data, the type and frequency of selected concomitant conditions, the amount of opioids used, and duration of anaesthesia and hospitalisation (Table I).

The results for arterial tension and heart rate did not differ significantly between the groups. Similarly, there were reportedly no statistically significant differences for the values of arterial blood oxygenation, assessed using the pulse oximetry method. During the procedure and early in the postoperative period we did not record any complications or adverse events in either of the study groups. None of the patients required blood product transfusion.

The time from the moment we stopped administering the sleeping agent until the BIS score reached 90 did not differ significantly between the groups. They also did not differ significantly in the time it took the subjects to regain consciousness, assessed according to the Aldrete scale. The documented score in the first minute after administering anaesthesia was 8 pts., in the fifth 9 pts., and in the 10<sup>th</sup> it was 10 pts., in both groups.

The analysis of pain severity, using the NRS scale, also did not show any differences between the groups.

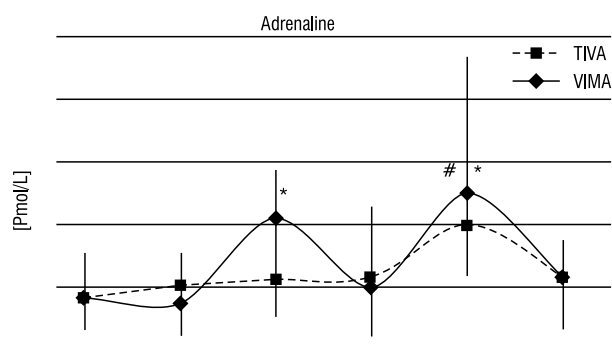
During the surgeon's assessment of the abdominal cavity we documented a statistically significant difference between the groups in the BIS values.

We recorded statistically significant differences between the two groups in the monitored hormonal parameters.

A significantly higher adrenaline concentration was recorded during the assessment of the abdominal cavity organs in the group with VIMA anaesthesia. The assessment of the recorded values within the group showed a more than three-fold increase in adrenaline concentration during the assessment of the abdominal cavity and a two-fold increase within 30 minutes after the anaesthesia was stopped, in comparison with the initial values of the VIMA group. In the TIVA group, a more than two-fold increase in adrenaline concentration, in comparison with the initial values, was recorded 30 minutes after the procedure (Fig. 1).

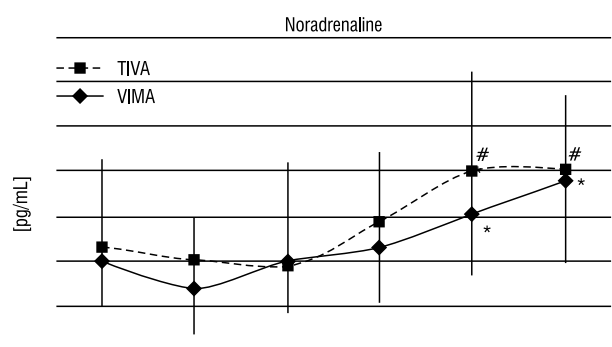
The analysis of the recorded values for noradrenaline concentration did not show any significant differences between the groups. However, in both groups the values recorded 30 minutes after the procedure and during the first 24 hours were about two-fold higher, in comparison with the initial and morning values on the day of the procedure (Fig. 2).

The comparison of cortisol concentration did not show any statistically significant differences between the groups. An assessment of the serum cortisol concentration within the groups showed that after the tumour was removed and 30 minutes after the procedure the concentration of the hormone increased two-fold, in comparison with initial and morning values (Fig. 3).



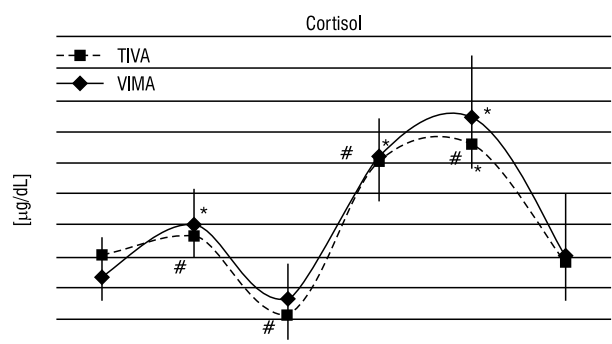
**Figure 1.** Serum adrenaline concentrations at selected time points: prior to, during, and after the surgery; \*significant intergroup difference ( $p < 0.05$ ), #significantly different than the baseline value in TIVA group ( $p < 0.05$ ), and significantly different than the baseline value in VIMA group ( $p < 0.05$ )

**Rycina 1.** Stężenia adrenaliny w surowicy w wybranych punktach czasowych: przed, w trakcie i po zabiegu



**Figure 2.** Serum noradrenaline concentrations at selected time points prior to, during, and after the surgery; #significantly different than the baseline value in TIVA group ( $p < 0.05$ ), and significantly different than the baseline value in VIMA group ( $p < 0.05$ )

**Rycina 2.** Stężenia noradrenaliny w surowicy w wybranych punktach czasowych: przed, w trakcie i po zabiegu



**Figure 3.** Serum cortisol concentrations at selected time points prior to, during, and after the surgery; #significantly different than the baseline value in TIVA group ( $p < 0.05$ ), and significantly different than the baseline value in VIMA group ( $p < 0.05$ )

**Rycina 3.** Stężenia kortyzolu w surowicy w wybranych punktach czasowych: przed, w trakcie i po zabiegu

## Discussion

The analysis of stress hormone levels during anaesthesia has been the subject of studies since the 1990s. We analysed different factors that can affect the stress reaction in the perioperative period. One of them was the extent of the performed procedures. Oncological surgeries within the abdominal cavity or pelvis minor, being intracavity procedures, cause a significant stress reaction in the course of the procedure. This reaction is the most frequently caused by necessary invasive and extensive operative methods. Stress-causing factors can constitute: manual examination of abdominal cavity organs, pulling the mesentery, disrupting the continuity of many nerve fibres, and, finally, the location of the tumour or removing large mass tumours. Many authors describe the disparity in stress reaction during laparotomy and much less invasive laparoscopy, with the reaction being more severe in the case of the former procedure [5–8]. This is a result of not only the size of the incision, but also of the surgical technique itself. According to authors who study this phenomenon, an increase of the intraabdominal pressure accompanying the laparoscopic technique does not cause as significantly high levels of stress hormones as those that accompany an oncological surgery on an open abdominal cavity [9, 10].

This corroborates own results, which in both studied groups showed an increase in adrenaline concentration during the assessment of the abdominal cavity by a surgeon, and in cortisol after the tumour was removed.

The type and applied technique of anaesthesia also affect perioperative stress. Recently, VIMA underwent many modifications, and introducing sevoflurane marked a breakthrough in inhalation anaesthesia because it allowed induction and maintenance of anaesthesia solely with an inhalational anaesthetic. Even not so long ago, commonly used isoflurane did not meet the conditions allowing it to be used for inducing general anaesthesia. Moreover, it gave way to propofol in terms of the stability of the stress reaction. Adams et al. [11] showed significantly greater suppression of adrenaline, noradrenaline, and cortisol hormones during TIVA anaesthesia used in surgical procedures, in comparison with inhalational isoflurane.

Different results were presented by Castillo et al. [12], who performed complex anaesthesia using isoflurane and compared it with TIVA. The researchers assessed the stress reaction to intubation and incision of the skin, drawing from the existing assessment of the concentration of typical stress hormones. The surprising result — in the context of results by other authors analysing this issue — of higher concentrations of stress hormones in the TIVA group can be questioned. The concentration of the inhalational anaesthetic, isoflurane, used in the

study was 0.5–0.6 Vol% (Et), which constitutes a lower dose than recommended by guidelines of inhalation anaesthesia. Castillo's results are also controversial in the context of the results of most studies, which report that TIVA anaesthesia is more efficient in suppressing stress reaction caused by intubation and incision of the skin. Using isoflurane as an inhalation anaesthetic useful in suppressing stress reaction is debatable. A much more useful inhalation agent, with a suppressive component affecting the stress reaction, and thus more and more frequently used, is sevoflurane [13]. Its quality in reducing the concentration of stress hormones was proven by Nishiyama et al. [14]. In the study, where prolonged, 10-hour inhalation of anaesthesia was used, they showed that adrenaline and noradrenaline concentration in the 5<sup>th</sup> and 10<sup>th</sup> hour of anaesthesia were significantly higher in the case of sevoflurane, in comparison with isoflurane, with identical MAC values for both anaesthetics. Another argument undermining Castillo's results is the fact that propofol, which has qualities stopping afferent impulses during laryngoscopy and intubation, also from the operative field, alleviates the stress reaction, in comparison with other intravenous agents. This was proven in a study on a group of patients subjected to thyroid resection with subclinical hyperthyroidism, with initially higher levels of selected stress hormones [15].

Satani et al. [16] compared TIVA with balanced inhalation anaesthesia using sevoflurane in lung resection procedures. An assessment of the stress reaction hormones (noradrenaline, adrenaline, cortisol, and ACTH) was limited to the following points: prior, post, and within the first and third 24 hours after anaesthesia. The authors did not assess how the body's reaction to stress caused by induction and conduction of anaesthesia and surgical manipulation changed, which was the subject of this study. Moreover, the analysis of changes in the concentration of adrenaline and noradrenaline after two or three days from anaesthesia can in no way be the effect of agents or methods used to induce or maintain anaesthesia.

The effect of adrenaline and noradrenaline is a simultaneous increase of vascular peripheral resistance and cardiac output, and thus arterial tension. Significantly, the described cardio-vascular effects are observed quite quickly (seconds, minutes) from the time the stimulus takes effect. Moreover, both hormones circulate in the blood for 1–3 minutes, which can explain the slightly prolonged effect even of short-term activation of the sympathetic system. It is believed that endogenous adrenaline is the priority hormone in wakeful stress reactions. On the other hand, changes to the excretion of noradrenaline cause the activation of muscle fibres and physical adaptation to the stimulus [17–21]. In this study, we assumed intraoperative taking of blood samples at the moment a strong stimulus

took effect, such as palpation assessment of the organs after the abdominal cavity was opened or right after the tumour was extracted. Due to the properties of catecholamines, we focused on the dynamics of changes in hormone concentration, instead of absolute values.

Another controversial study, the methodology of which prevents a constructive discussion, was conducted by Graziola et al. [22]. Due to the complete lack of homogeneity of the comparative groups (I Group: propofol/fentanyl/isoflurane; II Group: TIVA propofol/remifentanyl), it is questionable whether the authors can draw any conclusions on the benefits of one of the techniques of anaesthesia (TIVA) and its effect on the levels of stress hormones.

We should stress that the assumptions of this study were correct, in view of the fact there are no clear results in the available sources. We have shown, in both the case of intravenous (TIVA) and inhalation (VIMA) general anaesthesia, a comparable increase in the concentration of studied stress hormones. The only exception is the moment when the abdominal cavity is assessed, with significantly higher adrenaline concentration documented for the group which received inhalation anaesthesia, sevoflurane.

Furthermore, the most recent reports show the ambiguity of assessing the stress reaction, which is the result of the application of different techniques of anaesthesia, using only the assessment of known stress hormones adrenaline and noradrenaline.

The interpretation of the effect of different cytokines on modulating the response of the hypothalamic-pituitary-adrenocortical axis (HPA) to a strong impulse when a patient is being anaesthetised for a surgical procedure is a cause for hope [23–26]. Schneemilch et al. [27] showed that patients administered inhalation anaesthesia had a stronger inflammatory response, characterised by higher IL-6 values. They also noticed an increase in adrenaline concentration after the procedure in patients anaesthetised with sevoflurane, in comparison with patients anaesthetised with propofol. This study showed an increase in adrenaline concentration after the procedure in both groups, which was probably caused by the return to consciousness. It is difficult to compare the results of this study with the results reported by Schneemilch et al., because in the TIVA group the anaesthesia was maintained with propofol and single doses of sufentanil and in the VIMA group with 1.5 Vol% sevoflurane. We are concerned by the fact that when describing their methodology the authors give no information on using any opioids in the group that received inhalation anaesthesia.

Another protein from the cytokine group secreted by the fat tissue cells is leptin, the concentration of which changes rapidly when the body experiences operative

stress, and high levels of this cytokine stop the response of the hypothalamic-pituitary-adrenocortical axis to the stressor [28]. The regulation of leptin secretion and the activity of the HPA axis is subject to negative feedback [28, 29]. In their study, Marana et al. [29] showed that a high concentration of catecholamines — according to the negative feedback rule — causes the leptin level to drop. The authors recorded high levels of stress hormones in the group anaesthetised with sevoflurane. This can be explained by a lack of effect of the inhalation anaesthetic — contrary to propofol — on the suppression of operative stress-related secretion of hypothalamic corticotropin (CRH). However, curiously the nociceptive impulsion in the group anaesthetised with sevoflurane was insufficiently suppressed, even though fentanyl was administered according to guidelines (3 µg/kg for the entire procedure). The results were compared with the TIVA group, where analgesia was achieved using remifentanyl according to dosage guidelines. As could have been expected, the concentration of stress hormones (ACTH, adrenaline, noradrenaline, and cortisol) was significantly lower in the group of patients who received continuous doses of the opioid (remifentanyl), according to dosage guidelines. The effect of an entirely intravenous (using propofol) or entirely inhaled (using sevoflurane) anaesthesia on the secretion of leptin resulting from operative stress remains unexplained.

A significant factor modulating the stress reaction is the scope of surgical trauma. The smaller the trauma the smaller the stress response [30, 31]. Minimal stress reaction, as a response to surgical stimuli from the operative field, accompanies ophthalmic procedures [32, 33]. Therefore, Kushikata et al. [34, 35] conducted two studies in which they compared the neuroendocrine stress response to entirely intravenous anaesthesia, using propofol, with anaesthesia with balanced sevoflurane, in patients undergoing scheduled eye-related surgical procedures. The authors monitored the adrenaline, noradrenaline, orexin, and propofol levels. They did not observe any changes of catecholamine concentrations during the introduction of anaesthesia. However, 15 minutes after extubation they did observe an increase in noradrenaline and orexin concentration in both groups and adrenaline concentration in the group administered only inhalation anaesthesia. The results of that study corroborate our own results on changes of noradrenaline concentration in the postoperative period. In contrast to the results of Kushikata et al., we determined that in both groups adrenaline concentrations 30 min after the procedure were significantly higher than prior to the procedure, and in the following day fell significantly. Similar results — of the effect of regaining consciousness on the increase of catecholamine levels — in the case of surgical treatment for scoliosis were documented

by Eroglu et al. [36]. In their study, higher levels of adrenaline and noradrenaline were recorded during an intraoperative “wake-up” test performed to assess the spinal cord function. An increase of the monitored hormone concentration was documented regardless of the type of anaesthesia used — sevoflurane or propofol.

In their studies, Kushikata et al. [34, 35] point out a significant increase of orexin level after the procedure, and the positive correlation with the level of other hormones. Orexin (hypocretin) is a neuropeptide produced in neurons of the hypothalamus, which probably plays a significant part in regulating the hypothalamic-pituitary-adrenocortical axis and stress response of the body [37]. Orexin is considered to be a key factor in maintaining alertness and activating the hypothalamic-pituitary-adrenocortical axis [38]. Thus, high hopes are placed on it in the context of monitoring and evaluating operative stress.

Stress hormones: adrenaline and noradrenaline directly affect the cardio-vascular system. Available sources document different observations and conclusions regarding the effect of stress hormones on the response of the cardio-vascular system. In this study, the increased concentration of stress hormones did not translate into significant changes in the haemodynamic response.

We recorded significantly higher bispectral index values during the surgeon’s assessment of the abdominal cavity in the VIMA group. There can be two explanations for this finding.

Our methodological assumption was based on the scarce available data, suggesting that 0.8 MAC is sufficient for this type of surgery, assuring anaesthesia will be maintained on the proper level. Our results corroborate the legitimacy of applying this dosage at all times while inducing the anaesthesia and during the procedure. The strong stress stimulus, i.e. the manual assessment of the abdominal cavity by the surgeon, is connected with the simultaneous recording of higher BIS values in the group anaesthetised with sevoflurane, in comparison with values recorded for the group anaesthetised with propofol, which at the same time correlates with higher adrenaline values in that moment.

Differences of the bispectral index in different types of general anaesthesia analysed regardless of hormone concentration can be explained and corroborated by the results of Salmi et al. [39], which explicate the details of mechanisms of both agents in different areas of CNS. The authors, using positron tomography emission of CNS, corroborate the thesis that anaesthetics work through GABAergic receptors, at the same time showing that the used anaesthetics, propofol and sevoflurane, work through the same receptors but in different regions of CNS. Sevoflurane activates GABA receptors in the entire brain, apart from the pons and white matter,

and propofol activates it in the area of the cerebellum, thalamus, and lobes: frontal, temporal, and occipital. Despite the fact that sevoflurane affected different areas of the brain than propofol, the monitored BIS values were higher in the group that received inhalation anaesthesia. Different metabolism in the brain caused by different anaesthetics was also described by other authors using modern imaging techniques. They showed that propofol causes a decrease in glucose metabolism mostly in the cortex area and it is significantly stronger than in the case of any inhalation anaesthetic [40]. The suppression of glucose metabolism after sevoflurane is marked mainly in the diencephalon area and the entire cerebrum [41], which suggests that the area analysed with BIS (cortex) is not the only site of the effects of sevoflurane on CNS. The changes of the metabolic activity of the brain are also affected by a dose of propofol. Increasing the dose of propofol over the standard amount prescribed for anaesthesia causes an expansion of the area of metabolic suppression beyond the cerebrum to subcortical centres: the thalamus and hippocampus. Similar dependence on the dose was not documented for sevoflurane. Kurehara et al. [42] compared the effect of changes in the concentration of inhalation anaesthetics, sevoflurane and isoflurane, on the values of the bispectral index — BIS. The values were comparable up until 1.2 MAC. A further increase in isoflurane concentration caused a further decrease in BIS values, contrary to sevoflurane, where no differences in the bispectral index were observed.

Significantly higher BIS values can be explained by a different mechanism of affecting the CNS; however, in this study the described changes were accompanied by an increase in adrenaline concentration in the VIMA group. In view of the abovementioned results, it seems proper that prior to a planned assessment of abdominal cavity organs, the dosage of the inhalation anaesthetic be increased to prevent such aftereffects as BIS and adrenaline increase.

Such action is all the more justified because the scheduled intraoperative analgesia schema was sufficient. Comparable doses of opioids used to anaesthetise all patients and no documented difference in haemodynamic parameters suggest that increased adrenaline concentration during the assessment of the abdominal cavity was not related to insufficient analgesia, but rather to the previously described lower level of unconsciousness or another mechanism of both anaesthetics.

#### *Grants or other funding sources*

None.

#### *Conflict of interest*

None.

## References

- Lewandowski KC, Malicka K, Dąbrowska K, et al. Addison's disease concomitant with corticotropin deficiency and pituitary CRH resistance - a case report. *Endokrynol Pol.* 2017; 68(4): 468–471, doi: [10.5603/EP.2017.0052](#), indexed in Pubmed: [28819949](#).
- Zukowski Ł, Myśliwiec J, Górska M. Diagnostics of hypercortisolism - comparison between the clinical usefulness of salivary and serum cortisol measurements. *Endokrynol Pol.* 2013; 64(4): 263–267, indexed in Pubmed: [24002952](#).
- Gaszyński T, Wieczorek A. A comparison of BIS recordings during propofol-based total intravenous anaesthesia and sevoflurane-based inhalational anaesthesia in obese patients. *Anaesthesiol Intensive Ther.* 2016; 48(4): 239–247, doi: [10.5603/AIT.2016.0044](#), indexed in Pubmed: [27797096](#).
- Wang J, Ma H, Zhou H, et al. Effect of preoperative intravenous oxycodone administration on sufentanil consumption after retroperitoneal laparoscopic nephrectomy. *Anaesthesiol Intensive Ther.* 2016; 48(5): 300–304, doi: [10.5603/AIT.2016.0052](#), indexed in Pubmed: [27834984](#).
- Zielińska M, Bartkowska-Śniatkowska A, Mierzewska-Szmidt M, et al. The consensus statement of the Paediatric Section of the Polish Society of Anaesthesiology and Intensive Therapy on general anaesthesia in children over 3 years of age. Part I - general guidelines. *Anaesthesiol Intensive Ther.* 2016; 48(2): 71–78, doi: [10.5603/AIT.2016.0022](#), indexed in Pubmed: [27248284](#).
- Hewitt PM, Ip SM, Kwok SP, et al. Laparoscopic-assisted vs. open surgery for colorectal cancer: comparative study of immune effects. *Dis Colon Rectum.* 1998; 41(7): 901–909, indexed in Pubmed: [9678378](#).
- Marana E, Scambia G, Maussier ML, et al. Neuroendocrine stress response in patients undergoing benign ovarian cyst surgery by laparoscopy, minilaparotomy, and laparotomy. *J Am Assoc Gynecol Laparosc.* 2003; 10(2): 159–165, indexed in Pubmed: [12732764](#).
- Whelan RL, Franklin M, Holubar SD, et al. Postoperative cell mediated immune response is better preserved after laparoscopic vs open colorectal resection in humans. *Surg Endosc.* 2003; 17(6): 972–978, doi: [10.1007/s00464-001-8263-y](#), indexed in Pubmed: [12640542](#).
- Muzli L, Marana R, Marana E, et al. Evaluation of stress-related hormones after surgery by laparoscopy or laparotomy. *J Am Assoc Gynecol Laparosc.* 1996; 3(2): 229–234, indexed in Pubmed: [9050631](#).
- Luo K, Li JS, Li LT, et al. Operative stress response and energy metabolism after laparoscopic cholecystectomy compared to open surgery. *World J Gastroenterol.* 2003; 9(4): 847–850, indexed in Pubmed: [12679946](#).
- Adams HA, Schmitz CS, Baltes-Götz B. [Endocrine stress reaction, hemodynamics and recovery in total intravenous and inhalation anesthesia. Propofol versus isoflurane]. *Anaesthesist.* 1994; 43(11): 730–737, indexed in Pubmed: [7840401](#).
- Castillo V, Navas E, Naranjo R, et al. [Changes in the concentrations of catecholamines and cortisol in balanced anesthesia and total intravenous anesthesia]. *Rev Esp Anestesiol Reanim.* 1997; 44(2): 52–55, indexed in Pubmed: [9148356](#).
- Marana E, Annetta MG, Meo F, et al. Sevoflurane improves the neuroendocrine stress response during laparoscopic pelvic surgery. *Can J Anaesth.* 2003; 50(4): 348–354, doi: [10.1007/BF03021031](#), indexed in Pubmed: [12670811](#).
- Nishiyama T, Yamashita K, Yokoyama T. Stress hormone changes in general anesthesia of long duration: isoflurane-nitrous oxide vs sevoflurane-nitrous oxide anesthesia. *J Clin Anesth.* 2005; 17(8): 586–591, doi: [10.1016/j.jclinane.2005.03.009](#), indexed in Pubmed: [16427527](#).
- Misiołek H, Wojcieszek E, Dyaczyńska-Herman A. Comparison of influence of thiopentone, propofol and midazolam on blood serum concentration of noradrenaline and cortisol in patients undergoing non-toxic struma operation. *Med Sci Monit.* 2000; 6(2): 319–324, indexed in Pubmed: [11208330](#).
- Satani M, Hamada T, Nakada K, et al. [Comparison of total intravenous anesthesia and inhalation anesthesia regarding hormonal responses during lung lobectomy]. *Masui.* 2005; 54(10): 1109–1115, indexed in Pubmed: [16231763](#).
- Pflug AE, Halter JB. Effect of spinal anesthesia on adrenergic tone and the neuroendocrine responses to surgical stress in humans. *Anesthesiology.* 1981; 55(2): 120–126, indexed in Pubmed: [7258714](#).
- Akerstedt T, Gillberg M, Hjemdahl P, et al. Comparison of urinary and plasma catecholamine responses to mental stress. *Acta Physiol Scand.* 1983; 117(1): 19–26, doi: [10.1111/j.1748-1716.1983.tb07174.x](#), indexed in Pubmed: [6858703](#).
- Orgacka H, Ryszka E, Zych F. Wpływ różnych czynników na poziom katecholamin w ustroju. *Post Higieny Med Dosw.* 1983; 37: 483–504.
- Jørgensen LS, Bönlökke L, Christensen NJ. Plasma adrenaline and noradrenaline during mental stress and isometric exercise in man. The role of arterial sampling. *Scand J Clin Lab Invest.* 1985; 45(5): 447–452, indexed in Pubmed: [4035281](#).
- Rasmus A, Gaszyński W. Fizjologiczne podstawy odpowiedzi ustroju na stres operacyjny. *Anest Inten Ter.* 1993; 25: 253–261.
- Graziola E, Elena G, Gobbo M, et al. [Stress, hemodynamic and immunological responses to inhaled and intravenous anesthetic techniques for video-assisted laparoscopic cholecystectomy]. *Rev Esp Anestesiol Reanim.* 2005; 52(4): 208–216, indexed in Pubmed: [15901026](#).
- Gilliland HE, Armstrong MA, Carabine U, et al. The choice of anesthetic maintenance technique influences the antiinflammatory cytokine response to abdominal surgery. *Anesth Analg.* 1997; 85(6): 1394–1398, indexed in Pubmed: [9390615](#).
- Kelbel I, Weiss M. Anaesthetics and immune function. *Curr Opin Anaesthesiol.* 2001; 14(6): 685–691, indexed in Pubmed: [17019166](#).
- El Azab SR, Rosseel PMJ, De Lange JJ, et al. Effect of VIMA with sevoflurane versus TIVA with propofol or midazolam-sufentanil on the cytokine response during CABG surgery. *Eur J Anaesthesiol.* 2002; 19(4): 276–282, indexed in Pubmed: [12074417](#).
- Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. *J Anesth.* 2008; 22(3): 263–277, doi: [10.1007/s00540-008-0626-2](#), indexed in Pubmed: [18685933](#).
- Schneemilch CE, Bank U. [Release of pro- and anti-inflammatory cytokines during different anesthesia procedures]. *Anaesthesiol Reanim.* 2001; 26(1): 4–10, indexed in Pubmed: [11256129](#).
- Kain ZN, Zimolo Z, Heninger G. Leptin and the perioperative neuroendocrinological stress response. *J Clin Endocrinol Metab.* 1999; 84(7): 2438–2442, doi: [10.1210/jcem.84.7.5850](#), indexed in Pubmed: [10404818](#).
- Marana E, Scambia G, Colicci S, et al. Leptin and perioperative neuroendocrine stress response with two different anesthetic techniques. *Acta Anaesthesiol Scand.* 2008; 52(4): 541–546, doi: [10.1111/j.1399-6576.2008.01589.x](#), indexed in Pubmed: [18339160](#).
- Karayiannakis AJ, Makri GG, Mantzioka A, et al. Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. *Br J Surg.* 1997; 84(4): 467–471, indexed in Pubmed: [9112894](#).
- Haque Z, Rahman M, Siddique MA, et al. Metabolic and stress responses of the body to trauma: produced by the laparoscopic and open cholecystectomy. *Mymensingh Med J.* 2004; 13(1): 48–52, indexed in Pubmed: [14747786](#).
- Barker JP, Vafidis GC, Robinson PN, et al. Plasma catecholamine response to cataract surgery: a comparison between general and local anaesthesia. *Anaesthesia.* 1991; 46(8): 642–645, indexed in Pubmed: [1887969](#).
- Schwall B, Jakob W, Sessler DI, et al. Less adrenergic activation during cataract surgery with total intravenous than with local anesthesia. *Acta Anaesthesiol Scand.* 2000; 44(3): 343–347, indexed in Pubmed: [10714852](#).
- Kushikata T, Yoshida H, Kudo M, et al. Plasma orexin A increases at emergence from sevoflurane-fentanyl anesthesia in patients undergoing ophthalmologic surgery. *Neurosci Lett.* 2010; 482(3): 212–215, doi: [10.1016/j.neulet.2010.07.037](#), indexed in Pubmed: [20655366](#).
- Kushikata T, Yoshida H, Kudo M, et al. Changes in plasma orexin A during propofol-fentanyl anaesthesia in patients undergoing eye surgery. *Br J Anaesth.* 2010; 104(6): 723–727, doi: [10.1093/bja/aeq098](#), indexed in Pubmed: [20430767](#).
- Eroglu A, Solak M, Ozen I, et al. Stress hormones during the wake-up test in scoliosis surgery. *J Clin Anesth.* 2003; 15(1): 15–18, indexed in Pubmed: [12657405](#).
- Kukkonen JP, Holmqvist T, Ammoun S, et al. Functions of the orexinergic/hypocretinergic system. *Am J Physiol Cell Physiol.* 2002; 283(6): C1567–C1591, doi: [10.1152/ajpcell.00055.2002](#), indexed in Pubmed: [12419707](#).
- Dong H, Niu J, Su B, et al. Activation of orexin signal in basal forebrain facilitates the emergence from sevoflurane anesthesia in rat. *Neuropeptides.* 2009; 43(3): 179–185, doi: [10.1016/j.npep.2009.04.006](#), indexed in Pubmed: [19464733](#).
- Salmi E, Kaisti KK, Metsähonkala L, et al. Sevoflurane and propofol increase 11C-flumazenil binding to gamma-aminobutyric acidA receptors in humans. *Anesth Analg.* 2004; 99(5): 1420–6; table of contents, doi: [10.1213/01.ANE.0000135409.81842.31](#), indexed in Pubmed: [15502041](#).
- Alkire MT, Pomfrett CJ, Haier RJ, et al. Functional brain imaging during anesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism. *Anesthesiology.* 1999; 90(3): 701–709, indexed in Pubmed: [10078670](#).
- Jeong YB, Kim JS, Jeong SM, et al. Comparison of the effects of sevoflurane and propofol anaesthesia on regional cerebral glucose metabolism in humans using positron emission tomography. *J Int Med Res.* 2006; 34(4): 374–384, doi: [10.1177/147323000603400406](#), indexed in Pubmed: [16989493](#).
- Kurehara K, Horiuchi T, Takahashi M, et al. [Relationship between minimum alveolar concentration and electroencephalographic bispectral index as well as spectral edge frequency 95 during isoflurane/epidural or sevoflurane/epidural anesthesia]. *Masui.* 2001; 50(5): 512–515, indexed in Pubmed: [11424467](#).