Pozaanestetyczne działanie anestetyków wziewnych

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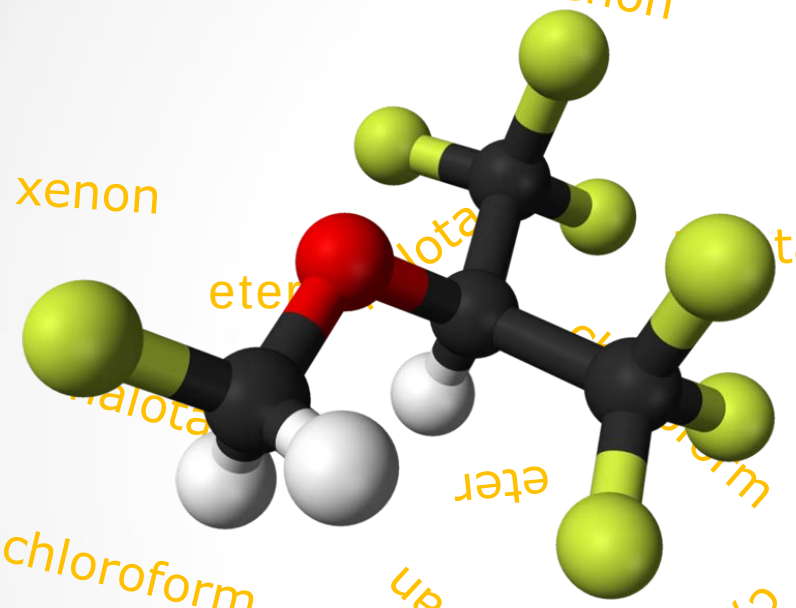

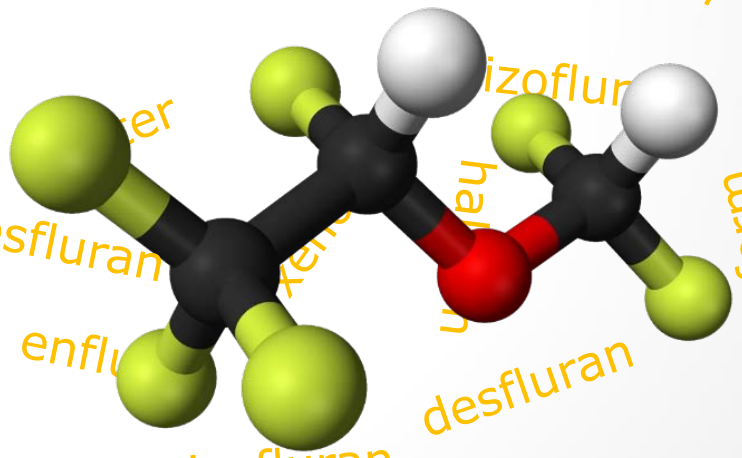

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2012; 70, supl. I: S 1–S 100
ISSN 0022–9032

Dzic

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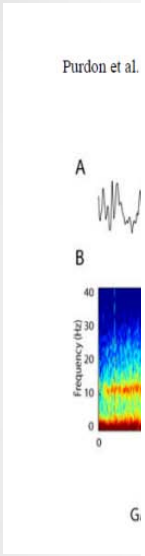
Europejskie wytyczne dotyczące zapobiegania chorobom serca i naczyń w praktyce klinicznej na 2012 rok

Piąta Wspólna Grupa Robocza Europejskiego Towarzystwa Kardiologicznego i Innych Towarzystw Naukowych ds. Zapobiegania Chorobom Serca i Naczyń w Praktyce Klinicznej (*Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice*) utworzona przez przedstawicieli dziewięciu towarzystw oraz zaproszonych ekspertów

hartowanie mięśnia sercowego przez niedokrwienie (*ischaemic pre-conditioning*). Jest to proces, dzięki któremu przemijające niedokrwienie mięśnia sercowego podczas wysiłku zwiększa tolerancję mięśnia na późniejszy dłużej trwający stres niedokrwienny, zmniejszając w ten sposób uszkodzenie mięśnia sercowego i ryzyko potencjalnie śmiertelnych tachyarytmii komorowych. Do tych kardioprotekcyjnych mechanizmów należą zmiany anatomiczne w tętnicach wieńcowych, indukcja ekspresji białek szoku cieplnego w mięśniu sercowym, wzrost aktywności cyklooksygenazy typu 2 w miokardium, indukcja białek stresowych w retikulum endoplazmatycznym, zwiększenie wytwarzania tlenu azotu, poprawa czynności kanałów potasowych zależnych od trifosforanu adenozyny (ATP) w sarkolemie i/lub błonach mitochondrialnych, wzrost aktywności antyoksydacyjnej mięśnia sercowego, zwiększenie ekspresji głównych enzymów o działaniu przeciwutleniającym, a także wywoływanie takich zmian fenotypu mitochondriów, które chronią przed działaniem bodźców stymulujących apoptozę [327].

Isoflurane but Not Sevoflurane or Desflurane Aggravates Injury to Neurons In Vitro and In Vivo via p75^{NTR}-NF-κB Activation

Nils Schallner, MD,* Felix Ulbrich, MD,* Helen Engelstaedter, MD,* Julia Biermann, MD,† Volker Auwaerter, PhD,‡ Torsten Loop, MD,* and Ulrich Goebel, MD*



BACKGROUND: General anesthesia in patients with or at risk for neuronal injury remains challenging due to the controversial influence of volatile anesthetics on neuronal damage. We hypothesized that isoflurane, sevoflurane, and desflurane would exert variable degrees of neurotoxicity in vitro and in vivo via activation of the p75 neurotrophin receptor (p75^{NTR}).

METHODS: SH-SY5Y cells were exposed to oxygen–glucose deprivation (OGD, 16 hours), preceded or followed by incubation with isoflurane, sevoflurane, or desflurane (1.2 minimal alveolar concentration, 2 hours). Neuronal cell death was analyzed by flow cytometry (mitochondrial membrane potential, Annexin V/propidium iodide [AV/Pi]) and quantification of lactate dehydrogenase release. We analyzed NF-κB activity by DNA-binding ELISA and luciferase assay. The role of p75^{NTR} was studied using the p75^{NTR}-blocking peptide TAT-pep5 and siRNA knockdown. The effect of isoflurane ±p75^{NTR} inhibition on retinal ischemia-reperfusion injury (IRI) in adult Sprague-Dawley rats was assessed by analyzing retinal ganglion cell (RGC) density.

RESULTS: Isoflurane but not sevoflurane or desflurane postexposure aggravated OGD-induced neuronal cell death (AV/Pi positive cells: OGD 41.1% [39.0/43.3] versus OGD + isoflurane 48.5% [46.4/63.4], $P = 0.001$). Isoflurane significantly increased NF-κB DNA-binding and transcriptional activity of NF-κB (relative Luminescence Units: OGD 500 [499/637] versus OGD + isoflurane 1478 [1363/1643], $P = 0.001$). Pharmacological inhibition or siRNA knockdown of p75^{NTR} counteracted the aggravating effects of isoflurane. Isoflurane increased RGC damage in vivo (IRI 1479 RGC/mm^2 [1311/1697] versus IRI + isoflurane 1170 [1093/1211], $P = 0.03$), which was counteracted by p75^{NTR}-inhibition via TAT-pep5 ($P = 0.02$).

CONCLUSIONS: Isoflurane but not sevoflurane or desflurane postexposure aggravates neurotoxicity in preinjured neurons via activation of p75^{NTR} and NF-κB. These findings may have implications for the choice of volatile anesthetic being used in patients with or at risk for neuronal injury, specifically in patients with a stroke or history of stroke and in surgical procedures in which neuronal injury is likely to occur, such as cardiac surgery and neurovascular interventions. (Anesth Analg 2014;119:1429–41)

Neurotoksyczność

Pediatric Anesthesia 2007 17: 347–352

Midazolam does not reduce emergence delirium after sevoflurane anesthesia in children

CHRISTIAN RÖSCH, MANUELA PLATZER, HARO STETTNER

Summary

Background: Behavioral disturbance in children following sevoflurane anesthesia is a relatively frequent event. The aim of this study was to evaluate whether a higher dose of preoperatively administered midazolam compared with a lower would alleviate this. Furthermore the impact of these two doses at induction of anesthesia *Methods:*

doi:10.1111/j.1460-9592.2006.02101.x

Comparison of the Neuroapoptotic Properties of [illegible]potent Anesthetic Concentrations of Desflurane, or Sevoflurane in Neonatal Mice

Anesthesiology 2010; 112:567–75

Bumetanide Alleviates Epileptogenic and Neurotoxic Effects of Sevoflurane in Neonatal Rat Brain

David A. Edwards, M.D., Ph.D.,* Hina P. Shah, M.D.,† Wengang Cao, M.D.,‡ Nikolaus Gravenstein, M.D.,§ Christoph N. Seubert, M.D., Ph.D.,‖ Anatoly E. Martynyuk, Ph.D., D.Sc.#

ABSTRACT

Background: We tested the hypothesis that in newborn rats, sevoflurane may cause seizures, neurotoxicity, and impairment in synaptic plasticity—effects that may be diminished by the Na^+–K^+ $2Cl^-$ cotransporter 1 inhibitor, bumetanide.

Methods: Electroencephalography, activity, pocampal long-term potentiation 2.1% sevoflurane for

Results:

Anesthesiology 2010; 112:1404–16

Anesthetic Sevoflurane Causes Neurotoxicity Differently in Neonatal Naïve and Alzheimer Disease Transgenic Mice

Yan Lu, M.D., Ph.D.,* Xu Wu, M.D., Ph.D.,† Yuanlin Dong, M.D., M.S.,‡ Zhipeng Xu, M.[illegible] Yiying Zhang, M.D.,‖ Zhongcong Xie, M.D., Ph.D.#

ABSTRACT

Background: Recent studies have suggested that children undergoing surgery under anesthesia could be at an increased risk for the development of learning disabilities, but whether anesthetics contribute to this learning disability is unclear. Therefore, the authors set out to assess the effects of sevoflurane, the most commonly used inhalation anesthetic, on caspase activation, apoptosis, β-amyloid protein levels, and neuroinflammation in the brain tissues of neonatal naïve and Alzheimer disease (AD) transgenic mice.

Methods: Six-day-old naïve and AD transg Tg[amyloid precursor protein swe, PSEN1dE9]8 were treated with sevoflurane. The mice were kille of the anesthesia, and the brain tissues were harvest subjected to Western blot, immunocytochemistry, enz immunosorbent assay, and real-time polymerase chain

Results: Herein, the authors show for the first time tha rane anesthesia induced caspase activation and apoptosis amyloid precursor protein processing, and increased β-a protein levels in the brain tissues of neonatal mice. Further sevoflurane anesthesia led to a greater degree of neurotoxic the brain tissues of the AD transgenic mice when compared naïve mice and increased tumor necrosis factor-α levels in brain tissues of only the AD transgenic mice. Finally, inosi 1,4,5-trisphosphate receptor antagonist 2-aminoethoxydiph nyl borate attenuated sevoflurane-induced caspase-3 activation and β-amyloid protein accumulation *in vivo*.

Conclusion: These results suggest that sevoflurane may induce neurotoxicity in neonatal mice. AD transgenic mice could be more vulnerable to such neurotoxicity. These findings should promote more studies to determine the potential neurotoxicity of anesthesia in animals and humans, especially in children.

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ORIGINAL CONTRIBUTION

The Common Inhalational Anesthetic Sevoflurane Induces Apoptosis and Increases β-Amyloid Protein Levels

Yuanlin Dong, MD; Guohua Zhang, MD, PhD; Bin Zhang, MD; Robert D. Moir, PhD; Weiming Xia, PhD; Edward R. Marcantonio, MD; Deborah J. Culley, MD; Gregory Crosby, MD; Rudolph E. Tanzi, PhD; Zhongcong Xie, MD, PhD

Objective: To assess the effects of sevoflurane, the most commonly used inhalation anesthetic, on apoptosis and β-amyloid protein (Aβ) levels in vitro and in vivo.

Subjects: Naive mice, H4 human neuroglioma cells, and H[illegible] human neuroglioma cells stably transfected to express full-length amyloid precursor protein.

Interventions: Human H4 neuroglioma cells stably transfected to express full-length amyloid precursor protein were exposed to 4.1% sevoflurane for 6 hours. Mice received 2.5% sevoflurane for 2 hours. Caspase-3 activation, apoptosis, and Aβ levels were assessed.

Results: Sevoflurane induced apoptosis and elevated levels of β-site amyloid precursor protein–cleaving enzyme and Aβ in vitro and in vivo. The caspase inhibitor Z-VAD decreased the effects of sevoflurane on apoptosis and Aβ. Sevoflurane-induced caspase-3 activation was attenuated by the γ-secretase inhibitor L-685,458 and was potentiated by Aβ. These results suggest that sevoflurane induces caspase activation which, in turn, enhances β-site amyloid precursor protein–cleaving enzyme and Aβ levels. Increased Aβ levels then induce further rounds of apoptosis.

Conclusions: These results suggest that inhalational anesthetic sevoflurane may promote Alzheimer disease neuropathogenesis. If confirmed in human subjects, it may be prudent to caution against the use of sevoflurane as an anesthetic, especially in those suspected of possessing excessive levels of cerebral Aβ.

Arch Neurol. 2009;66(5):620-631

What We Al[illegible] about This Topic

[illegible]ras and programmed cell death [illegible]s

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[illegible] of respiratory irrita- [illegible]e sevoflurane one of [illegible], particularly in pe- [illegible]lurane, similar to reported to cause [illegible]ity and seizure- [illegible]nts in neonates [illegible]ause they may cognitive de- [illegible]e of neonatal [illegible]ons in mem- [illegible]eonatal rat brain in-

A Novel Mechanism for Sevoflurane Preconditioning-induced Neuroprotection

Neuroprotekcja

348 GENERAL ANESTHESIA

Sevoflurane improves the neuroendocrine stress response during laparoscopic pelvic surgery

[Le sévoflurane améliore la réaction neuro-endocrinienne au stress pendant une intervention chirurgicale laparoscopique pelvienne]

Elisabetta Marana MD,* Maria Giuseppina Annetta MD,* Francesco Meo MD,* Raffaella Parpaglioni MD,* Marina Galeone MD,* Maria Luisa Maussier MD,† Riccardo Marana MD‡

Purpose: Stress response to surgery is modulated by several factors, including magnitude of the injury, type of procedure (e.g., laparoscopy vs laparotomy) and type of anesthesia. Our purpose was to compare intra- and postoperative hormonal changes during isoflurane vs sevoflurane anesth... clinical model of well defined operative stress (laparos...

Method: In this prospective ra... requiring laparoscopic pelvic surg... either a standard isoflurane plu... plus fentanyl anesthesia (Grou... preoperatively, 30 min after th... surgery after extubation, and ... surgery. Intra- and postopera... epinephrine, adrenocortico... growth hormone (GH) and ...

Results: Catecholamine lev... in both groups. Nonetheles... showed a significant decre... vs B at the end of surgery: ... cortisol 45 ± 8 vs 23 ± ... ng·mL⁻¹; $P < 0.001$ for a... min after the beginning of ... at the end of surgery: 10 ... for both).

Conclusions: In the ... surgery, the type of vol... response; the change ... more favourable met... isoflurane.

Objectif : *La réaction au stress chirurgical dépend, entre autres, de l'importance du traumatisme chirurgical, du type d'intervention (laparoscopie vs laparotomie) et d'anesthésie. Nous voulions comparer les changements hormonaux pendant et après l'opération sous anesthésie à l'isoflurane, ou au sévoflurane, selon un modèle clinique bien défini de stress opératoire (intervention chirurgicale par laparo-... a été faite*

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Advance Access publication 22 October 2013 · doi:10.1093/bja/aet338

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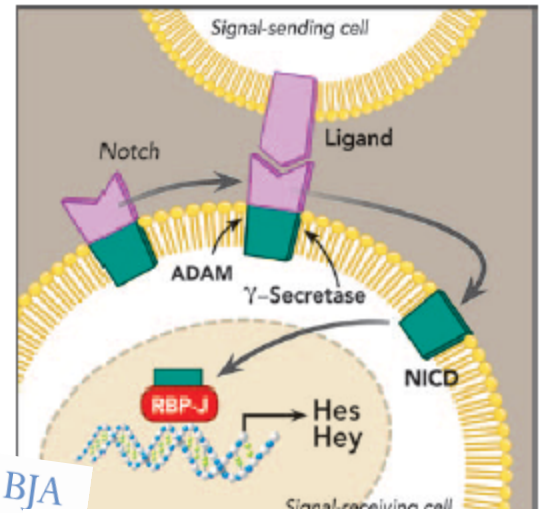

are subjected to two cleavages in series: first by a disintegrin and metalloproteinase and then by γ-secretase. This process ultimately produces the Notch intracellular domain (NICD) that then travels to the nucleus to associate with the DNA-binding protein (RBP-J). This complex regulates the expression of target proteins, such as Hes and Hey, that are transcription factors.[11,12] Thus, the Notch signaling pathway is unique because it does not require a separate intracellular signaling molecule to transmit the signaling to

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NEUROSCIENCES AND NEUROANAESTHESIA

Activation of K_2P channel–TREK1 mediates the neuroprotection induced by sevoflurane preconditioning

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Editor's key points

- Volatile anaesthetic preconditioning can provide protection from ischaemia–reperfusion injury.
- Sevoflurane preconditioning reduced cell death, infarct size, and neurological injury in cellular and animal models of neuronal ischaemia.
- Knockdown of TREK-1 reduced sevoflurane-induced neuroprotection, indicating a role for this

Background. Preconditioning with volatile anaesthetic agents induces tolerance to focal cerebral ischaemia, although the underlying mechanisms have not been clearly defined. The present study analyses whether TREK-1, a two-pore domain K^+ channel and target for volatile anaesthetics, plays a role in mediating neuroprotection by sevoflurane.

Methods. Differentiated SH-SY5Y cells were preconditioning with sevoflurane and challenged by oxygen–glucose deprivation (OGD). Cell viability and expression of caspase-3 and TREK-1 were evaluated. Rats that were preconditioned with sevoflurane were subjected to middle cerebral artery occlusion (MCAO), and the expression of TREK-1 protein and mRNA was analysed. Neurological scores were evaluated and infarction volume was examined.

Results. Sevoflurane preconditioning reduced cell death in differentiated SH-SY5Y cells challenged by OGD. Sevoflurane preconditioning reduced infarct volume and improved neurological outcome in rats subjected to MCAO. Sevoflurane preconditioning increased levels of TREK-1 mRNA and protein. Knockdown of TREK-1 significantly attenuated sevoflurane preconditioning-induced neuroprotective effects *in vitro* and *in vivo*.

Conclusions. Sevoflurane preconditioning-induced neuroprotective effects against transient cerebral ischaemic injuries involve TREK-1 channels. These results suggest a novel mechanism for sevoflurane preconditioning-induced tolerance to focal cerebral ischaemia.

Keywords: anaesthetics volatile, sevoflurane; brain, ischaemia; neuroprotection; preconditioning; TREK-1

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Anesthetics and Cerebral Protection in Patients Undergoing Carotid Endarterectomy

Miomir Jovic, MD, PhD,*† Dragana Unic-Stojanovic, MD,* Esma Isenovic, PhD,* Olivera Cekic, MD,* Nenad Ilijevski, MD, PhD,†‖ Srdjan P...

CEREBRAL ISCHEMIA/HYPOXIA may occur in a v... ety of perioperative circumstances. The main pathop... siologic aspects involved in cerebral ischemia/reperfusion i... caused by adenosine triphosphate (ATP) consumption, t... excitotoxic actions of glutamate, changes in ionic homeostasi... and formation of free radicals (Fig 1). Outcomes from suc... events range from subclinical neurocognitive deficits to cata... strophic neurologic morbidity or death.[1] Stroke is a severe... complication that occurs rarely, perioperatively, but when it ... happens, stroke is associated with a high mortality or results in ... serious disability. Also, because of limited options, stroke is ...

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Sevoflurane preconditioning-induced neuroprotection is associated with Akt activation via carboxy-terminal modulator protein inhibition

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Editor's key points

- The mechanisms by which sevoflurane preconditioning protects against cerebral ischaemia are unclear.
- In a rat model of focal cerebral ischaemia, sevoflurane preconditioning reduced infarct size and neurological dysfunction.
- The protective effect involved preservation of Akt signalling by down-regulation of an endogenous inhibitor.
- Identification of this inhibitor reveals a novel target for neuroprotective

Background. Sevoflurane preconditioning has a neuroprotective effect, but the underlying mechanism is not fully understood. The aim of the present investigation was to evaluate whether sevoflurane-induced cerebral preconditioning involves inhibition of carboxy-terminal modulator protein (CTMP), an endogenous inhibitor of Akt, in a rat model of focal cerebral ischaemia.

Methods. Male Sprague–Dawley rats were exposed to 2.7% sevoflurane for 45 min. One hour later, rats were subjected to 60 min of focal cerebral ischaemia. The phosphoinositide 3-kinase inhibitor wortmannin and LY294002 were administered 10 min before preconditioning. Rats in the sevoflurane preconditioning group received an intracerebroventricular injection of lentiviral vector U6-MCS-CTMP 3 days before ischaemia. Neurological deficits and infarct volumes were evaluated 24 h and 7 days after reperfusion. Phosphorylation of Akt, glycogen synthase kinase 3β (GSK3β), and expression of CTMP were determined at 1, 3, 12, and 24 h after reperfusion. Akt activity was measured at 3 h after reperfusion.

Results. Sevoflurane preconditioning improved neurological score and reduced infarct size at 24 h of reperfusion. Pretreatment with wortmannin or LY294002 attenuated these neuroprotective effects. Expression of CTMP correlated with reduced Akt activity after ischaemia, while sevoflurane preconditioning preserved Akt activity and increased phosphorylation of GSK3β. CTMP over-expression diminished the beneficial effects of sevoflurane preconditioning.

Conclusions. Activation of Akt signalling via inhibition of CTMP is involved in the mechanism of neuroprotection provided by sevoflurane preconditioning.

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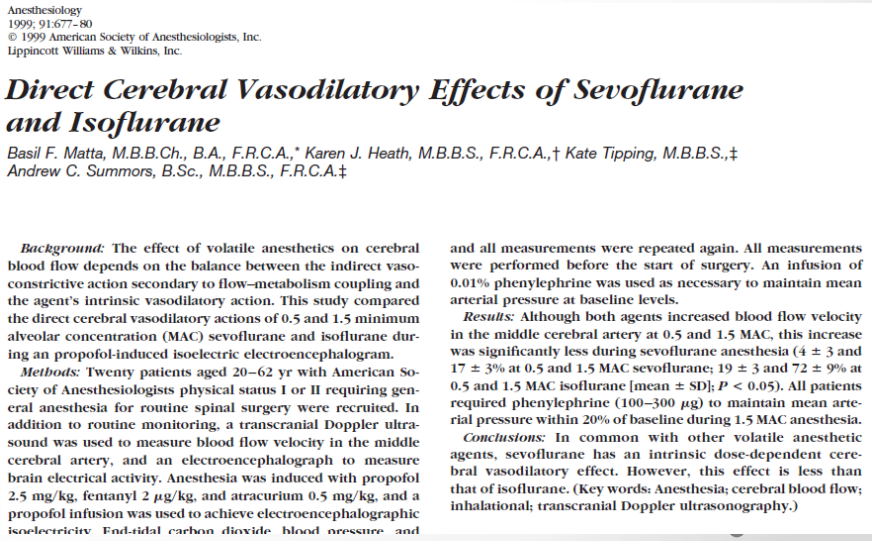
tne

Neuroprotekcja - mechanizmy

- ✓ modulacja perfuzji mózgowej
- ✓ stabilizacja autoregulacji naczyń mózgowych i odpowiedzi na zmiany CO_2
- ✓ stabilizacja i redukcja metabolizmy ośrodkowego układu nerwowego
- ✓ stabilizuje barierę krew-mózg i komórki nerwowe
- ✓ działanie przeciwzapalne
- ✓ hamuje aktywność enzymów
- ✓ hamuje apoptozę
- ✓ cykl kynureninowy
- ✓ mitochondrialne kanały potasowe K_{ATP}



Anesthesiology
1999; 91:677–80

Direct Cerebral Vasodilatory Effects of Sevoflurane and Isoflurane

Basil F. Matta, M.B.B.Ch., B.A., F.R.C.A.,* Karen J. Heath, M.B.B.S., F.R.C.A.,† Kate Tipping, M.B.B.S.,‡ Andrew C. Summors, B.Sc., M.B.B.S., F.R.C.A.‡

Background: The effect of volatile anesthetics on cerebral blood flow depends on the balance between the indirect vasoconstrictive action secondary to flow–metabolism coupling and the agent's intrinsic vasodilatory action. This study compared the direct cerebral vasodilatory actions of 0.5 and 1.5 minimum alveolar concentration (MAC) sevoflurane and isoflurane during an propofol-induced isoelectric electroencephalogram.

Methods: Twenty patients aged 20–62 yr with American Society of Anesthesiologists physical status I or II requiring general anesthesia for routine spinal surgery were recruited. In addition to routine monitoring, a transcranial Doppler ultrasound was used to measure blood flow velocity in the middle cerebral artery, and an electroencephalograph to measure brain electrical activity. Anesthesia was induced with propofol 2.5 mg/kg, fentanyl 2 μg/kg, and atracurium 0.5 mg/kg, and a propofol infusion was used to achieve electroencephalographic isoelectricity. End-tidal carbon dioxide, blood pressure, and all measurements were repeated again. All measurements were performed before the start of surgery. An infusion of 0.01% phenylephrine was used as necessary to maintain mean arterial pressure at baseline levels.

Results: Although both agents increased blood flow velocity in the middle cerebral artery at 0.5 and 1.5 MAC, this increase was significantly less during sevoflurane anesthesia (4 ± 3 and 17 ± 3% at 0.5 and 1.5 MAC sevoflurane; 19 ± 3 and 72 ± 9% at 0.5 and 1.5 MAC isoflurane [mean ± SD]; $P < 0.05$). All patients required phenylephrine (100–300 μg) to maintain mean arterial pressure within 20% of baseline during 1.5 MAC anesthesia.

Conclusions: In common with other volatile anesthetic agents, sevoflurane has an intrinsic dose-dependent cerebral vasodilatory effect. However, this effect is less than that of isoflurane. (Key words: Anesthesia; cerebral blood flow; inhalational; transcranial Doppler ultrasonography.)

Neuroprotekcja – perfuzja mózgowa

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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2004.00505.x

Effects of subanaesthetic and anaesthetic doses of sevoflurane on regional cerebral blood flow in healthy volunteers. A positron emission tomographic study

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[1]*Department of Neuroanaesthesiology,* [3]*Neurophysiology and* [2]*PET Centre, Aarhus University Hospital, Aarhus, Denmark*

Background: We tested the hypothesis that escalating drug concentrations of sevoflurane are associated with a significant decline of cerebral blood flow in regions subserving conscious brain activity, including specifically the thalamus.
Methods: Nine healthy human volunteers received three escalating doses using 0.4%, 0.7% and 2.0% end-tidal sevoflurane inhalation. During baseline and each of the three levels of anaesthesia one PET scan was performed after injection of $H_2^{15}O$. Cardiovascular and respiratory parameters were monitored and electroencephalography and bispectral index (BIS) were registered.
Results: Sevoflurane decreased the BIS values dose-dependently. No significant change in global cerebral blood flow (CBF) was observed. Increased regional CBF (rCBF) in the anterior cingulate (17–21%) and decreased rCBF in the cerebellum (18–35%) were identified at all three levels of sedation compared to baseline. Comparison between adjacent levels sevoflurane initially (0 vs. 0.2 MAC) decreased rCBF significantly in the inferior temporal cortex and the lingual gyrus. At the next level (0.2 MAC vs. 0.4 MAC) rCBF was increased in the middle temporal cortex and in the lingual gyrus, and decreased in the thalamus. At the last level (0.4 MAC vs. 1 MAC) the rCBF was increased in the insula and decreased in the posterior cingulate, the lingual gyrus, precuneus and in the frontal cortex.
Conclusion: At sevoflurane concentrations at 0.7% and 2.0% a significant decrease in relative rCBF was detected in the thalamus. Interestingly, some of the most profound changes in rCBF were observed in structures related to pain processing (anterior cingulate and insula).

Accepted for publication 17 June 2004

Key words: Anaesthesia; cerebral blood flow; PET; sevoflurane.

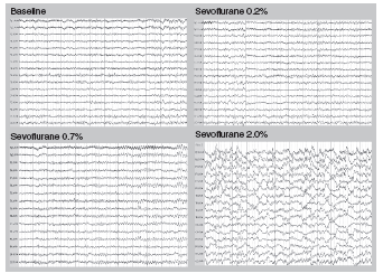
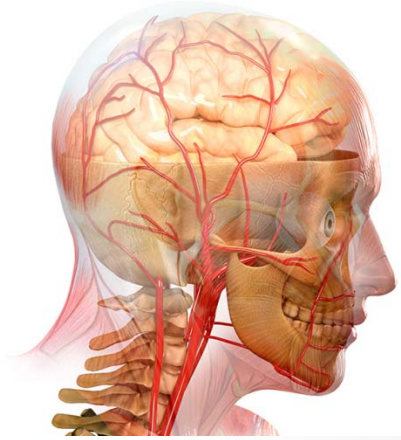


Fig. 1. Representative electroencephalographic (EEG) recordings from participants in different conditions of sedation levels.

Absolute cerebral blood flow
The mean absolute whole-brain CBF at each level of anaesthesia is summarized in Table 3. No significant changes were observed in global CBF during the three anaesthetic regimens compared to baseline.

Regional cerebral blood flow
Stereotactic coordinates of the areas of significant change of relative rCBF between the waking state and



orbital gyrus (22%), right inferior frontal gyrus (22%) and right precuneus 24%) (Table 4 and Figs 2 and 3).

Discussion

This study revealed that sevoflurane at ET concentrations of 0.4% to 2.0% caused no changes of global CBF, but produced significant regional changes that most likely represent the brain structures affected by sevoflurane in subanaesthetic and anaesthetic doses. Some of the most profound changes were observed in brain structures (anterior cingulate and insula) related to pain processing (23–25). When the volunteer's consciousness was slowly compromised a significant decrease in relative rCBF was observed in the thalamus.

Relative effects of sevoflurane on rCBF and gCBF
During all three anaesthetic regimens, a marked increase of relative rCBF occurred in the anterior cingulate, which is a critical location for maintenance of attention and which is activated during learning and selection of responses (26, 27). The anterior cingulate is also a main target of opioid receptor-binding ligands and the region most frequently reported active in pain studies (28). It has extensive connections

Neuroprotekcja – perfuzja mózgowa

- ✓ odmienność działania na różne struktury mózgu
- ✓ stabilizacja metabolizmy komórek nerwowych

Acta Anaesthesiol Scand 2010; **54**: 610–615
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2009.02181.x

Regional cerebral blood flow responses to hyperventilation during sevoflurane anaesthesia studied with PET

L. Schlünzen[1], M. S. Vafaee[2], N. Juul[1] and G. E. Cold[1]
[1]*Department of Neuroanaesthesiology and* [2]*PET Centre, Aarhus University Hospital, Aarhus, Denmark*

Background: Arterial carbon dioxide tension ($PaCO_2$) is an important factor controlling cerebral blood flow (CBF) in neurosurgical patients. It is still unclear whether the hypocapnia-induced decrease in CBF is a general effect on the brain or rather linked to specific brain regions. We evaluated the effects of hyperventilation on regional cerebral blood flow (rCBF) in healthy volunteers during sevoflurane anaesthesia measured with positron emission tomography (PET).
Methods: Eight human volunteers were anaesthetized with sevoflurane 1 MAC, while exposed to hyperventilation. During 1 MAC sevoflurane at normocapnia and 1 MAC sevoflurane at hypocapnia, one $H_2^{15}O$ scan was performed. Statistical parametric maps and conventional regions of interest analysis were used for estimating rCBF differences. vealed wide variations in CBF between regions. The greatest values of vascular responses during hypocapnia were observed in the thalamus, medial occipitotemporal gyrus, cerebellum, precuneus, putamen and insula regions. The lowest values were observed in the superior parietal lobe, middle and inferior frontal gyrus, middle and inferior temporal gyrus and precentral gyrus. No increases in rCBF were observed.
Conclusions: This study reports highly localized and specific changes in rCBF during hyperventilation in sevoflurane anaesthesia, with the most pronounced decreases in the sub cortical grey matter. Such regional heterogeneity of the cerebral vascular response should be considered in the assessment of cerebral perfusion reserve during hypocapnia.

Acta Anaesthesiol Scand 2006; **50**: 306–312
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2006.00954.x

Effects of dose-dependent levels of isoflurane on cerebral blood flow in healthy subjects studied using positron emission tomography

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Background: In this study, we tested the hypothesis that escalating drug concentrations of isoflurane are associated with a significant decline in cerebral blood flow (CBF) in regions sub-serving conscious brain activity, including specifically the thalamus.
Methods: Nine human volunteers received three escalating drug concentrations: 0.2, 0.4 and 1.0 MAC end-tidal inhalation. During waking, baseline and the three levels of sedation, a $H_2^{15}O$ PET scan was performed.
Results: Isoflurane decreased the bispectral index (BIS) values dose-dependently. Cardiovascular and respiratory parameters were maintained constant over time. No significant change in global CBF was observed. Throughout all three MAC levels of the insula and decreased in the thalamus, the cuneus and lingual gyrus. Compared with flow distribution in awake volunteers, 1 MAC of isoflurane significantly raised relative activity in the anterior cingulate and insula regions. In contrast, a significant relative flow reduction was identified in the thalamus, the cerebellum and lingual gyrus.
Conclusions: Isoflurane, like sevoflurane, induced characteristic flow redistribution at doses of 0.2–1.0 MAC. At 1 MAC of isoflurane, rCBF decreased in the thalamus. Specific areas affected by both isoflurane and sevoflurane included the anterior cingulate, insula regions, cerebellum, lingual gyrus and thalamus.

Neuroprotekcja – perfuzja mózgowa

Table 2

Coordinates of the pixels in which significant relative CBF changes were identified.

Region hypocapnia minus rest	Coordinate (*x*, *y*, *z*)	*t*-value	% change rCBF	Vascular response (%/mmHg)
Thalamus	−3, −14, 5	−9.1	−57	4.5
Cerebellum	20, −62, −17	−8.5	−53	4.1
Medial occipitotemporal gyrus	−24, −50, −15	−8.4	−53	4.1
Precuneus	4, −60, 21	−8.2	−52	4.1
Putamen	−17, 9, −11	−8.1	−51	4.0
Insula	−28, 13, −14	−8.1	−51	4.0
Brain stem	7, −23, −3	−8.0	−50	3.9
Lingual gyrus	0, −78, −2	−7.8	−49	3.8
Cingulate	3, −33, 47	−7.7	−48	3.8
Precentral gyrus	49, 12, 29	−7.0	−44	3.4
Middle temporal gyrus	49, −52, 15	−6.5	−41	3.2
Inferior temporal gyrus	−55, −50 −17	−6.4	−40	3.1
Inferior frontal gyrus	43, 46, 8	−6.3	−39	3.0
Middle frontal gyrus	44, 40, 23	−6.2	−39	3.0
Superior parietal lobe	13, −65, 50	−5.1	−32	2.5

Acta Anaesthesiol Scand 2010; **54**: 610–615
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2009.02181.x

Regional cerebral blood flow responses to hyperventilation during sevoflurane anaesthesia studied with PET

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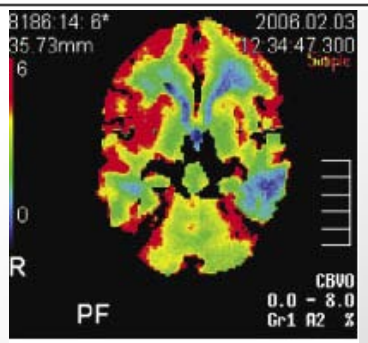
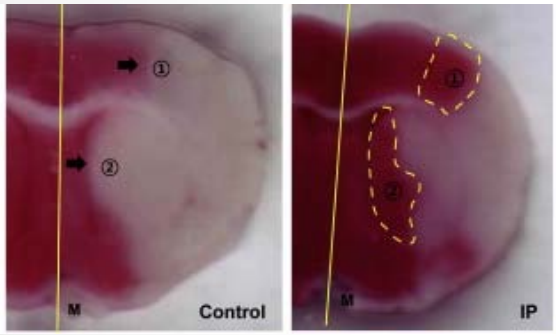
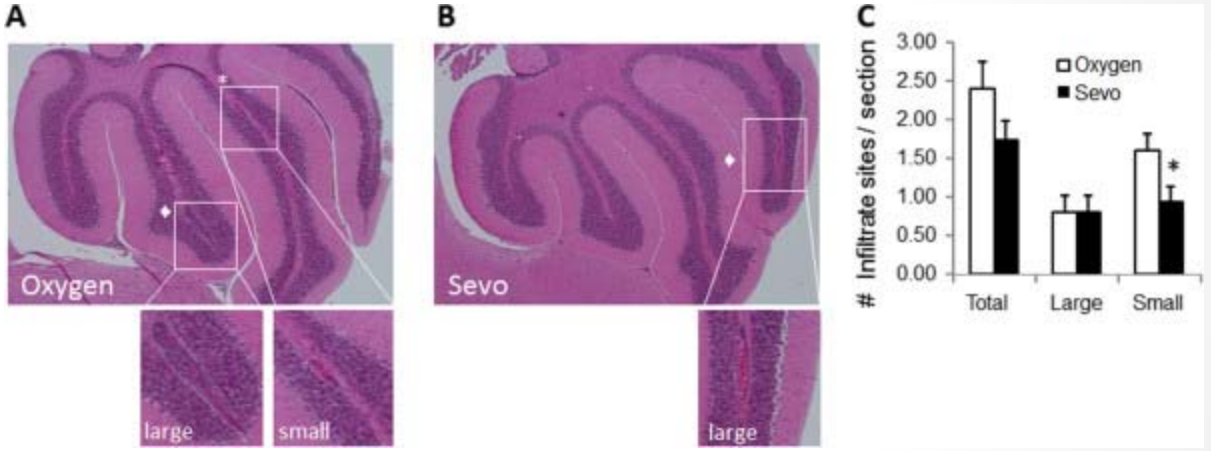
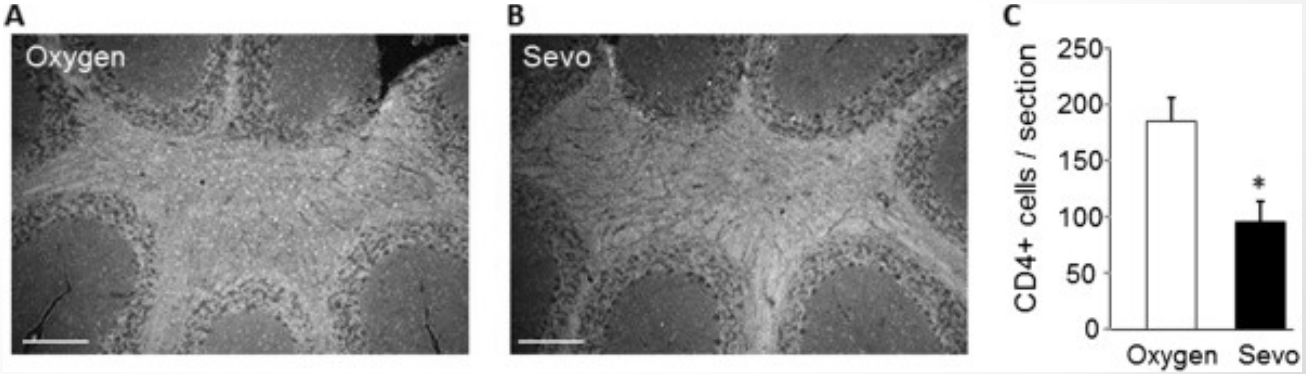


Neuroptotekcja – działanie przeciwzapalne

- ✓ hamowanie infiltracji limfocytów
- ✓ redukcja aktywności astrocytów i mikrogleju
- ✓ redukcja IFNγ



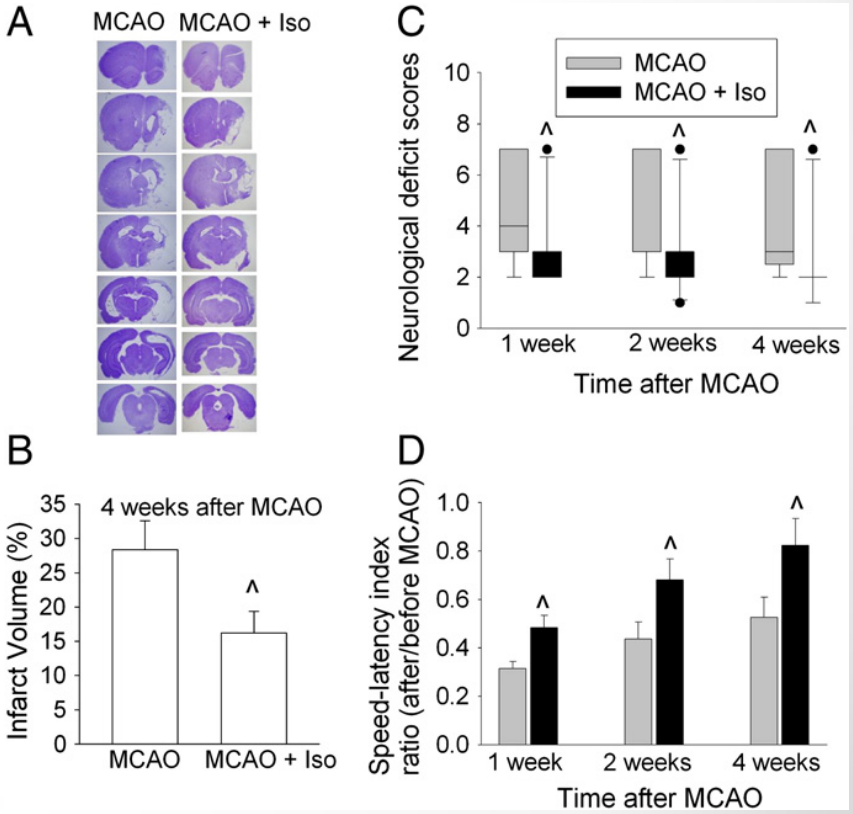




- Joo et al. Neuroscience 2013; 243: 149
  Polak et al. J Neuroinflammation 2012; 9: 272

Neuroptotekcja – działanie przeciwzapalne

- ✓ redukcja odpowiedzi zapalnej indukowanej SAH
- ✓ uszczelnienie bariery krew-mózg
- ✓ zmniejszenie infiltracji granulocytów
- ✓ hamowanie produkcji IL 1β
- ✓ uszczelnienie błon mitochondrialnych



Altay et al. Neurobiol Dis 2014; 62: 365
Altay et al. Stroke 2012; 43: 2513
Iadecola and Anrather. Nat Med. 2011, 17: 796
Lii and Zhuo. Neuroscience 2011; 199: 44

Neuroprototekcja - enzymy

Volatile Anesthetics Reduce Biochemical Markers of Brain Injury and Brain Magnesium Disorders in Patients Undergoing Coronary Artery Bypass Graft Surgery

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Jacek Pilat, MD, PhD,‡ Piotr Wacinski, MD, PhD,§ Edyta Kotlinska, MD, PhD,* Małgorzata Sztanke, MD, PhD,‖
Krzysztof Sztanke, PhD,‖ Krzysztof Stazka, MD,‖ and Kazimierz Pasternak, MD, PhD‖

Objectives: **Neuropsychological disorders are some of the most common complications of coronary artery bypass graft (CABG) surgery. The early diagnosis of postoperative brain damage is difficult and mainly based on the observation of specific brain injury markers. The aim of this study was to analyze the effects of volatile anesthesia (VA) on plasma total and ionized arteriovenous magnesium concentrations in the brain circulation (a-vtMg and a-viMg), plasma matrix metalloproteinase-9 (MMP-9), and glial fibrillary acidic protein (GFAP) in adult patients undergoing CABG surgery.**

Design: **An observational study.**

Setting: **The Department of Cardiac Surgery in a Medical University Hospital.**

Patients and Methods: **Studied parameters were measured in 92 patients undergoing CABG surgery with cardiopulmonary bypass (CPB) and divided into 2 groups: group O, patients who received opioid-based anesthesia; and group SEV, patients who received sevoflurane.**

Results: **Ninety-two patients were examined. CABG surgery increased MMP-9 and GFAP. The highest MMP-9, GFAP, and the most dramatic disorders in a-vtMg and a-viMg were noted in group O.**

Conclusions: **Cardiac surgery increased plasma MMP-9 and GFAP concentrations. Changes in MMP-9, GFAP, and arteriovenous tMg and iMg were significantly higher in group O. Volatile anesthetics, such as ISO or SEV, reduced plasma MMP-9, GFAP concentrations, and disturbances in a-vtMg and a-viMg.**

Applied Cardiopulmonary Pathophysiology 14: 139-148, 2010

Volatile anaesthetics reduce serum S100β concentrations in patients undergoing elective cardiac surgery

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[1]Department of Anaesthesiology, Intensive Therapy, Medical University of Lublin, Poland; [2]Department of Cardiac Surgery, Medical University of Lublin, Poland

Abstract

Background: The effect of volatile anaesthetics on plasma S100β protein has not been well-documented in cardiac surgery patients. The aim of the study was to analyse the effect of sevoflurane or isoflurane anaesthesia on plasma S100β concentration in patients undergoing elective, uncomplicated coronary artery bypass graft surgery.

Methods: One hundred thirty seven patients were prospectively randomized and allocated into three groups: A – patients, who didn't receive volatile anaesthetics, B – who received sevoflurane and C – who received isoflurane. S100β was measured during anaesthesia and postoperative days 1 and 2.

Results: In all patients, S100β increased during anaesthesia and at the postoperative day 1 and 2. In group A, S100β increased during anaesthesia and postoperative days 1 and 2 but in groups B and C only during anaesthesia. Plasma S100β concentrations were significantly higher in group A than in group B and C.

Conclusions: 1) cardiac surgery resulted in S100β elevation, 2) isoflurane and sevoflurane significantly reduced plasma S100β concentrations.

Li *et al. Molecular Brain* 2014, **7**:69
http://www.molecularbrain.com/content/7/1/69

Molecular Brain

RESEARCH Open Access

Sevoflurane preconditioning ameliorates neuronal deficits by inhibiting microglial MMP-9 expression after spinal cord ischemia/reperfusion in rats

Xiao-Qian Li, Xue-Zhao Cao, Jun Wang, Bo Fang, Wen-Fei Tan and Hong Ma*

Abstract

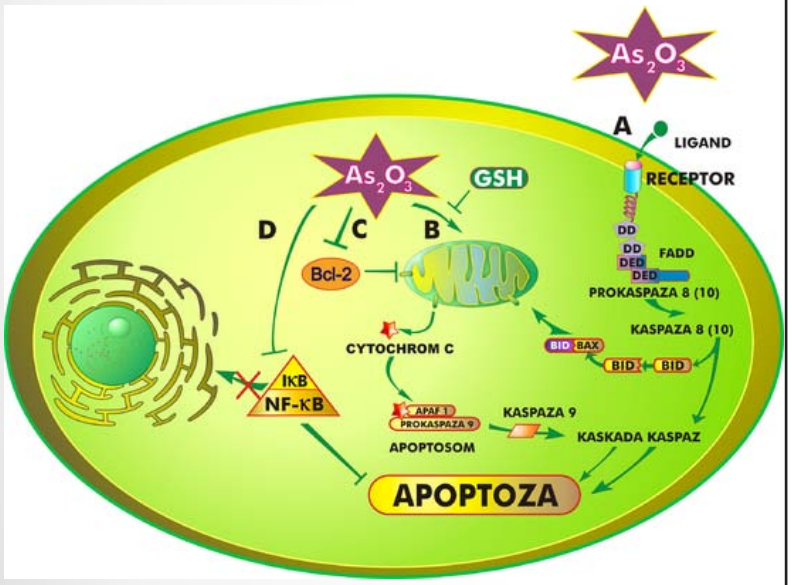
Background: Microglia are the primary immune cells of the spinal cord that are activated in response to ischemia/reperfusion (IR) injury and release various neurotrophic and/or neurotoxic factors to determine neuronal survival. Among them, matrix metalloproteinase-9 (MMP-9), which cleaves various components of the extracellular matrix in the basal lamina and functions as part of the blood spinal cord barrier (BSCB), is considered important for regulating inflammatory responses and microenvironmental homeostasis of the BSCB in the pathology of ischemia. Sevoflurane has been reported to protect against neuronal apoptosis during cerebral IR. However, the effects of sevoflurane preconditioning on spinal cord IR injury remain unclear. In this study, we investigated the role of sevoflurane on potential genetic roles of microglial MMP-9 in tight junction protein breakdown, opening of the BSCB, and subsequent recruitment of microglia to apoptotic spinal cord neurons.

Results: The results showed significant upregulation of MMP-9 in rats with IR-induced inflammation of the BSCB compared to that of the sham group, manifested as dysfunctional BSCB with increased Evans blue extravasation and reduced expression of occludin protein. Increased MMP-9 expression was also observed to facilitate invasion and migration of activated microglia, imaging as high Iba-1 expression, clustered to neurons in the injured spinal cord, as shown by double immunofluorescence, and increased proinflammatory chemokine production (CXCL10, CCL2). Further, sevoflurane preconditioning markedly improved motor function by ameliorating neuronal apoptosis, as shown by reduced TUNEL-positive cell counts and expression of cleaved caspase-3. These protective effects were probably responsible for downregulation of MMP-9 and maintenance of normal expression of occludin protein indicating BSCB integrity from inflammatory damage, which was confirmed by decreased protein levels of Iba-1 and MMP-9, as well as reduced production of proinflammatory chemokines (CXCL10, CCL2) and proinflammatory cytokines (IL-1β). Intrathecal injection of specific siRNAs targeting MMP-9 had similar protective effects to those of sevoflurane preconditioning.

Conclusions: Preconditioning with 2.4% sevoflurane attenuated spinal cord IR injury by inhibiting recruitment of microglia and secretion of MMP-9; thus inhibiting downstream effects on inflammatory damage to BSCB integrity and neuronal apoptosis.

Neuroprotekcja – enzymy

- ✓ poprawa funkcji motorycznych
- ✓ redukcja apoptozy
- ✓ redukcja aktywności MMP-9



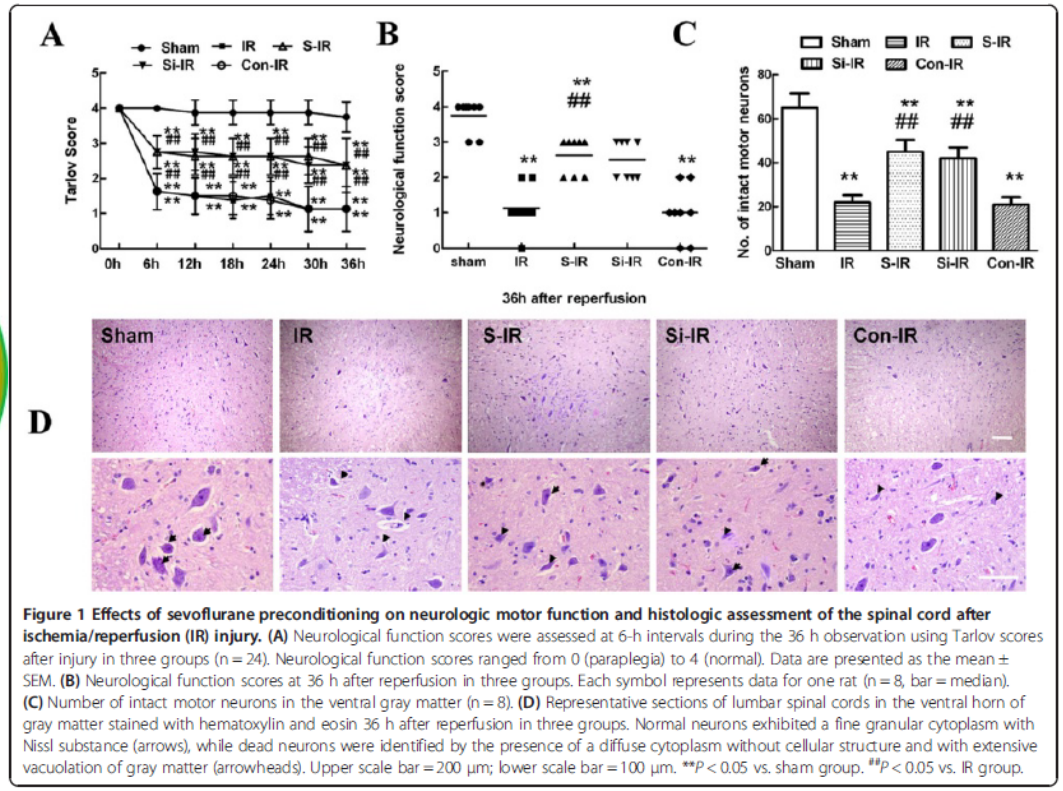


Figure 1 Effects of sevoflurane preconditioning on neurologic motor function and histologic assessment of the spinal cord after ischemia/reperfusion (IR) injury. (A) Neurological function scores were assessed at 6-h intervals during the 36 h observation using Tarlov scores after injury in three groups (n = 24). Neurological function scores ranged from 0 (paraplegia) to 4 (normal). Data are presented as the mean ± SEM. **(B)** Neurological function scores at 36 h after reperfusion in three groups. Each symbol represents data for one rat (n = 8, bar = median). **(C)** Number of intact motor neurons in the ventral gray matter (n = 8). **(D)** Representative sections of lumbar spinal cords in the ventral horn of gray matter stained with hematoxylin and eosin 36 h after reperfusion in three groups. Normal neurons exhibited a fine granular cytoplasm with Nissl substance (arrows), while dead neurons were identified by the presence of a diffuse cytoplasm without cellular structure and with extensive vacuolation of gray matter (arrowheads). Upper scale bar = 200 μm; lower scale bar = 100 μm. $^{**}P < 0.05$ vs. sham group. $^{\#\#}P < 0.05$ vs. IR group.

Li et al. Mol Brain 2014;7:69

Neuroprotekcja - apoptoza

- ✓ hamowanie aktywności enzymów proapoptotycznych

British Journal of Anaesthesia **114** (2): 327–35 (2015)
Advance Access publication 2 September 2014 · doi:10.1093/bja/aeu271

BJA

Sevoflurane preconditioning-induced neuroprotection is associated with Akt activation via carboxy-terminal modulator protein inhibition

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Editor's key points

- The mechanisms by which sevoflurane preconditioning protects against cerebral ischaemia are unclear.
- In a rat model of focal cerebral ischaemia, sevoflurane preconditioning reduced infarct size and neurological dysfunction.
- The protective effect involved preservation of Akt signalling by down-regulation of an endogenous inhibitor.
- Identification of this inhibitor reveals a novel target for neuroprotective drugs.

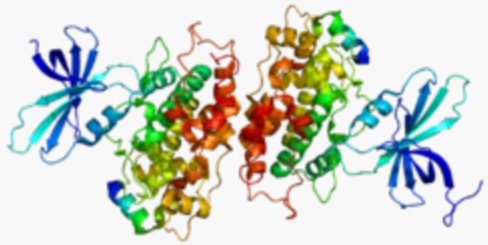
Background. Sevoflurane preconditioning has a neuroprotective effect, but the underlying mechanism is not fully understood. The aim of the present investigation was to evaluate whether sevoflurane-induced cerebral preconditioning involves inhibition of carboxy-terminal modulator protein (CTMP), an endogenous inhibitor of Akt, in a rat model of focal cerebral ischaemia.

Methods. Male Sprague–Dawley rats were exposed to 2.7% sevoflurane for 45 min. One hour later, rats were subjected to 60 min of focal cerebral ischaemia. The phosphoinositide 3-kinase inhibitors wortmannin and LY294002 were administered 10 min before preconditioning. Rats in the lentiviral transduction group received an intracerebroventricular injection of lentiviral vector Ubi-MCS-CTMP 3 days before ischaemia. Neurological deficits and infarct volumes were evaluated 24 h and 7 days after reperfusion. Phosphorylation of Akt, glycogen synthase kinase-3β (GSK3β), and expression of CTMP were determined at 1, 3, 12, and 24 h after reperfusion. Akt activity was measured at 3 h after reperfusion.

Results. Sevoflurane preconditioning improved neurological score and reduced infarct size at 24 h of reperfusion. Pretreatment with wortmannin or LY294002 attenuated these neuroprotective effects. Expression of CTMP correlated with reduced Akt activity after ischaemia, while sevoflurane preconditioning preserved Akt activity and increased phosphorylation of GSK3β. CTMP over-expression diminished the beneficial effects of sevoflurane preconditioning.

Conclusions. Activation of Akt signalling via inhibition of CTMP is involved in the mechanism of neuroprotection provided by sevoflurane preconditioning.

Glycogen synthase kinase 3 beta



Anesthesiology 2009; 110:1271–8

Sevoflurane Preconditioning against Focal Cerebral Ischemia

Inhibition of Apoptosis in the Face of Transient Improvement of Neurological Outcome

Jean-Laurent Codaccioni, M.D., Lionel J. Velly, M.D.,† Chahrazad Moubarik, Ph.D.,‡ Nicolas J. Bruder, M.D.,§ Pascale S. Pisano, Ph.D.,‖ Benjamin A. Guillet, Ph.D.#*

Background: Preconditioning the brain with volatile anesthetics seems to be a viable option for reducing ischemic cerebral injury. However, it is uncertain whether this preconditioning effect extends over a longer period of time. The purpose of this study was to determine if sevoflurane preconditioning offers durable neuroprotection against cerebral ischemia.

Methods: Rats (Sprague-Dawley) were randomly allocated to two groups: nonpreconditioned control group (n = 44) and preconditioned group (n = 45) exposed to 2.7 vol% sevoflurane (45 min) 60 min before surgery. Animals in both groups were anesthetized with 3.0vol% sevoflurane and subjected to transient middle cerebral artery occlusion. After 60 min of awake focal ischemia, the filament was removed. Functional neurologic outcome (range 0–18; 0 = no deficit), cerebral infarct size (Nissl staining), and apoptosis (Terminal deoxynucleotidyl transferase-mediated 2′-deoxyuridine 5′-triphosphate nick-end labeling; cleaved caspase-3 staining) were evaluated at 3, 7, and 14 days after ischemia.

Results: Sevoflurane preconditioning significantly improved functional outcome and reduced infarct volume (109 ± 43 *vs.* 148 ± 56 mm^3) 3 days after ischemia compared to the control group. However, after 7- and 14-day recovery periods, no significant differences were observed between groups. The number of apoptotic cells was significantly lower in the preconditioned group than in the control group after 3- and 7-day recovery periods. Fourteen days after ischemia, no differences

been shown to reduce *in vitro* hippocampal neuronal damage after hypoxia[5] and *in vivo* after global cerebral ischemia.[12] Most of these studies on cerebral APC have assessed histopathological and neurologic outcomes for a period of less than 7 days after injury. It is therefore uncertain whether this preconditioning effect extends over a longer period of time. As Kawaguchi *et al.*[13] reported in their study on the direct neuroprotection afforded by volatile anesthetics, the role of neuronal apoptosis is central in the pathogenesis of cerebral ischemia. This study shows that volatile anesthetics delayed but did not prevent neuronal apoptosis after focal cerebral ischemia. The effect of APC on neuronal apoptosis is still poorly explored. Only indirect effects have been reported by Zhao *et al.*[14] who showed during APC against neonatal hypoxic-ischemic brain injury an increase in expression of the antiapoptotic protein B-cell lymphoma-2.

In this context, we first studied the time-course of neuroprotection induced by sevoflurane preconditioning by using an *in vivo* model of transient focal cerebral

Neuroprotekcja – apoptoza

- ✓ stymulacja fosforylacji mitochondrialnego GSK-3β
- ✓ hamowanie aktywności kaspazy 3 i kaspazy 9

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Neuroprotection induced by sevoflurane-delayed post-conditioning is attributable to increased phosphorylation of mitochondrial GSK-3β through the PI3K/Akt survival pathway

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Apoptosis

ABSTRACT

Background and purpose: Post-conditioning with volatile anesthetics can create ischemic tolerance against cerebral ischemia–reperfusion injury. The present study was designed to determine whether delayed exposure to sevoflurane could induce ischemic tolerance and if this effect was dependent on increasing phosphorylated Akt-Ser473 and GSK-3β-Ser9 expression in the mitochondria, *via* a mechanism involving the PI3K/Akt pathway.
Methods: Adult male Sprague–Dawley rats were subjected to focal cerebral ischemia. Sevoflurane post-conditioning was achieved by administration of 2.5% sevoflurane for 60 min, 15 min after reperfusion. Phosphorylated Akt-Ser473 and GSK-3β-Ser9 in the cytosol and mitochondria of the ischemic penumbra were evaluated 4, 12, 24, and 72 h after reperfusion. Neurological deficit score and activity of caspase-3 and -9 were evaluated 24 and 72 h after reperfusion. Apoptosis, as measured by TUNEL staining and cerebral infarct size,was determined 24 h after reperfusion.
Results: Sevoflurane-delayed post-conditioning significantly increased levels of phosphorylated Akt-Ser473 and GSK-3β-Ser9 in the mitochondria and inhibited the activities of caspase-3 and -9, showing an improved neurological deficit score and a decreased infarct size. However, LY294002, a selective PI3K inhibitor, not only eliminated the neuroprotection of sevoflurane, as indicated by an increased infarct size and a larger number of TUNEL-positive cells, but also reversed the elevation of p-Akt and p-GSK-3β expression in the mitochondria induced by sevoflurane post-conditioning.
Conclusions: Our data suggested that delayed application of sevoflurane after reperfusion provides neuroprotection by activating phosphorylated Akt-Ser473 and GSK-3β-Ser9 in the mitochondria *via* the PI3K/Akt pathway.

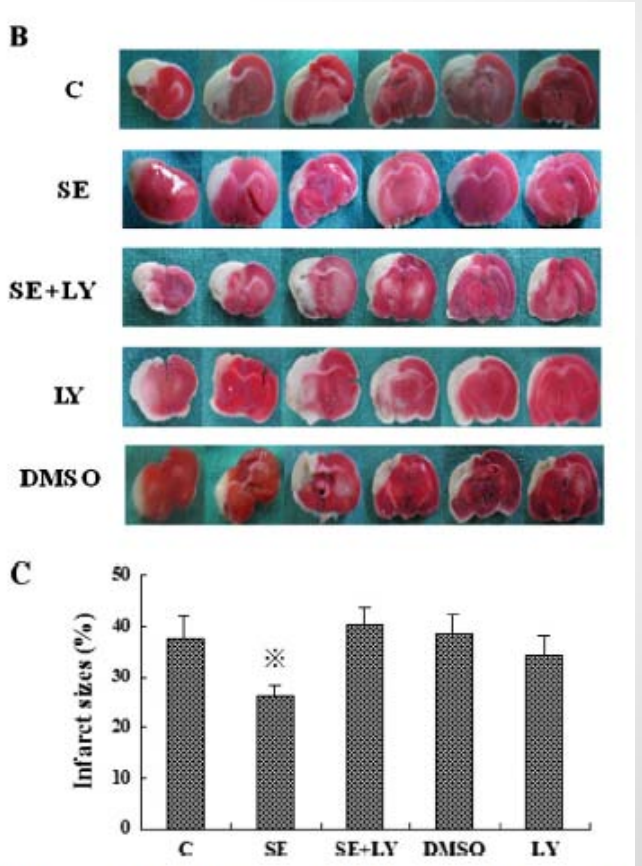

Fig. 1. Improvement of neurological outcome by sevoflurane-delayed post-conditioning after focal cerebral ischemia. A. Neurological deficit scores were evaluated immediately before the animals were sacrificed. ※$P < 0.05$, *vs.* control group. $n \geq 5$ for each group. B. Columns show representative TTC staining from rat brains. C. Graphs show infarct size measurements 24 h after stroke for each group ($n = 8$). Data are expressed as mean ± S.D. ※$P < 0.05$, *vs.* control group.

Qiu et al. BMC Anesthesiology (2015) 15:25
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BMC Anesthesiology

RESEARCH ARTICLE Open Access

Ne

Effect of apoptosis in neural stem cells treated with sevoflurane

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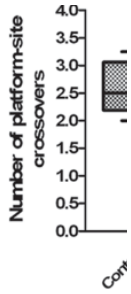


Jianlei Qiu[1,2], Pengcai Shi[3], Wude Mao[4], Yuyi Zhao[1], Wenshuai Liu[5] and Yuelan Wang[2,3*]

Abstract

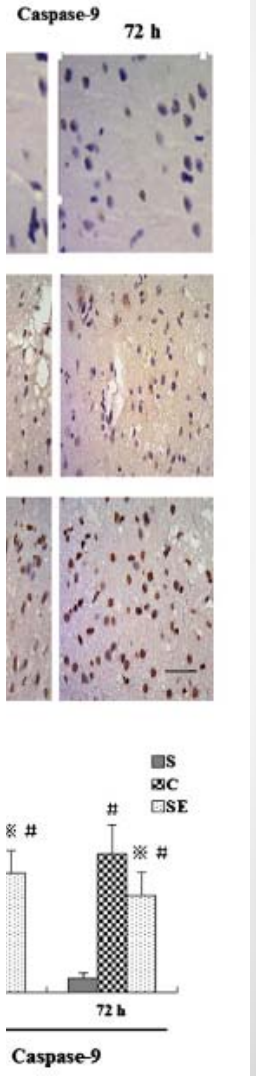
Background: At present, sevoflurane inhalation anesthesia used on infants is well-known. But long-time exposure to inhalation anesthetic could cause neurologic disorder, especially nerve degeneration in infant and developing brain. The central nervous system degeneration of infants could affect the memory and cognitive function. γ-Aminobutyric acid (GABA) is a known inhibitory neurotransmitter in central nervous system. Inhalation anesthetic sevoflurane may activate $GABA_A$ receptor to inhibit central nervous system, leading to apoptosis of neural degeneration, cognitive dysfunction in the critical period of brain development.

Methods: Neural stem cells were derived from Wistar embryos, cultured *in vitro*. Third generation of neural stem cells were randomly divided into four groups according to cultured suspension: Sevoflurane group (Group S), $GABA_A$ receptor antagonists, Bicuculline group (Group B), Sevoflurane + $GABA_A$ receptor antagonists, Bicuculline group (Group S + B), dimethyl sulphoxide (DMSO) group (Group D). Group B and Group D did not receive sevoflurane preconditioning. Group S and Group S + B were pretreated with 1 minimum alveolar concentration (MAC) sevoflurane for 0 h, 3 h, 6 h, and 12 h. Group S + B and Group B were pretreated with bicuculline (10 uM). Group D was treated with DMSO (10 uL/mL). After treatments above, all groups were cultured for 48 h. Then we measured the cells viability by Cell Counting Kit (CCK-8) assay, cytotoxicity by Lactate Dehydrogenase (LDH) assay, apoptosis ratio with Annexin V/propidium iodide (PI) staining by flow cytometry, and the expression of $GABA_AR$, anti-apoptotic protein Bcl-2, pro-apoptotic protein Bax and Caspase-3 by western blotting.

Results: After exposing to sevoflurane for 0 h, 3 h, 6 h, and 12 h with 1MAC, we found that cell viability obviously decreased and cytotoxicity increased in time-dependent way. And Annexin V/PI staining indicated increased apoptosis ratio by flow cytometry. The protein level of $GABA_A$ receptor, pro-apoptotic protein Bax and apoptosis protein Caspase-3 increased; while anti-apoptotic protein Bcl-2 decreased. And bicuculline could reverse all detrimental results caused by sevoflurane.

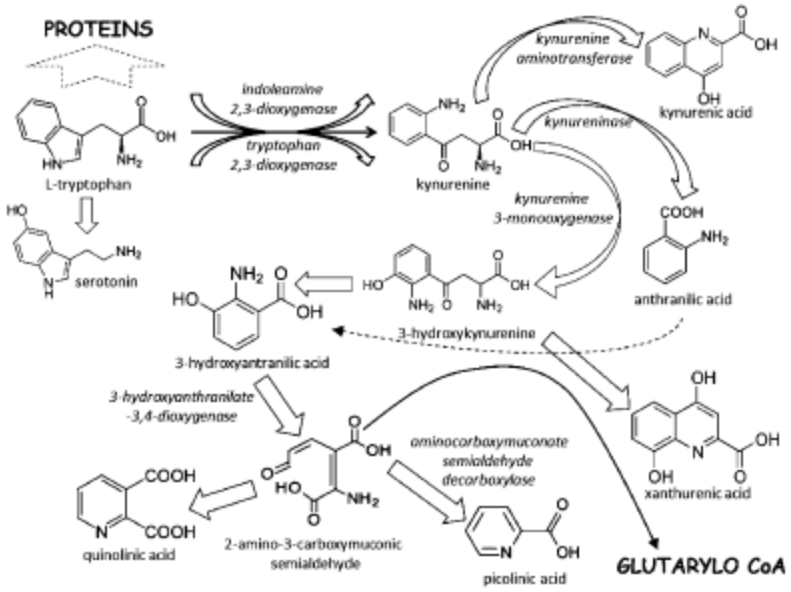
Conclusion: Sevoflurane can inhibit the central nervous system by activating $GABA_A$, resulting in apoptosis of neural stem cells, thus leading to the NSCs degeneration.

Keywords: Sevoflurane, γ-Aminobutyric acid, Apoptosis, Neural Stem Cells



Neuroptotekcja – cykl kynureninowy

Fig. 1 Kynurenine pathway



Arch. Immunol. Ther. Exp. (2015) 63:129–137
DOI 10.1007/s00005-014-0312-z

ORIGINAL ARTICLE

Plasma Kynurenic Acid Concentration in Patients Undergoing Cardiac Surgery: Effect of Anaesthesia

Edyta Kotlinska-Hasiec · Patrycja Nowicka-Stazka · Jolanta Parada-Turska · Krzysztof Stazka · Janusz Stazka · Przemyslaw Zadora · Wojciech Dabrowski

Received: 24 March 2014 / Accepted: 20 May 2014 / Published online: 10 September 2014

Abstract Increases in plasma kynurenic acid (KYNA) concentration relate to the severity of inflammation. The aim of this study was to analyse changes in plasma KYNA concentration and neutrophil/lymphocyte ratio (NLR) in cardiac surgery patients. Additionally, the effect of anaesthesia was analysed. Adult cardiac surgery patients under intravenous general anaesthesia were studied. Additionally, some patients received sevoflurane (SEV) prior to cardiopulmonary bypass. Plasma KYNA concentration and NLR were measured before anaesthesia, just after surgery and on postoperative days 1, 2 and 3. Patients were assigned to two groups: patients who did not receive SEV (NonSEV group) and patients who received SEV (SEV group). Forty-three patients were studied. Twenty-four of them received SEV. KYNA increased immediately after surgery and remained elevated through postoperative day 3 in the NonSEV group, whereas it was similar to the preoperative concentration in the SEV group. NLR increased immediately after surgery in both groups, and higher values were noted in the NonSEV group than in the SEV group at postoperative days 2 and 3. Plasma KYNA concentration correlated with NLR in the NonSEV group. Cardiac surgery caused an increase in NLR. Plasma KYNA increased in the NonSEV group and correlated with NLR. Administration of SEV inhibited the increase in KYNA, most likely due to its anti-inflammatory properties.

Keywords Kynurenic acid · Neutrophil/lymphocyte ratio · Sevoflurane · Cardiac surgery · General anaesthesia

Introduction

- ✓ hamuje produkcję kwasu kynureninowego
- ✓ zmniejsza stężenie kwasu kynureninowego we krwi

Neuroprotekcja – kanały potasowe

Table 1. Natural and chemical effectors of K_{2P} channels, remarkable features and interacting partners

Name	Activators	Inhibitors	Remarkable features	Interacting partners
TWIK1 K2P1.1[1]	Gi-coupled receptor-mediated trafficking to the cell surface[2]	Acid pHi[1] Protein kinase C[1]	Endosomal distribution[2]/ SUMO silencing[3] Dynamic ion selectivity[4] Heteromerization with other K_{2P}[5,6] Weak inward rectification[1]	EFA6/ARF6$_{GDP}$[7] SUMO ?[3]
TWIK2 K2P6.1[8–10]			Slow inactivation[10]	
KCNK7 K2P7.1[11]			No current[11]	
TREK1 K2P2.1[12]	NO[13] Copper[14] Gβγ[15] ML67-33[16] Substituted caffeate esters[17] Acid pHi[18,19] Volatile anesthetics (halothane, isoflurane, chloroform)[19,20] Mechanical stretch[19,21,22] PUFA[19,23,24] LP[25] Temperature[26,27] Riluzole[19,28]	Zinc[14] Acid pH$_o$[29] Fluoxetine[30] Spadin[31] G_s, G_q (protein kinase A, protein kinase C)[12,19]	Multiple unitary conductances[32,33] Alternative transcription initiation[34,35]	COP-I[36] PrP$_c$[37] AKAP150[38] Mtap2[39] Phospholipase D2[40]
TREK2 K2P10.1[19,24]	Acid pH$_o$[41] Gi[19]	Alkaline pHo[41] Fluoxetine[42]		
TRAAK1 K2P4.1[23]	Alkaline pHi[43]	Acid pH[41] Ruthenium Red[44]		
TASK1 K2P3.1[45]	Alkaline pH$_o$[45] Volatile anesthetics (halothane, isoflurane)[20,46]	Hypoxia[47] Copper[14] Zinc[14] Ruthenium Red[44] Acid pH$_o$[45,48,49] G_q[50] Sanshool[51]	Heteromerization TASK1/TASK3[44,52] No Cys bond in the cap[45,48,49] Dynamic ion selectivity[53] Relatively slow time-dependent activation[54,55]	p11[56] Syntaxin-8[57] 14.3-3[58,59] COP-I[58,59]
TASK3 K2P9.1[48,49]				
TASK5 K2P15.1[60,61]			No current[60,61]	
TASK2 K2P5.1[62] **TALK1** K2P16.1[66] **TALK2** K2P17.1[66]	Alkaline pHi[63] NO and reactive oxygen species[67] Alkaline pH$_o$[62,64]	Gβγ[65]	Relatively slow time-dependent activation[62]	
THIK1 K2P13.1[68]	Arachidonic acid[68]	Hypoxia[69] Halothane[68,70]	No pH sensitivity[68] ER retention[70,72] Heteromerization THIK1/THIK2[71]	
THIK2 K2P12.1[66,68]				
TRESK K2P18.1[73]	Volatile anesthetics[74] Calcium[75] Gq[75] Protein kinase C[76]	PUFA[73] Sanshool[51]	Asymmetrical gating behavior[75] No pH sensitivity in the physiological range[73]	14.3-3[77] Calcineurin[75] Tubulin[78]

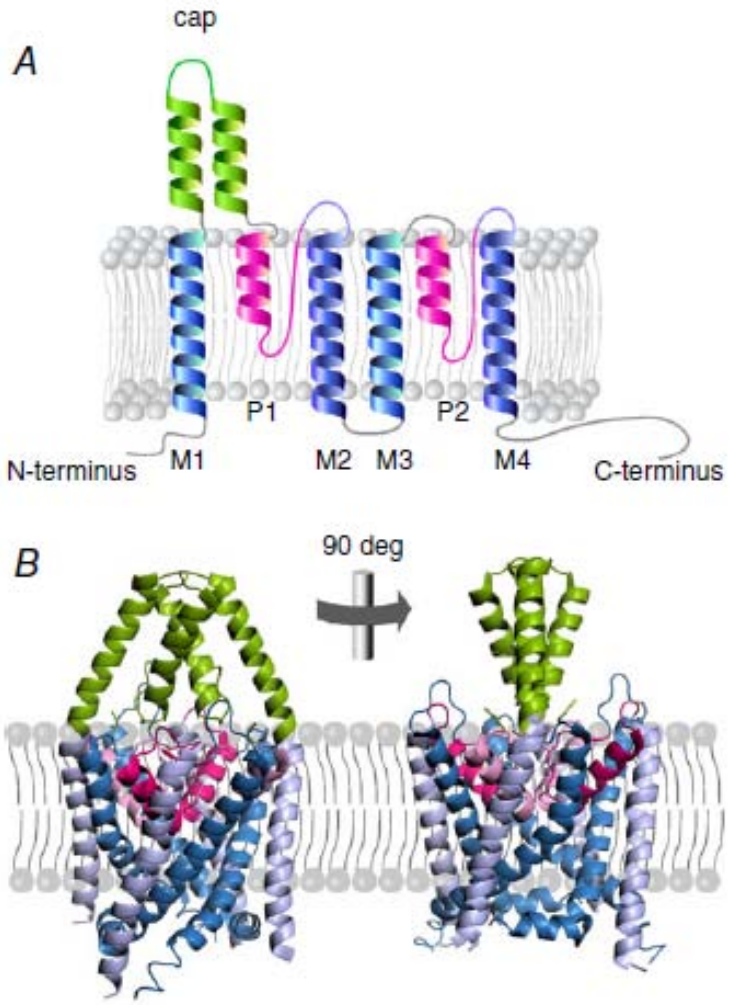


Table 2. Pathophysiologies of K_{2P} channels deduced from cell, and animal models and implications in human pathologies

Name	Physiology/Pathophysiology		Human pathologies	
TWIK1 K2P1.1[1]	Phosphate and water reabsorption in kidney[2]		Cancer?[3] Paradoxical depolarization of cardiomyocytes in hypokaliemia/arrythmia[4]	
TWIK2 K2P6.1[5–7]	Vascular[8] and pulmonary hypertension[9]			
KCNK7 K2P7.1[10]	No altered phenotype[11]			
TREK1 K2P2.1[12]	Cytoskeletal organization during neuronal morphogenesis[13] Depression[14] Neuroprotection[15] Integrity of blood-brain barrier[16] Vasodilatation[17,18]	Modulation of thermal and mechanical nociception, and hyperalgesia in inflammation conditions[19–21]	Cancer ?[22]	
TREK2 K2P10.1[23,24]				
TRAAK1 K2P4.1[25]	Brain metabolism[26]			
TASK1 K2P3.1[27]	Adrenal gland zonation[28] Modulation of auto-immune inflammation[29]	Aldosterone secretion[30–32] Proliferation/apoptosis[33]	Pulmonary arterial hypertension[34] Atrial fibrillation[35]	Cancer ?[36,37]
TASK3 K2P9.1[38,39]	Sleep mechanisms and cognitive functions[40] Neuronal migration during development[41] Depression[42]		Birk-Barel syndrome[43]	
TASK5 K2P15.1[44,45]				
TASK2 K2P5.1[46]	Bicarbonate reabsorption[47] Volume control in kidney proximal tubule[48] Volume regulation of T-cells[49] Central chemoreception[50]		Cancer ?[51]	
TALK1 K2P16.1[52]				
TALK2 K2P17.1[52]			Cardiac conduction disorder[53]	
THIK1 K2P13.1[54]				
THIK2 K2P12.1[52,54]				
TRESK K2P18.1[55]	Temperature nociception[56]		Migraine[57,58]	

J Physiol 0.0 (2015) pp 1–17

SYMPOSIUM REVIEW

The family of K_{2P} channels: salient structural and functional properties

Sylvain Feliciangeli, Frank C. Chatelain, Delphine Bichet and Florian Lesage

Neuroprotekcja

ORIGINAL ARTICLE

Comparison of intraoperative brain condition, hemodynamics and postoperative recovery between desflurane and sevoflurane in patients undergoing supratentorial craniotomy

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Arvind Chaturvedi,
Parmod Bithal,
Hari Hara Dash[1]

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ABSTRACT

Background: Post operative recovery has been reported to be faster with desflurane than sevoflurane anesthesia in previous studies. The use of desflurane is often criticized in neurosurgery due to the concerns of cerebral vasodilation and increase in ICP and studies comparing desflurane and sevoflurane in neurosurgey are scarce. So we compared the intraoperative brain condition, hemodynamics and postoperative recovery in patients undergoing elective supratentorial craniotomy receiving either desflurane or sevoflurane. **Materials and Methods**: Fifty three patients between 18-60yr undergoing elective supratentorial craniotomy receiving N_2O and oxygen (60%:40%) and 0.8-1.2 MAC of either desflurane or sevoflurane were randomized to group S (Sevoflurane) or group D (Desflurane). Subdural intra cranial pressure (ICP) was measured and brain condition was assessed.. Emergence time, tracheal extubation time and recovery time were recorded. Cognitive behavior was evaluated with Short Orientation Memory Concentration Test (SOMCT) and neurological outcome (at the time of discharge) was assessed using Glasgow Outcome Score (GOS) between the two groups. **Results**: The emergence time [Group D 7.4 ± 2.7 minutes vs. Group S 7.8 ± 3.7 minutes; P = 0.65], extubation time [Group D 11.8 ± 2.8 minutes vs. Group S 12.9 ± 4.9 minutes; P = 0.28] and recovery time [Group D 16.4 ± 2.6 minutes vs. Group S 17.1 ± 4.8 minutes; P = 0.50] were comparable between the two groups. There was no difference in ICP [Group D; 9.1 ± 4.3 mmHg vs. Group S; 10.9 ± 4.2 mmHg; P = 0.14] and brain condition between the two groups. Both groups had similar post-operative complications, hospital and ICU stay and GOS. **Conclusion**: In patients undergoing elective supratentorial craniotomy both sevoflurane and desflurane had similar intra-operative brain condition, hemodynamics and post operative recovery profile.

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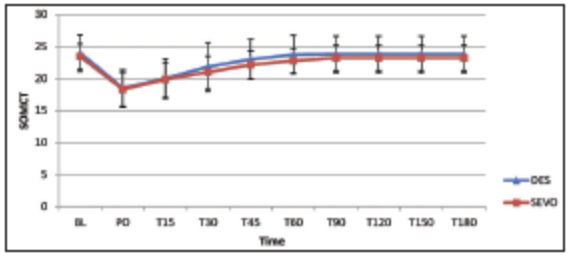


Figure 5: Short Orientation Memory Concentration Test score of the patients at different intervals. BL: Base line; PO: Baseline postoperative on Intensive care unit (ICU) admission; T15-T180: From 15 min of ICU admission to 180 min of ICU admission

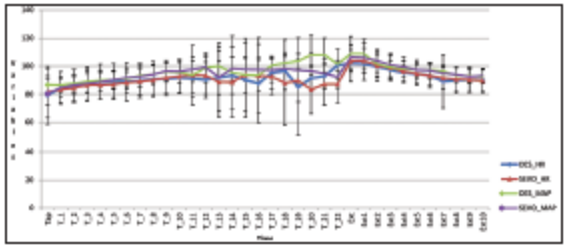


Figure 3: Figure showing heart rate and mean arterial pressure from tapering of inhalational agents till 10 min after extubation. Tap: Tapering of inhalational agents; T_1 to T_22: At 1 min interval from tapering of inhalational agents till extubation; Ext: At extubation; Ext1-Ext10: At 1 min interval from extubation till 10 min of extubation

Neuroprotekcja

Can J Anesth/J Can Anesth (2014) 61:347–356
DOI 10.1007/s12630-014-0118-9

EVIDENCE-BASED CLINICAL UPDATE

Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis

Comparaison entre propofol et agents volatils pour le maintien de l'anesthésie pendant les interventions de craniotomie non urgentes : revue méthodique et méta-analyse

Jason Chui, MBChB · Ramamani Mariappan, MD · Jigesh Mehta, MD · Pirjo Manninen, MD · Lashmi Venkatraghavan, MD

Received: 4 September 2013 / Accepted: 16 January 2014 / Published online: 31 January 2014

Abstract

Background *Both propofol and volatile anesthetics are commonly used for maintenance of anesthesia in patients undergoing neurosurgical procedures. The effects of these two classes of drugs on cerebral hemodynamics have been compared in many clinical trials The objectives of this review were to evaluate the cerebral he... effects, operative conditions, recovery profiles, ... operative complications, and neurological outcomes of ... fol-based vs volatile-based anesthesia for craniotomy.*

Methods *MEDLINE®, EMBASE™, Cochrane, and oth... relevant databases were searched for randomized control... trials that compared propofol-maintained anesthesia with volatile-maintained anesthesia in adult patients undergoing elective craniotomy. The primary outcome measure was the intraoperative brain relaxation score. Secondary outcome measures inc... (intracranial p... [CPP]), cardio... postoperative co... (neurological morbi... analysis was conduc... compare the outcomes ...*

Results *Fourteen studi... criteria and were analyze... similar between the two ... however, ICP was lower (n... 5.2 mmHg; 95% confidence i... was higher (weighted mean ... 95% confidence interval 12.2 ... received propofol-maintained ane... complicati... and recovery profiles ... the two groups, except for postope... and vomiting being less frequent with pr... maintained anesthesia. There were inadequate data to perform a meta-analysis on clinical outcome.*

Conclusion *Propofol-maintained and volatile-maintained anesthesia were associated with similar brain relaxation scores, although mean ICP values were lower and CPP values higher with propofol-maintained anesthesia. There are inadequate data to compare clinically significant outcomes such as neurological morbidity or mortality.*

1819 Patients

This article is accompanied by an editorial. Please see Can J Anesth 2014; 61: this issue.

Author contributions *Jason Chui, Ramamani Mariappan, Mehta Jigesh, Pirjo Manninen, and Lashmi Venkatraghavan* helped conduct the study and write the manuscript.

Electronic supplementary material The online version of this article (doi:10.1007/s12630-014-0118-9) contains supplementary

A Combination of Mild Hypothermia and Sevoflurane Affords Long-Term Protection in a Modified Neonatal Mouse Model of C...rebral Hypoxia-Ischemia

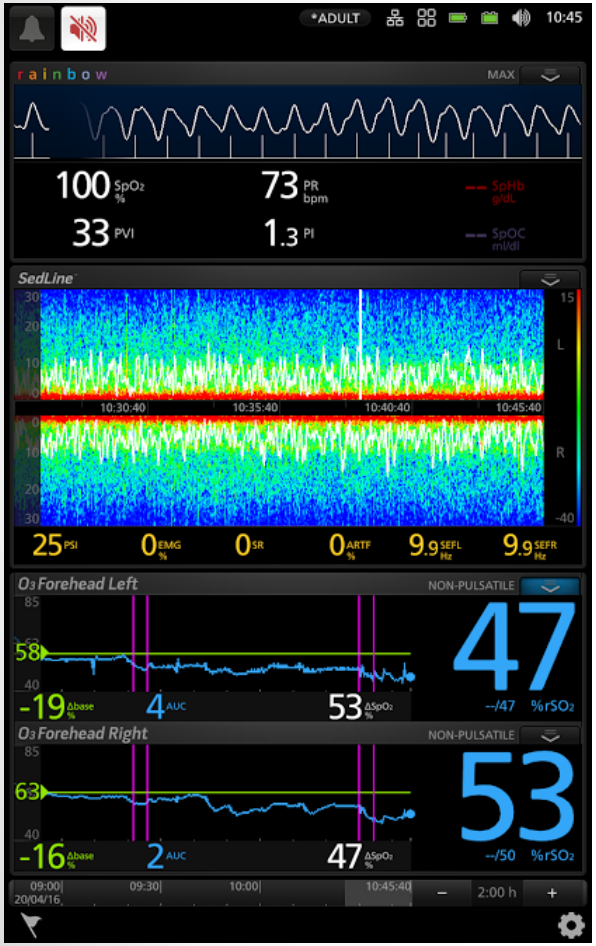
Erica P. Lin, MD,*†§ Li... ...abeth A. Hughes, BS,* John C. McCann, BS,* Charles V. Vorhe... ...ffe, MD, MBA,*†§ and Andreas W. Loepke, MD, PhD*†§

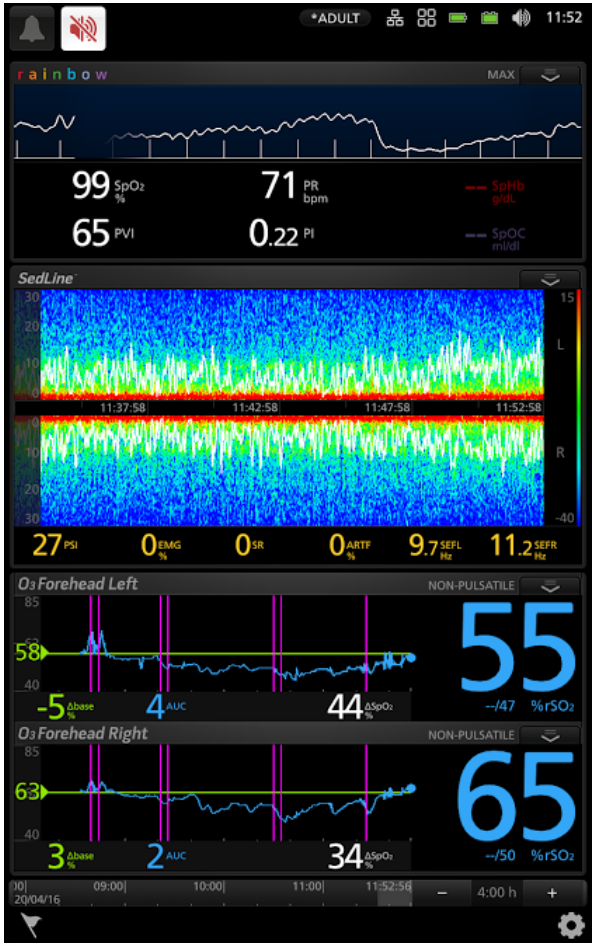
... hypoxia-ischemia (HI) can lead to life-long impairment, ...hort-term but not long-term protection has been dem- ... brain ischemia model (RVM) by volatile anesthetic ...ring HI has not been tested. In the current study, we ... mild hypothermia as a protective approach during ...ntubation and mechanical ventilation to the RVM. ...s ligated in 10-day-old mice during brief sevoflu- ...th the dam. Littermates were then randomized ... for 60 minutes (the classical RVM); HI-Protect ...d mechanical ventilation with 3.5% sevoflurane ... spontaneously breathing room air for 60 minutes. In ...ration was monitored in the area at risk and the contralat- ...rotect using visible-light spectroscopy (Spectros Corp). Mean ...d heart rate were measured. Arterial blood gases were obtained. ...pheric weight ratios and brain damage scores were determined 1 week ...er group, learning and behavior were assessed in young adulthood (9 weeks) ...aneous locomotion, Morris water maze, and apomorphine injection.

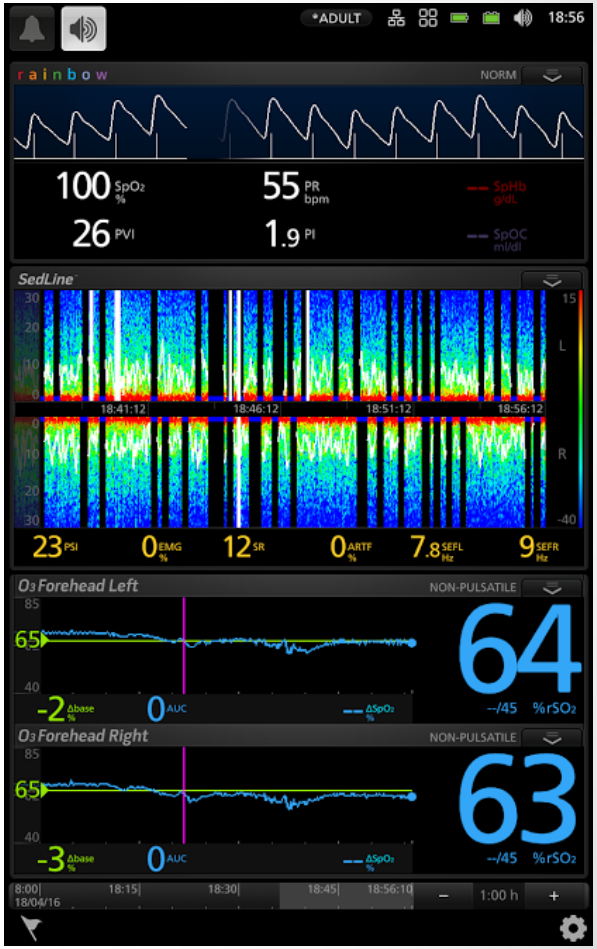
RESULTS: During HI, ipsilateral and contralateral brain oxygenation, arterial blood pressures, blood gases, and glucose levels were similar in both ischemic groups, while heart rate was slower in the HI-Protect group. One week after ischemia, brain hemispheric weight ratios and injury scores in several brain regions were significantly worse after HI, compared with HI-Protect. Nine weeks after HI, Morris water maze hidden platform and reversal platform escape latencies, measures of spatial memory function, were superior after HI-Protect, compared with HI ($P < 0.0001$). HI-Protect animals demonstrated significantly less circling behavior after an apomorphine challenge ($P < 0.0001$), a measure of striatal integrity.

CONCLUSIONS: To test the neuroprotective effects of volatile anesthetics during neonatal brain ischemia, we developed a modification of the RVM. By using mechanical ventilation and endotracheal intubation, sevoflurane administration during HI was survivable. The combination of sevoflurane administration and mild hypothermia during HI conferred not only short-term structural, but also long-term functional protection, compared with littermates treated according to the RVM. These findings warrant further studies to improve neurological outcome in critically ill infants. (Anesth Analg 2014;119:1158–73)

Przykłady zmian obserwowanych technologią SeTLine w trakcie znieczulenia do operacji z użyciem krążenia pozaustrojowego







Materiał pokazany za zgodą dr n. med. Michała Kowalczyka
Katedra i I Klinika Anestezjologii i Intensywnej Terapii UM w Lublinie

Działanie przeciwzapalne

- ✓ hamowanie ekspresji genów
- ✓ wewnątrzkomórkowe IkappaBalpha oraz GSK3β i cykl AKT/GSK3β
- ✓ mitochondrialne K^+_{ATP}
- ✓ hamowanie uwalniania cytokin min z makrofagów
- ✓ stymulacja produkcji NO
- ✓ hamowanie funkcji neutrofili (P-selektyna i ICAM-1)
- ✓ zmniejszenie produkcji ROS przez aktywowane neutrofile (hamowanie oksydazy NADPH i kinazy białka C)
- ✓ hamowanie aktywności komórek *NK*
- ✓ hamowanie uwalniania IFN-γ z limfocytów, apoptoza limfocytów
- ✓ cykl przemian tryptofanu – kwas kynureninowy

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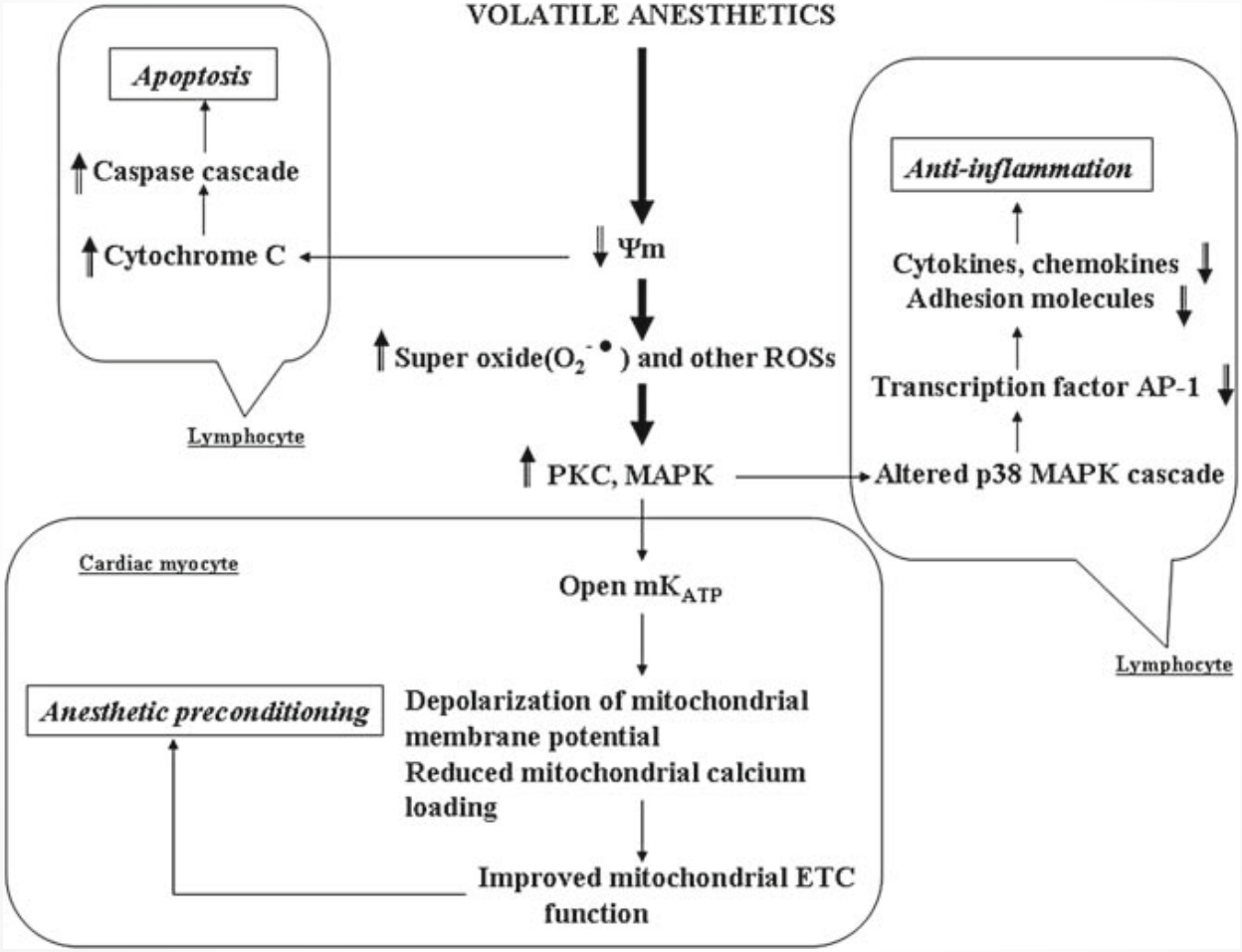
Watanabe et al. Br J Anaesth 2013; 110: 637
Kotlinska-Hasiec et al. Arch Immunol Ther Exp 2014; article in press

Działanie przeciwzapalne

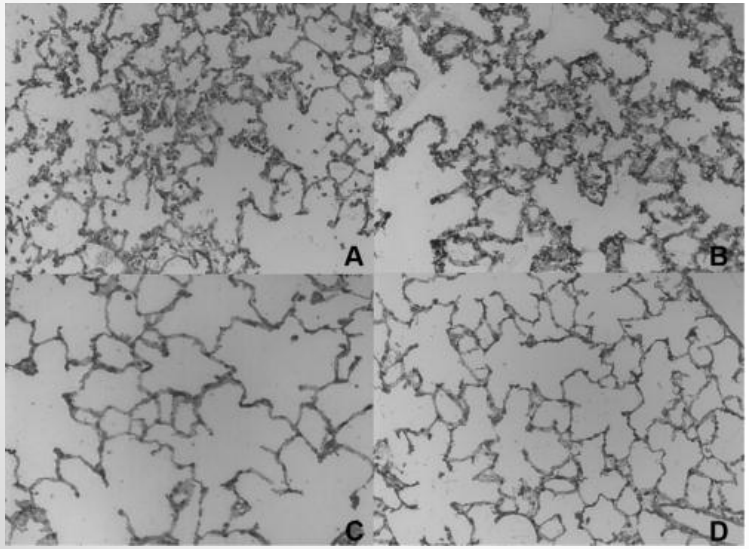


Kurosawa S and Kato M. J Anesth 2008; 22: 263

Układ oddechowy – badania eksperymentalne

- ✓ przepuszczalność naczyń płucnych
- ✓ metabolizm

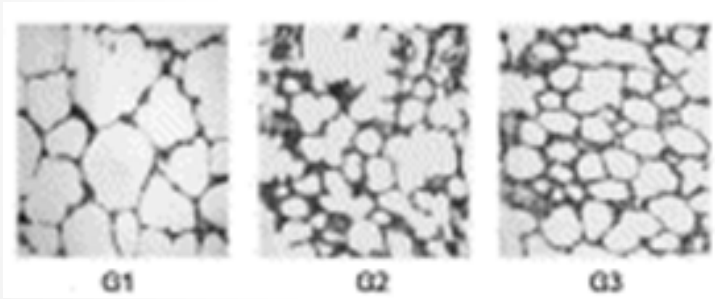
Li et al. Asian Pac J Trop Med 2014; 7: 276



Voigtsberger et al. Anaesthesiology 2009; 111: 1238

Układ oddechowy – badania eksperymentalne

- ✓ spadek stężenia neutrofili
  a surfaktancie pęcherzyków płucr
- ✓ długotrwała sztuczna wentylacja p



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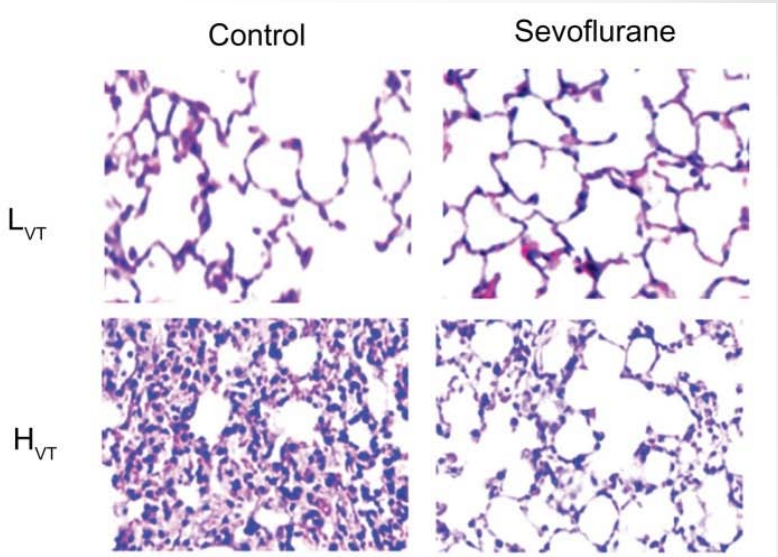
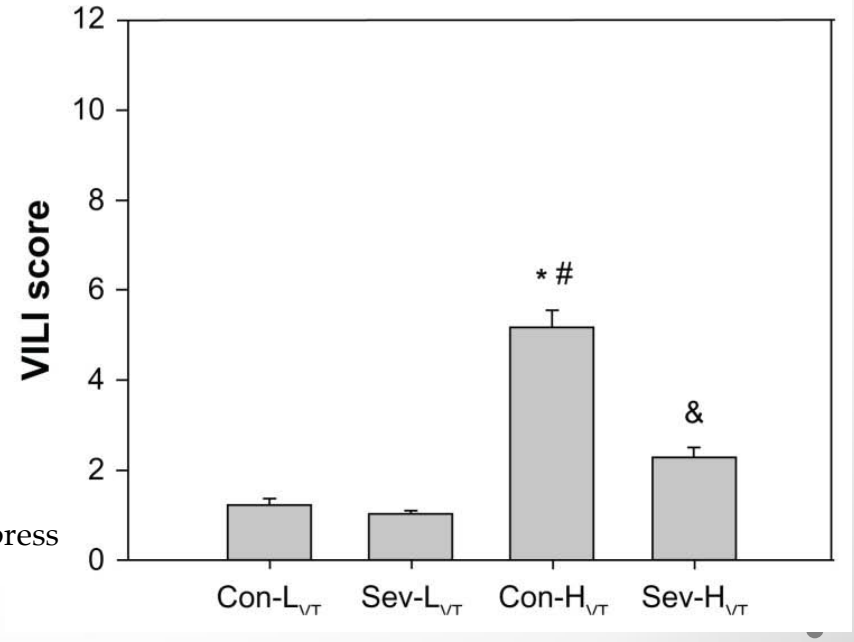
doi: 10.1016/j.pupt.2013.12.005.





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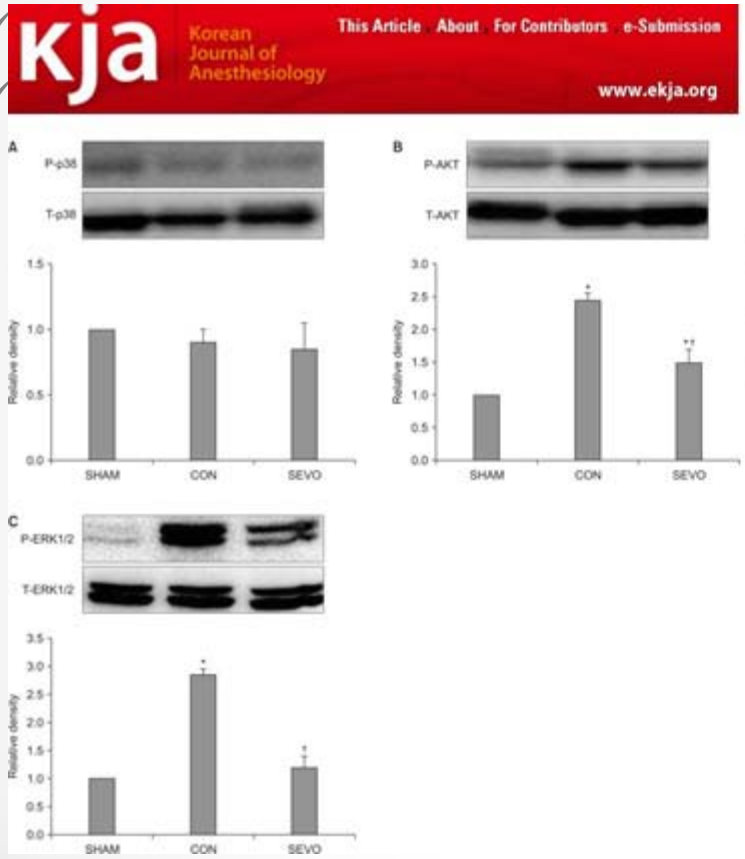
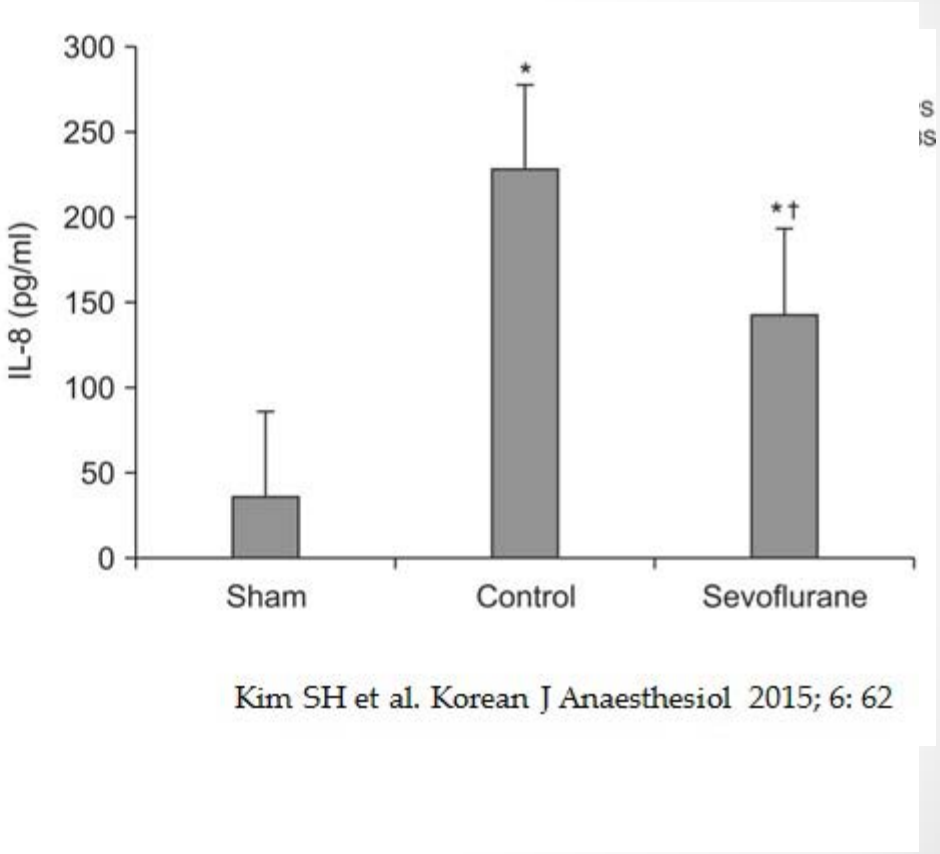
Xiong et al. Int J Nanomedicine 2013; 6: 1075
Somg et al. Asian Pac J Trop Med. 2013; 6: 53

Układ oddechowy – badania eksperymentalne





Kim SH et al. Korean J Anaesthesiol 2015; 6: 62

Układ oddechowy – badania eksperymentalne

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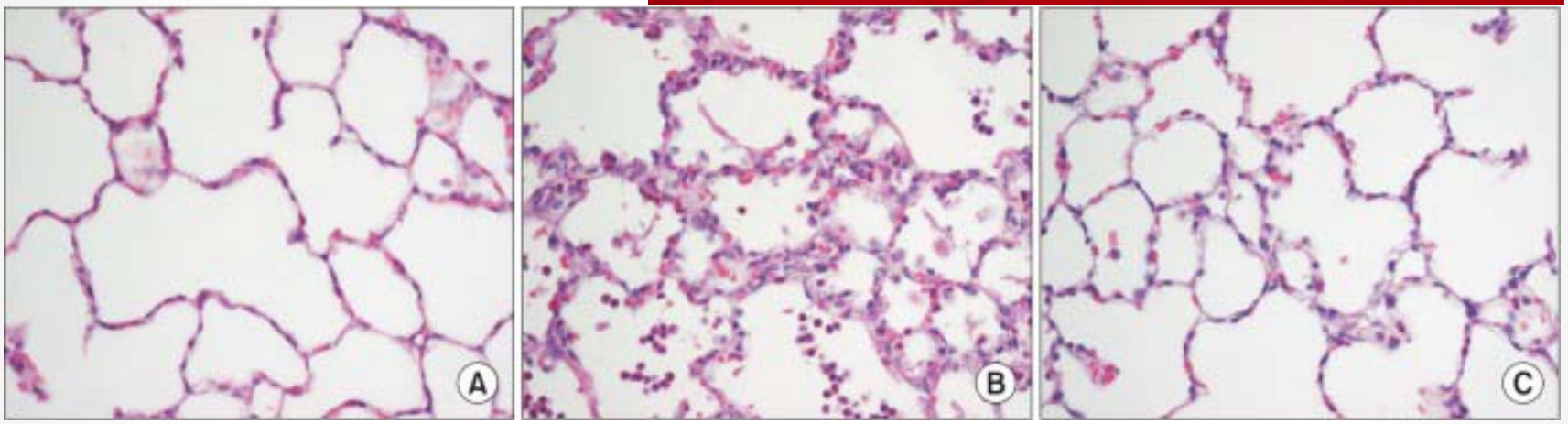
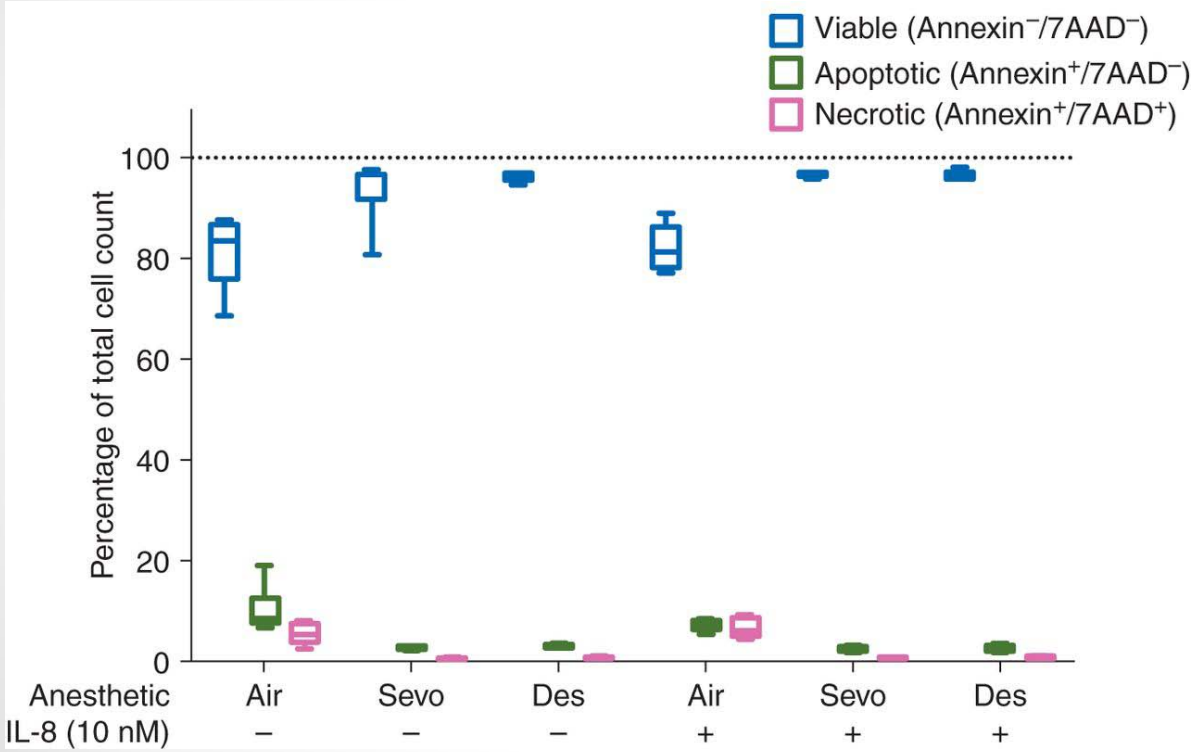
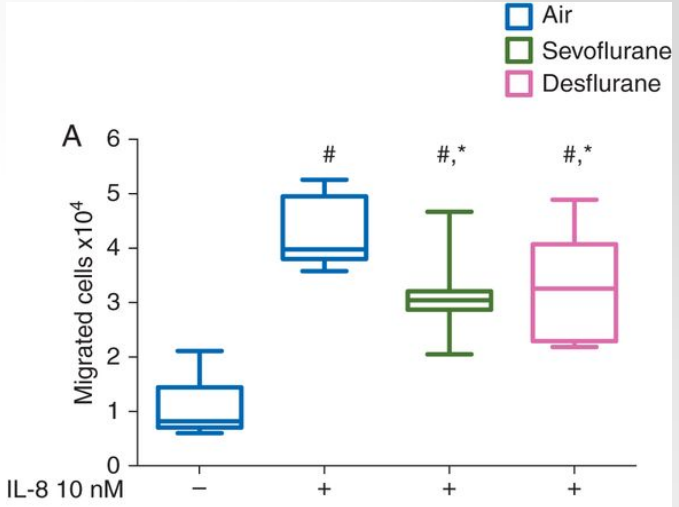


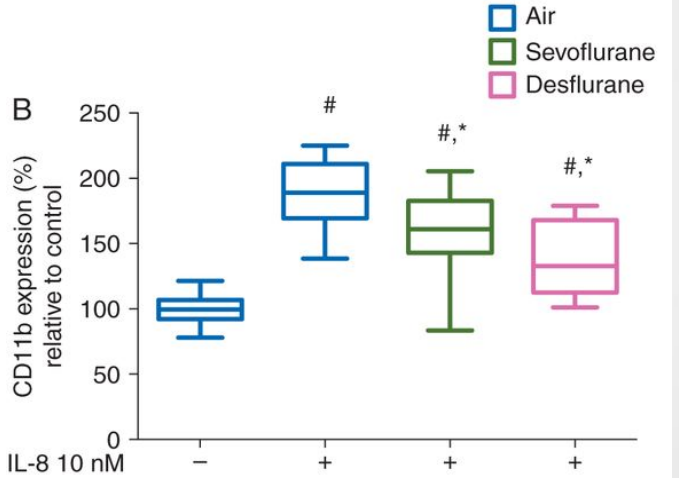
A – grupa kontrolna, B zapalenie płuc, C – zapalenie płuc + sewofluran

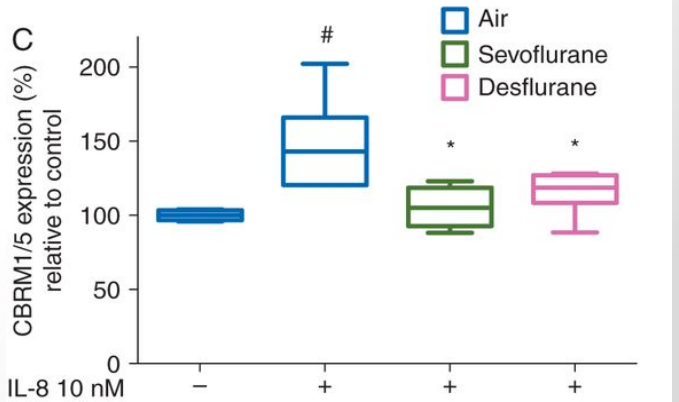
Kim SH et al. Korean J Anaesthesiol 2015; 6: 62

Układ oddechowy









Müller-Edenborm B et al. Br J Anesth 2015; 114: 143

BJA British Journal of Anaesthesia

Układ oddechowy – badania kliniczne

- ✓ stężenie cytokin prozapalnych a wentylacja jednego płuca

Comparison of inflammatory indicators and lung function parameters in the two patient groups.

Index	Group	T0	T1	T2	T3	T4	T5
TNF-α	S	15±3	18±5	27±6b	38±11ab	39±9ab	18±4
(pg/ml)	P	14±3	16±4	25±5b	27±9b	29±8b	15±4
IL-6	S	12±2	15±4	23±6b	31±9b	32±8b	16±5
(pg/ml)	P	12±3	14±3	20±7b	28±8b	30±7b	15±4
IL-10	S	18±4	20±5	25±7b	27±9ab	30±8ab	20±7
(pg/ml)	P	19±4	22±6	27±7b	35±8b	37±8b	22±7
PA-aDO2	S	24±2	221±30b	437±53ab	246±34ab	232±29b	27±3
(mmHg)	P	23±2	212±26b	385±43b	220±31b	215±27b	25±2
Qs/Qt	S	9.2±1.8	11.5±2.3	26.7±4.2ab	15.6±2.5b	14.2±2.3	9.8±2.2
(%)	P	8.9±1.7	10.2±1.8	18.3±3.7b	13.1±1.9	12.5±2.1	9.5±2.3

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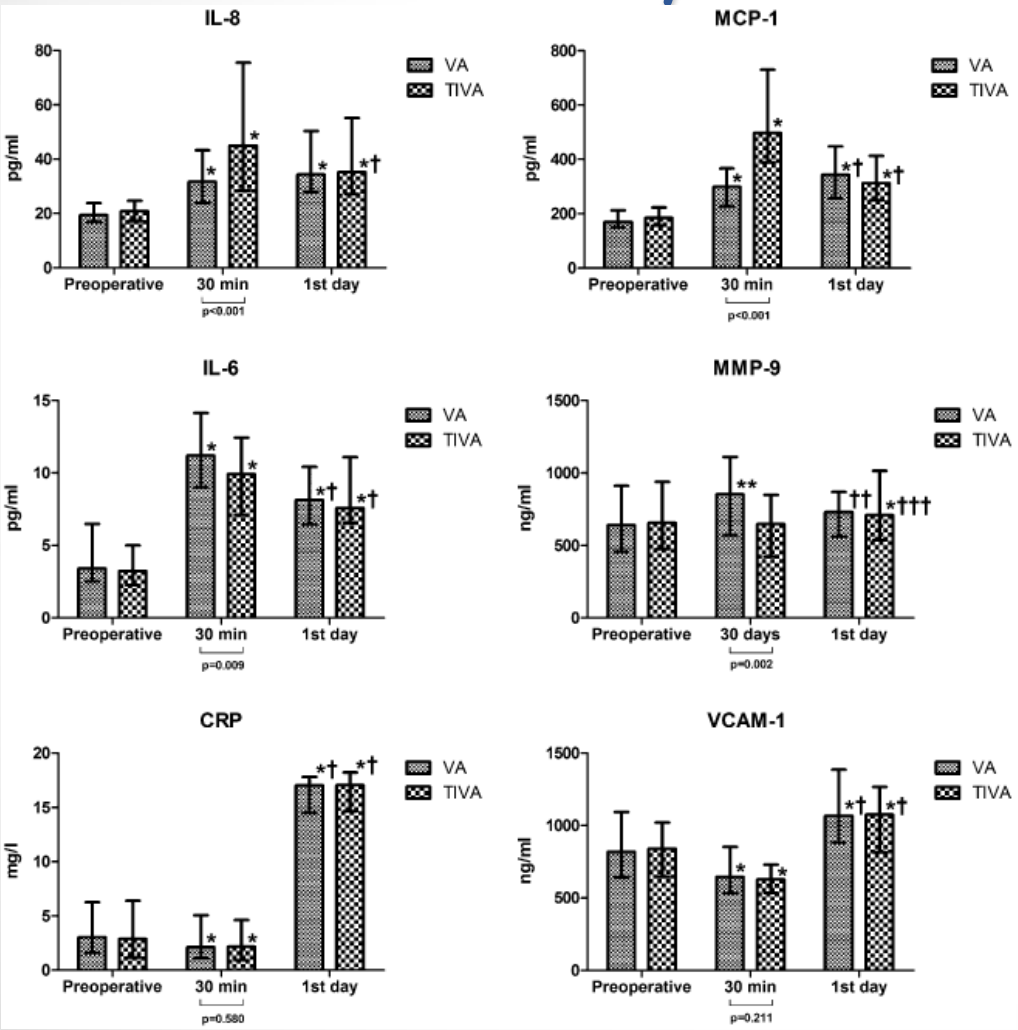
Układ oddechowy – badania kliniczne



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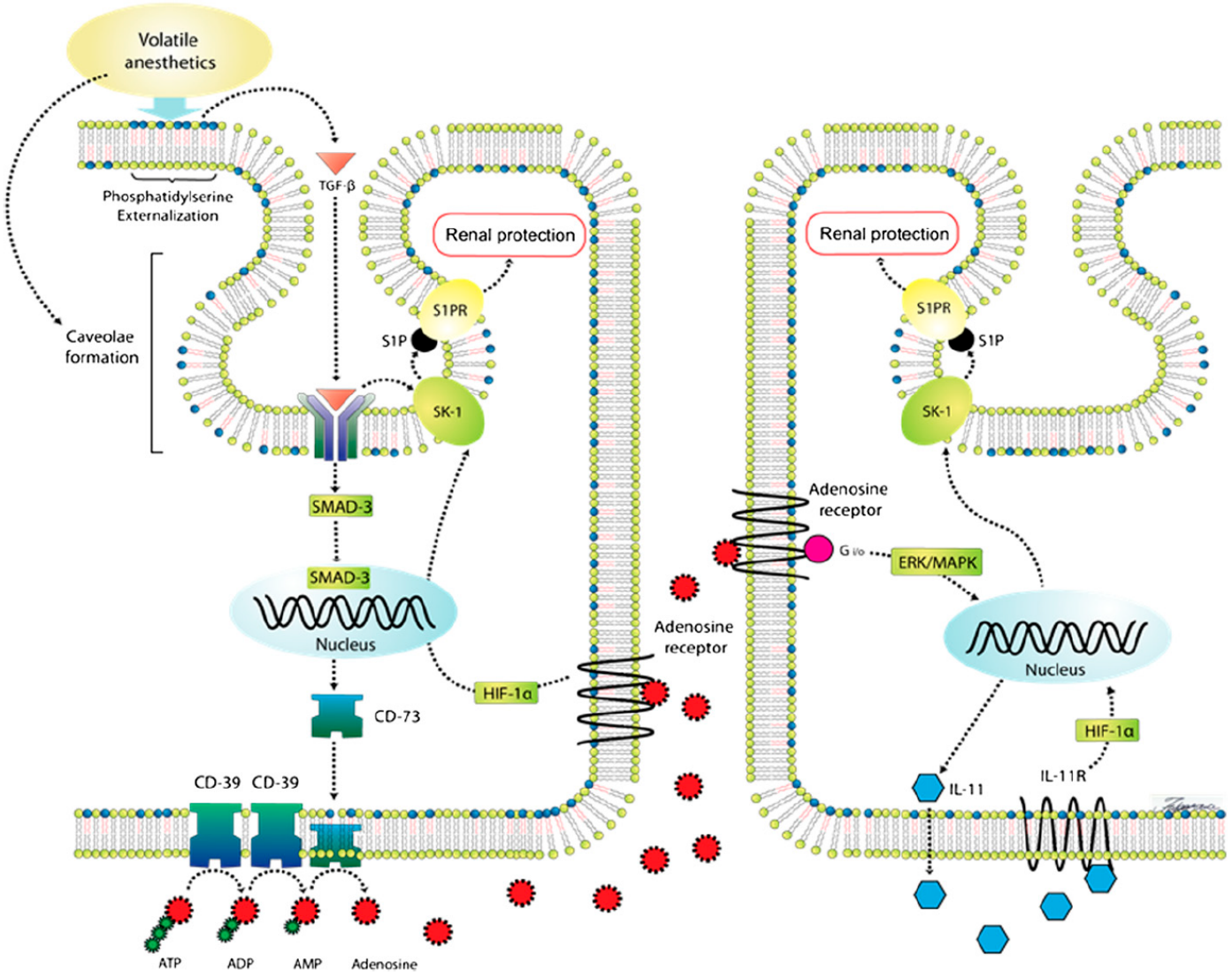

Figure 3. Proposed renal protection mechanisms of volatile anesthetics. Volatile anesthetics interact with the plasma membrane lipid bilayer in renal tubular cells and induce phosphatidylserine externalization and TGF-β1 generation. Volatile anesthetics also increase the formation of caveolae/caveolin lipid rafts in the buoyant fractions of the renal tubular plasma membranes and facilitate caveolae sequestration of several cytoprotective signaling intermediates (*e.g.*, SK-1, TGF-β1 receptors, and S1P). TGF-β1 generated by volatile anesthetics binds to the TGF-β1 receptor, leading to translocation of SMAD-3 to the nucleus to increase the expression of renal tubular CD73. Increased CD73 expression subsequently increases renal tubular adenosine generation. Activation of renal tubular and perhaps endothelial ARs increases SK-1 protein expression *via* induction of HIF-1α transcription factor. In addition, activation of A_1 ARs increases renal tubular IL-11 synthesis *via* ERK-MAPK activation. Finally, IL-11 also induces SK-1 generation *via* the HIF-1α pathway. CD, cluster of differentiation; ERK-MAPK: extracellular signal–regulated kinase mitogen-activated protein kinase; Gi/o, inhibitory regulative G protein; IL-11R, IL-11 receptor; S1PR, S1P receptor.