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Organoprotective Properties of Argon (Review)

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Органопротективные свойства аргона (обзор)

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Summary

The history of studying the organoprotective properties of argon (Ar) began in 1998 when a group of Russian researchers investigated the effect of hypoxic gas mixtures on mammalian organisms. Over several decades, evidence of the cardio-, neuro-, and nephroprotective effects of argon in various diseases and conditions in experimental models *in vivo* and *in vitro* have been accumulated. However, the lack of clinical studies to date has prompted us to carry out a systematic review analyzing the results of preclinical studies revealing organoprotective properties of argon, which could provide a rationale for its future clinical studies.

The aim of this review is to describe the mechanisms of organoprotective properties of argon determined in preclinical studies.

Material and methods. The search yielded 266 articles. The search algorithm was developed in accordance with the requirements and reporting guidelines for systematic reviews and meta-analysis (PRISMA) in the PubMed and Google Scholar databases. The methodology included using search queries, keywords (including MeSH), and logical operators. The keywords used for the search in the PubMed and Google Scholar databases were «argon», «ar», «protection», and «mechanism». The review included *in vivo* and *in vitro* studies.

Results. The following mechanisms of argon action were identified: activation of N-terminal c-Jun kinase (JNK), p38(ERK1/2), and ERK1/2 in models of airway epithelial cells, neuronal and astroglial cell cultures, as well as in models of retinal ischemia and reperfusion injury in rats and a rabbit model of ischemia-reperfusion myocardium. Significant neuroprotective effects of argon and its influence on apoptosis were shown using small rodent models.

Conclusion. The results of preclinical studies of argon have proved both its safety and organoprotective properties in *in vitro* and *in vivo* models. Analysis of the data provides a rationale for the initiation of clinical studies of argon, which could significantly improve outcomes in patients after cerebrovascular accidents, particularly post ischemic stroke.

Keywords: argon; organoprotective properties; neuroprotection; TBI; stroke; CPR

Conflict of interest. The authors declare no conflict of interest.

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Introduction

The history of studying the organoprotective properties of argon (Ar) dates back to 1998, when a group of Russian authors studied the effects of hypoxic gas mixtures based on argon on mammals [1]. Three experiments were performed in this study which showed that the addition of argon to hypoxic mixtures containing 4–5% oxygen increased the survival rate of animals compared to similar nitrogen-based mixtures.

Since then, a large number of papers have been published on this subject. Over several decades data on the cardio-, neuro-, and nephroprotective properties of argon in various diseases and conditions have been discovered in experimental models *in vivo* and *in vitro* [2–36]. New knowledge on the molecular mechanisms of argon action has been obtained, and the protective effects of argon and other noble gases, in particular xenon, have been compared [37–39].

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However, the lack of clinical studies on this subject has prompted us to conduct a systematic review with the analysis of preclinical studies demonstrating the organoprotective properties of argon, which would provide a rationale for initiation of its clinical investigation [40–42].

The aim of this review is to study the mechanisms of organoprotective properties of argon in preclinical settings.

Material and Methods

The paper is based on selection of relevant studies through searching published papers. The information search algorithm was developed in accordance with the requirements and reporting guidelines for systematic reviews and meta-analysis (PRISMA) [43] in PubMed and Google Scholar databases. It involved searching for studies using search queries, keywords (including MeSH), and logical operators. According to the search objective, abstracts, conference proceedings, and books were excluded. The search was limited by English-language sources. Keywords for the PubMed database and Google Scholar search included «argon», «ar», «protection», and «mechanism». *In vivo* and *in vitro* studies were included in the review. Papers containing «ar laser» and «ar coagulation» were excluded. The selection process of records for the study is shown in Fig. 1.

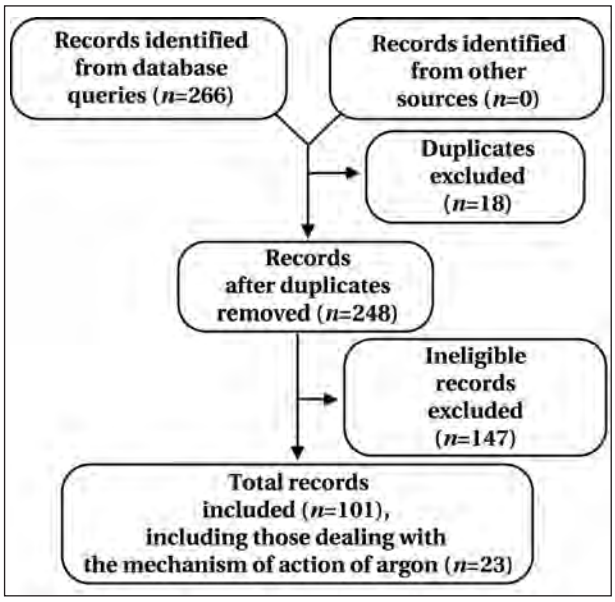

Fig. 1. Flowchart of source inclusion in the review.

Organoprotective properties

The results of recent studies on the organoprotective properties of argon using different models are presented in literature [44–48]. In these studies, either positive or neutral results of argon exposure were usually obtained, which most likely depended on gas concentration, duration of exposure, and experiment model [49, 50].

Table shows the main studies of the mechanism of action of argon in *in vitro* and *in vivo* experiments.

Figure 2 shows the main mechanisms of action of argon.

Neuroprotective properties

A model of traumatic brain injury. The neuroprotective effects of argon were examined in the *in vitro* and *in vivo* animal studies. The model of traumatic brain injury described by Grüßer L. et al. [26] was used for this purpose. In this study, the effects of 50-percent argon, 6-percent desflurane, alone and in combination, were investigated in an *in vitro* model of TBI with incubation time similar to the time intervals between drug administration in daily clinical practice. Injury severity was assessed by fluorescence imaging. The results showed that neither argon 50%, nor desflurane 6% nor their combination could significantly reduce the severity of injury compared to standard ambient. However, compared to desflurane, argon had a rather strong neuroprotective effect during the first 2 hours after focal mechanical injury (P=0.015).

The neuroprotective effects of argon after traumatic brain injury were also confirmed in a study [27, 51] comparing the effects of 24-hour inhalation of argon 70%/O_2 30% and N_2 70%/O_2 30% mixtures initiated within the first 10 min after a traumatic brain injury in a murine model of TBI. This study revealed a neuroprotective effect of argon in mice, manifested as a reduction in neurological deficits during the first week after injury (SNAP, P<0.001 and NeuroScore, P<0.01; beam walk, P<0.05) compared with the control group. On day 3 after the traumatic injury, the argon inhalation group showed a decrease in brain lesion on MRI examination compared with the control group (6.3±0.4 and 9.6±0.5 mm^3; P<0.001), as well as faster memory recovery to 6 weeks (mean latency: 14±2 and 32±6 s, respectively; P<0.05).

In another large study conducted by Creed J. et al. [28], in a model of closed traumatic brain injury, argon inhalation for 24 hours with argon 70%/O_2 30% and argon 79%/O_2 21% mixtures had no advantages over N_2 70%/O_2 30% and N_2 79%/O_2 21% inhalation.

Ischemic injury model. Zhuang L. Yang et al. [16] in a study comparing the neuroprotective effects of inert gases showed that argon provides neuroprotection in both moderate and severe ischemic brain damage, probably due to stimulation of production of proteins preventing apoptosis. The study used argon 70%, helium, xenon, or nitrogen with oxygen in the hypoxia-ischemia brain injury model. Interestingly, argon improved cell survival, whereas

xenon and helium did not. Quantitative analysis showed that treatment with argon, helium, and xenon significantly increased the number of healthy cells in the right CA region of the hippocampus from 37±8 in the control group to 54±6, 48±5, and 47±5, respectively (F=25; P<0.001). Xenon and argon reduced brain infarct volume by 42% (F=4.4, P<0.05) and 38% (P<0.05) compared with controls. In addi-

Main studies of the argon mechanism of action.

Authors	Model	Argon	
		Protective effects	Mechanism of action
Hafner C., Qi H., Soto-Gonzalez L. et al. [2]	A549 (airway epithelial cells)	Increase of cellular viability, 5–47% (P<0.0001)	Activation of c-Jun N-terminal kinase (JNK), p38 (ERK1/2), ERK1/2, but not the Akt pathway.
Brücken A., Kurnaz P. et al. [3]	Cardiac arrest in rats	Reduced neuronal damage index in the neocortex CA, 3/4 hippocampal region	No effect on ATP-dependent potassium channels.
Lemoine S., Blanchart K. et al. [4]	Male Wistar rats and guinea pigs, human atrial appendages	Recovery of contractile force in human atrial appendages after hypoxia/reoxygenation in the argon group from from 51±2% in the unconditioned group to 83±7% in the argon-treated group (P<0.001)	Inhibition of the mitochondrial permeability transition pore opening.
Mayer B., Soppert J., Kraemer S. et al. [5]	*in vitro,* model of primary isolated cardiac myocytes	Increased viability 24 h after preconditioning (second window of preconditioning) (P=0.015)	Induction of the HSP27 gene transcripts. Increased expression of the heat shock protein (HSP) mRNA B1 (HSP27) (P=0.048), superoxide dismutase 2 (SOD2) (P=0.001), vascular endothelial growth factor (VEGF) (P<0.001) and inducible nitric oxide synthase (iNOS) (P=0.001).
Ulbrich F., Kaufmann K., Roesslein M. et al. [6]	Neuroblastoma cells (SH-SY5Y cell line; ATCC CRL-2266)	Antiapoptotic and neuroprotective effect through inhibition of TLR2, TLR4	Inhibition of AV-positive and PI-negative cells and caspase-3 activity. Reduction of TLR2 and TLR4 receptor density on the cell surface. Decreased IRAK phosphorylation, but not the MyD88 protein expression. Increased phosphorylation of ERK-1/2.
Ulbrich F., Lerach T., Biermann J. et al. [7]	Neuroblastoma cells (SH-SY5Y, ATCC CRL-2266)	Neuroprotective effect (reduced severity of retinal ischemia)	Inhibition of NF-κB and STAT3 transcription factors activation. Reduced expression of interleukin-8 *in vitro* and *in vivo.*
Spaggiari S., Kepp O., Rello Varona S. et al. [8]	Human osteosarcoma cell culture U2OS stably expressing the histone 2B red fluorescent protein (RFP-H2B) chimera (which labels chromatin)	Antiapoptotic effect	Inhibition of several STS-induced apoptosis manifestations, including dissipation of membrane potential and caspase-3 activation.
Fahlenkamp A. V., Rossaint R. et al. [9, 10]	Primary cultures of neurons and astroglia cells, BV-2 microglia cell line	Increased ERK1/2 activity in the microglia	Effect on the extracellular signal-regulated kinase (ERK1/2). Addition of the MEK inhibitor U0126 abolished the induced phosphorylation of ERK1/2.
Zhao H., Mitchell S. et al. [11]	Rat cortical neuronal cultures	Reduced brain infarction size	Activation of the PI-3K/Akt pathway, activation of HO-1 and inhibition of GSK-3β. Suppression of NF-κB activation. Activation of caspase-3 and nuclear factor-κB in the cortex and hippocampus.
Zhao H., Mitchell S. et al. [12]	Cortical cell cultures of seven-day-old rats *in vitro* and *in vivo*	Decreased activation and proliferation of hippocampal astrocytes	Activation of transcription factor NF-E2 related to the factor 2 (Nrf2) Increase in p-mTOR and nuclear factor (erythroid factor 2)

Main studies of the argon mechanism of action.

Authors	Model	Argon	
		Protective effects	Mechanism of action
Harris K., Armstrong S. P. et al. [13]	An *in vitro* model using organotypic sections of mouse brain hippocampus, injury	Reduction of secondary damage	No effect on TREK-1 currents, indicating that the potassium channel is not involved in argon neuroprotection.
David H. N., Haelewyn B. et al. [14]	Ischemic stroke, *in vivo*	Elevated thrombolytic and enzymatic activity	Discussion of the mechanism of interaction between argon and tPA.
Höllig A., Weinandy A. et al. [15]	Rats, subarachnoid hemorrhage	Reduction in the risk of premature death (death before scheduled euthanasia) to 20.6% compared to the control group (95% CI, 4.39–96.7)	Hypoxia-induced expression of heme oxygenase 1α, induced by the 1α factor, leading to improved neuronal survival, may contribute to the favorable effect of argon administration after subarachnoid hemorrhage.
Zhuang L., Yang T. et al. [16]	Model of asphyxia in rats	Reduction of hypoxic-ischemic damage	Increased Bcl-2 expression.
Fahlenkamp A. V., Coburn M. et al. [17]	Rats, two-hour transient occlusion of the middle cerebral artery	Neuroprotective properties	Increased expression of TGF-β, expression of IL-1β, IL-6, iNOS, TGF-β, and NGF.
Ulbrich F., Schallner N. et al. [18]	Retinal ischemia and reperfusion injury in rats	Decrease in the number of damaged retinal ganglion cells	Argon-mediated inhibition of NF-κB. Bcl-2, Bax, and caspase-3 expression, NF-κB.
Ulbrich F., Kaufmann K. B. et al. [19]	Retinal ischemia and reperfusion injury in rats	Reduction of ischemic and reperfusion damage to retinal cells	Increased phosphorylation of p38 and ERK-1/2, but not JNK MAP kinase. HSP expression. Alteration of HO-1.
Abraini J. H., Kriem B., Balon N. et al. [20]	Rats	Increase in the argon threshold pressure for the onset of loss-of-righting-reflex (P<0.005)	Action on GABA-receptors.
Faure A., Bruzzese L., Steinberg J. G., et al. [21]	Heterotopic kidney autotransplantation in pigs	Improved recovery of function as measured by creatinine clearance, excreted sodium	Increased expression of Hsp27. Expression of TNF-alpha, IL-1-beta, and IL-6.
Liu J., Nolte K., Brook G. et al. [22]	Rats, transient occlusion of the middle cerebral artery	Reduction of neurological deficit during the first week and preservation of neurons in the border zone of ischemia 7 days after the stroke	Shift in microglia/macrophage polarization toward the M2 phenotype after ischemic stroke. Change in the number of NeuN-positive cells in ROIs.
Quentin de Roux Q., Lidouren F. et al. [23]	Rabbits, ischemic injury	Increased cardiac output, decreased norepinephrine demand, decreased severity of metabolic acidosis, decreased kidney and liver damage	Initial decrease in HMGB1.
Qi H., Soto-Gonzalez L. et al. [24]	Myocardial ischemia/reperfusion model, rabbits	Reduction of ischemic myocardial damage	Activation of JNK, ERK1/2 and Akt pathways. Changes in LDH and mtDNA, interleukin 1β.
David H. N., Dhilly M. et al. [25]	Rats, drug administration	Block of motor sensitization and context-dependent motor activity induced by repeated administration of amphetamine over a long period of time	Inhibition of the mu-opioid receptor and vesicular monoamine-2 transporter. Reduction of dopamine release induced by KCl.

tion, the study showed increased expression of Bcl-2, which inhibits apoptosis. The Bcl XL expression was increased in the helium and xenon group compared to the control group (F=5.9; P=0.0025).

Koziakova M. et al. [29] used hypoxia-ischemia model *in vitro* to evaluate the neuroprotective properties of several noble gases, such as helium, neon, argon, krypton and xenon. Organotypic murine hippocampal brain sections were subjected to oxygen-glucose deprivation, and damage was assessed using propidium iodide fluorescence. Both xenon and argon were equally effective neuroprotectors, with 0.5 atm of xenon or argon reducing the severity of brain tissue damage by 96% (P<0.0001), whereas helium, neon, and krypton lacked any protective effect.

The study of Ulbrich F. et al. [7] *in vitro* and *in vivo* confirmed the protective effect of argon and reported the details of the molecular mechanism of its action (Fig. 2). Argon exhibited a neuroprotective effect by inhibiting the activation of NF-κB and STAT3 transcription factors. While STAT5 and CREB remained intact, inhibition of TLR2 and TLR4 prevented the action of argon on NF-κB and STAT3.

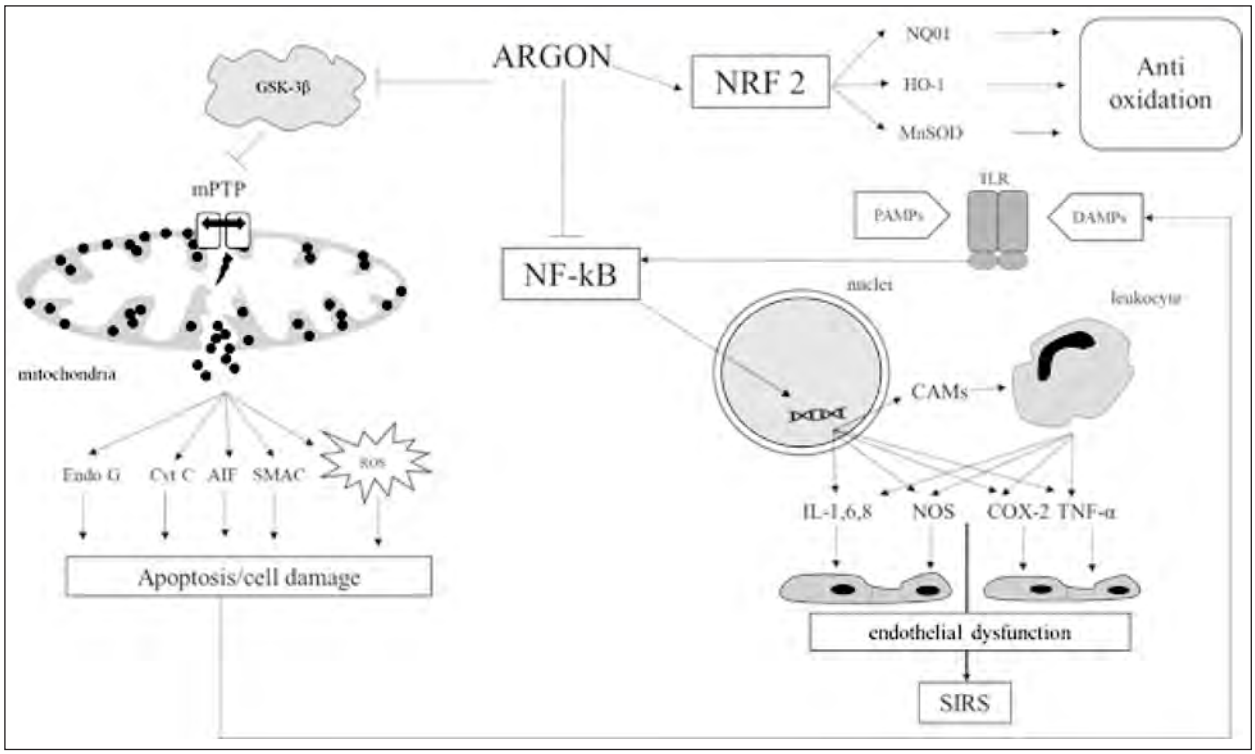

Fig. 2. Molecular mechanisms of the organoprotective properties of argon.
Note. GSK-3β — glycogen synthase kinase 3β; AIF — apoptosis-inducing factor; ROS — reactive oxygen species; Cyt C — cytochrome C; Endo G — endonuclease G; SMAC — apoptotic protein; CAM — cell adhesion molecules; COX — cyclooxygenase; I/R — ischemia/reperfusion; TLR — toll-like receptor; TNF-α — tumor necrosis factor-alpha; mPTP — nonspecific mitochondrial permeability transition pore; NOS — NO synthase; HO-1 — heme oxygenase; MnSOD — mitochondrial Mn-superoxide dismutase; NF-κB — nuclear factor κB; NRF — nuclear respiratory factor (redox sensitive transcription factor); NQ01 — quinone 1.

Inhibition of either NF-κB or STAT3 reversed the beneficial effects of argon. In addition, argon was found to have specific anti-inflammatory properties: IL-8 protein and mRNA expression was altered upon argon exposure. Argon exposure significantly decreased IL-8 protein expression (rotenone, 1.28±0.20 versus rotenone+argon, 0.90±0.13, P<0.001). Argon treatment also reduced IL-8 mRNA expression (untreated cells versus rotenone, 2.93±0.49, P<0.001; rotenone, 2.93±0.49 versus rotenone+argon, 1.54±0.25, P<0.01).

Large studies conducted by Ulbrich F. et al. [6, 7, 19] demonstrated the dose- and time-dependent effect of argon on neuronal protection which can be mediated through ERK1/2 and NF-kB-dependent pathway *in vivo*. Argon was found to be soluble in the cell culture medium, while the distribution equilibrium was reached in less than 2 hours. In addition, argon has a significant dose-dependent anti-apoptotic effect on human neurons (human neuroblastoma cell line model), with its concentration of 75 vol.% demonstrating the most dramatic effect. Argon inhibited rotenone-induced apoptosis, as evidenced by inhibition of AV-positive and propidium iodide (PI)-negative cells and caspase-3 activity. The proportion (%) of AV-positive and PI-negative cells was significantly higher in the FR180204+rotenone+argon 75 vol.% group [2 h] at 21.2±1.9%, P<0.001. The study revealed that argon mediates antiapoptotic signaling by reducing the density of TLR2 and TLR4 receptors on the cell surface.

Fahlenkamp A. et al. [9, 10] exposed primary cultures of neurons and astroglia cells as well as microglia cell line BV-2 to argon 50 vol.%. Further possible effects were studied after stimulation of microglia with LPS at a concentration of 50 ng/ml. Increased phosphorylation of ERK 1/2 after argon exposure was also found in astrocytes and neurons, but its change was not significant. Argon had no substantial effect on LPS-induced activation of ERK1/2 and induction of inflammatory cytokines in microglia. Addition of the MEK inhibitor U0126 eliminated induced phosphorylation of ERK 1/2. Cellular phosphatase activity and inactivation of phosphorylated ERK 1/2 were not altered by argon. Argon enhanced ERK 1/2 activity in microglia by «upstream» MEK kinase, probably through a direct activation pathway. Hence, this *in vitro* study determined the effect of argon on the ERK1/2 kinase regulated by extracellular signaling. This is a ubiquitous enzyme with numerous roles in cell proliferation and survival.

Zhao H. et al. [11] exposed neuronal cell cultures of rat cerebral cortex to oxygen and glucose *in vitro* for 90 min with 70% Ar or N2 with 5% CO_2 balanced with O_2 at 33°C for 2 h. Protein kinase-B (PI-3K/Akt pathway) activation, heme oxygenase (HO-1) activation, and GSK-3β inhibition have been demonstrated to be possible molecular mechanisms underlying the beneficial effects of argon both *in vivo* and *in vitro* [52, 53]. Furthermore, inhibition of HO-1 and PI-3K/Akt pathway activation significantly attenuated argon and hypothermia-induced neuroprotection in OGD-induced injury *in vitro* or *in vivo*. These data suggest that argon in combination with hypothermia could provide robust neuroprotection in a rat stroke model.

In the study, the authors suggested that argon during hypothermia increases HO-1 expression mainly in neurons, providing their cytoprotection, although it is likely that multiple molecular pathways may also be involved in protective mechanisms during ischemia. In addition, suppression of NF-κB activation has been shown to reduce neuronal damage in a model of global cerebral ischemia. NF-κB activation was suppressed by a combination of argon and hypothermia.

Zhao H. et al. [11] carried out the oxygen-glucose deprivation (OGD) of rat cortical neuronal cell culture *in vitro* for 90 min followed by exposure to 70% argon or nitrogen with 5% CO_2 and equilibrated with oxygen for 2 h. *In vivo*, seven-day-old rats underwent unilateral common carotid artery ligation followed by hypoxia-induced ischemia (8% oxygen balanced with nitrogen) for 90 minutes. Then they were exposed to 70% argon or nitrogen balanced with oxygen for 2 hours. *In vitro* exposure of cortical neuronal cultures to argon resulted in a significant increase in p-mTOR and nuclear factor (erythroid 2-like derivative, Nrf2) (P<0.05) and protection against OGD. Inhibition of mTOR by rapamycin or Nrf2 by siRNA abolished argon-mediated neuroprotection. *In vivo*, argon exposure significantly enhanced Nrf2 and its downstream effector NAD(P)H dehydrogenase, as well as quinone 1 (NQO1), and superoxide dismutase 1 (SOD1) (P<0.05). Argon potentially acts through the PI-3K cell signaling cascade as well as ERK, and, in addition, it may also work through cross pathways between P13K and ERK. This was also confirmed when using the PI-3K inhibitor wortmannin and the ERK1/2 inhibitor U0126. Thus, the neuroprotective mechanisms of argon have been shown to include activation of the transcription factor NF-E2 related to the Nrf2, which is considered to be a key mediator of organoprotection upregulating many antioxidants [54, 55].

The pathophysiology of secondary brain damage is complex and includes many cascades with the glutamate considered as a key player [56]. Harris K. et al. [13] showed that the neuroprotective properties of argon were not abolished by glycine, indicating that the neuroprotective effect of argon is not mediated by the glycine site of NMDA-receptor. This is confirmed by the electrophysiological data showing that argon has no effect on NMDA receptors at high or low concentrations of glycine. The lack of effect of argon on TREK-1 currents indicates that this potassium channel is also not involved in neuroprotection.

Jawad N. et al. [57] investigated the neuroprotective properties of krypton, argon, neon and helium in an in vitro model of neuronal damage. Pure cultures of neurons obtained from the brain cortex of embryonic BALB/c mice were subjected to oxygen-glucose deprivation. Cultures were exposed to either nitrogen hypoxia or hypoxia due to noble gas ventilation in a balanced salt solution without glucose for 90 minutes. Cultures were allowed to recover in normal culture medium for an additional 24 hours, in nitrogen or noble gas. Oxygen-glucose deprivation caused a reduction in cell recovery down to 0.56±0.04 in contrast to noble gas (P<0.001). Like xenon (0.92±0.10; P<0.001), argon provided neuroprotection (0.71±0.05; P<0.01). Argon showed improvement in recovery capacity to 1.15±0.11 (P<0.05). The study demonstrated that the inexpensive and widely available noble gas argon possesses potential neuroprotective properties.

The study by Höllig A. et al. [15] analyzed the effect of argon in subarachnoid hemorrhage. One hour after subarachnoid hemorrhage induction by endovascular perforation, a breathing gas mixture containing 50 vol.% argon/50 vol.% oxygen (argon group) or 50 vol.% nitrogen/50 vol.% oxygen (control group) was given for 1 hour. Argon postconditioning resulted in a 20.6% lower risk of premature death (death before scheduled euthanasia) compared to the control group (95% CI, 4.39–96.7). Expression of hypoxia-inducible factor 1α and heme oxygenase 1 in the hippocampus was increased in the argon group. Thus, hypoxia-induced factor 1α induces the expression of heme oxygenase 1, leading to improved neuronal survival, which may contribute to the positive effect of argon after subarachnoid hemorrhage.

The study of Fahlenkamp A. et al. [17] aimed to determine the protective mechanisms of argon treatment in a model of transient middle cerebral artery occlusion (tMCAO) in rats. The study identified several genes whose transcription was elevated 24 h after the intervention and whose expression levels differed significantly between the groups. In animals of the placebo group, the number of astrocytes, microglia, and neurons did not differ significantly between the study groups. After argon treatment, several inflammatory markers showed significantly higher expression levels 24 hours after the inter-

vention. The expression of interleukins IL-1β and IL-6 was significantly increased in the tMCAO+argon group compared to the tMCAO+placebo group (IL-1β: 1.7-fold increase, $P<0.05$; IL-6: 1.7-fold increase, $P<0.05$). The same was found for iNOS expression, which was significantly induced in the tMCAO+argon group (3.5-fold increase vs tMCAO+placebo, $P<0.001$). The study found that TGF-β expression was elevated after 24 h in the tMCAO+argon group, while it did not change in the tMCAO+placebo group.

The neuroprotective properties of argon were investigated by Ma S. et al. [58]. Prolonged inhalation of 70% argon for 24 hours after an *in vivo* stroke provides neuroprotection and improves neurological outcome and overall recovery after 7 days. Rats underwent middle cerebral artery occlusion followed by inhalation of 70% argon or nitrogen and 30% oxygen for 24 hours. On day 7 postoperatively, neurological status was assessed based on 48-point scale and the histological size of the lesion. After argon inhalation for 24 hours immediately after induction of «severe permanent ischemia», neurological outcome (Neuroscore, $P=0.034$), overall recovery (body weight, $P=0.02$), and cerebral infarct volume (total infarct volume, $P=0.0001$; cortical infarct volume, $P=0.0003$; subcortical infarct volume, $P=0.0001$) were significantly better compared with controls. At the same time, neurological outcome and overall recovery also improved significantly, even when argon treatment was delayed by 2 hours or until the end of reperfusion.

Kremer B. et al. [59] evaluated the neuroprotective and immunomodulatory properties of argon after experimental subarachnoid hemorrhage (SAH), studying different hippocampal and cortical regions with regard to neuronal damage and microglia activation 6, 24 and 72 hours after SAH. One hour after SAH (rat model with endovascular perforation), a gas mixture containing 50% argon (argon group) or 50% nitrogen (nitrogen group) was administered. Six hours after SAH, the reduction in neuronal damage of the hippocampal areas was found in the argon group vs the control one ($P<0.034$). The basal cortical areas did not show a different lesion pattern, but microglia activation was significantly reduced in the argon group 72 hours after SAH ($P=0.034$ vs the control group). Argon treatment only improved early hippocampal neuronal damage after SAH.

Liu J. et al. [22] were the first to show that argon promoted switching of microglia/macrophages polarization towards M2 phenotype after ischemic stroke.

The model of circulatory arrest. Brücken A. et al. [3] conducted a study to assess the effect of 70% argon when administered one hour after cardiac arrest in rats. According to the protocol, the animals were randomized into the argon group ventilated with either 70% or 40% vol.% argon 1 h after successful cardiopulmonary resuscitation, and into the control group without argon exposure. During seven days after the experiment, the neurological deficit severity was assessed prior to the animal withdrawal. The neurological deficit was more severe in the animals ventilated with 40% argon vs the 70% argon group ($P<0.05$). Concurrently, there was a significant decrease in the neuronal damage index in the neocortex and CA 3/4 hippocampus area (4.2 in the control group, 2.9 in the argon-ventilated group, $P<0.05$). Administration of the KATP channel antagonist 5-hydroxydecanoate (5-HD) did not abolish the positive effect on either the functional recovery or the histopathological changes observed in the argon exposure group.

Brücken A. et al. conducted another study to evaluate the neuroprotective effect of argon [60]. During the experiment, 7-minute cardiac arrest and 3-minute CPR were simulated in rats. Animals on argon showed significant improvement on the neurological disorders scale during all postoperative days even when argon administration was delayed by 3 hours ($P<0.05$). In addition, there was a significant decrease in the neuronal damage index in the neocortex and hippocampal CA 3/4 area in animals that received argon, regardless of the timing of its administration ($P<0.05$).

Zuercher P. et al. [61] tested the hypothesis that administration of 50% helium or 50% argon within 24 h after resuscitation improves clinical and histological results in the model of 8-minute cardiac arrest in rats. Cardiac arrest was induced in forty animals by administration of potassium and esmolol, after which they were randomized to be ventilated with either helium/oxygen, argon/oxygen, or air/oxygen for 24 h. The primary outcome was neuronal damage assessment in the CA1 hippocampal area in those animals that survived on day 5. The secondary outcome was behavioral assessment. Compared with rats in the air/oxygen group, where 80% [61–93] cell death of the hippocampal area (CA1) was observed, animals ventilated with the noble gas tended to have less damage (helium 53% [24–76], argon 59% [44–86], $P=0.09$). Thus, the results showed that replacing air with helium or argon in a 50:50 air/oxygen mixture for 24 h improved histological or clinical parameters in rats after an 8-minute cardiac arrest, but the differences in this experiment were not significant.

Fumagalli F. et al. [62] studied the neuroprotective effects of argon in a severe preclinically significant model of cardiac arrest in pigs. Animals were randomized to 4-hour post-resuscitation ventilation using 70% nitrogen + 30% oxygen (control), 50% argon, 20% nitrogen, 30% oxygen (Ar 50%)

and 70% argon, 30% oxygen (Ar 70%) groups. Hemodynamic parameters, myocardial function, and serial blood samples were monitored. The pigs were monitored for up to 96 hours to determine survival and neurological recovery. The Ar 50% and Ar 70% groups achieved good neurological recovery, unlike the control group (P<0.0001). Histologically, there was less neuronal degeneration in the cortex (P<0.05) (but not in the hippocampus) and less activation of reactive microglia in the hippocampus (P=0.007) after argon ventilation. Animals receiving argon showed a smaller increase in circulating biomarkers of brain damage (neuron-specific enolase, glial fibrillary acidic protein, ubiquitin c-terminal hydrolase) and markers of kynurenine pathway activation (P<0.05) vs the control group. A complete recovery of left ventricular function, lower infarct volume, and cardiac troponin release were observed in 70% of pigs on argon (P<0.01). Thus, lung ventilation with argon in the post-resuscitation period was shown to significantly improve neurological recovery and alleviate brain damage after cardiac arrest with prolonged interruption of blood flow. The effectiveness of 70% argon was higher than that of 50% argon.

Fumagalli F. et al. [63] also studied the effect of post-resuscitation argon treatment on neurological recovery in a model of cardiac arrest in pigs with acute myocardial infarction. Twelve pigs underwent occlusion of the left anterior descending coronary artery with subsequent cardiac arrest. After 8 minutes, cardiopulmonary resuscitation was performed for 5 minutes before defibrillation. After resuscitation, animals were subjected to 4-hour ventilation with 70% argon and 30% oxygen or 70% nitrogen and 30% oxygen. Myocardial function was evaluated by echocardiography and serum neuron-specific enolase was measured. Animals were observed for up to 72 h to assess survival and neurological recovery. Argon ventilation had no detrimental effect on hemodynamics and gas exchange. All six animals treated with argon showed rapid and complete 72-hour neurological recovery, in contrast to only two of the six control animals (P<0.05). The seventy-two-hour neurological alertness score and neurological deficit score were 100 and 0, respectively, in the argon group and 79 and 29 in the control group (P<0.01 and P<0.05). Significantly smaller increase in serum neuron-specific enolase levels (12% versus 234%) and minimal brain damage (neuronal degeneration was histologically 0 versus 1) were also observed in animals ventilated with argon.

Other models. Hafner C. et al. [2] studied airway epithelial cells exposed to a cytotoxic concentration of H_2O_2 after exposure to standard air, either 30 or 50% argon, 21% O_2, 5% CO_2 with an appropriate concentration of nitrogen in each mixture for 30, 45, or 180 minutes. Protective signaling pathways were identified by Western blotting. The study found that preconditioning with 50% argon for 30, 45, and 180 min and 30% argon for 180 min protected A549 cells from apoptosis, increasing cell viability by 5–47% (P<0.0001). Argon exposure resulted in early activation of the c-Jun N-terminal kinase (JNK) and p38 with a peak 10–30 min after the onset of preconditioning and delayed activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway.

Abraini J. et al. [20] administered drugs selective to GABA or GABA receptors to rats. Anesthesia was given using nitrogen, argon, or medical-grade nitrous oxide in a dose sufficient to induce complete loss of the righting reflex. Nitrogen and argon were delivered to the high-pressure chamber at a compression rate of 0.1 MPa/min, whereas nitrous oxide was delivered at a compression rate of 0.016 MPa/min. Hyperbaric helium induced increased excitability, which could affect both sensory and motor aspects of the reflex. The results confirmed the pharmacological rather than physiological antagonistic effect of gabazine and flumazenil in anesthesia induced by argon and nitrogen at elevated pressures. These results may be consistent with either a direct or indirect action of argon on GABA receptors.

Spaggiari S. et al. [8] in their study showed that argon is able to limit internal mitochondria-mediated apoptosis stimulated by the broad-spectrum kinase inhibitor staurosporine (STS), a DNA-damaging agent mitoxantrone (MTX) and several mitochondrial toxins. Argon inhibited several manifestations of STS-induced apoptosis, including $\triangle\psi$ mitochondrial inner membrane potential dissipation and caspase-3 activation.

Loetscher P. et al. [64] found neuroprotective properties of argon on organotypic sections of hippocampus in mice after treatment with argon at different concentrations (25, 50 and 74%). The 74% concentration of argon was the most effective (0.52±0.05), but concentrations of 25% (0.60±0.05) or 50% (0.56±0.03) also showed a significant reduction in the severity of brain damage ($P \leqslant 0.001$).

The effect of argon on production of NF-κB transcription factor was studied by Ulbrich F. et al. [18]. Postconditioning with argon inhibited the expression of Bax and Bcl-2 mRNA as well as the expression and cleavage of caspase-3 mRNA. A possible molecular mechanism of argon-mediated protection may involve suppression of the NF-κB transcription factor production. Interestingly, postconditioning with argon attenuated IRI-mediated leukocyte growth in peripheral blood. These results support the hypothesis that argon post-conditioning exerts neuroprotection by inhibiting apoptosis and thus provides cytoprotective effects after neuronal damage. In this study, NF-rB mRNA expression

was suppressed and phosphorylation of the p65-NF-κB subunit was attenuated by argon (75 vol%) in a time-dependent manner (up to three hours). Argon-mediated inhibition of NF-κB may be at least a possible molecular mechanism of apoptotic protein suppression.

Quentin de Roux Q. et al. [23] showed that argon reduces the level of HMGB1 in blood and also has a direct antiischemic effect, which decreases the passive release of nuclear HMGB1.

Alderliesten T. et al. studied the neuroprotective properties of argon on piglets. Several groups were formed in the experiment (the group on increasing concentrations of argon; the group exposed to hypoxia; the group of animals which underwent hypothermia after hypoxia). Inhalation of 80% argon had no effect on blood pressure, heart rate, cerebral saturation, and electrocortical activity of the brain in normoxic animals and in 50% of hypoxic animals, as well as in animals post hypoxia followed by therapeutic hypothermia [65].

Broad K. et al. [66] performed 45–50% argon inhalation in a model of newborn piglets after hypoxia-ischemia, which resulted in enhanced neuroprotective effect of hypothermia. Recovery of the baseline EEG was faster (P<0.01). Inhalation of 45–40% argon for 2–26 hours enhanced the protection against hypothermia 48 hours after hypoxia-ischemia.

Nephroprotective properties

The protective effects of argon during preconditioning, recovery and post-conditioning from renal ischemia-reperfusion in small rodents are quite well studied [67]. In this context, the hypothesis that postconditioning with argon inhalation will improve graft function in a pig kidney autotransplantation model was tested [49, 68]. The pigs underwent resection of the left kidney after 60 minutes of warm ischemia (renal artery and vein clamping). The removed kidney was autotransplanted in a separate procedure after 18 hours of cold storage, immediately after right-sided nephrectomy. After reperfusion, pigs were randomized to inhale control gas (70% nitrogen and 30% oxygen), argon (70% and 30% oxygen), or xenon (70% and 30% oxygen) for 2 hours. The primary outcome parameter was peak plasma creatinine concentration, while the secondary outcome parameters included additional markers of graft function (creatinine level, urine output), graft damage assessment (aspartate aminotransferase level, histology). Also, apoptosis and autophagy were examined, inflammatory mediators and markers of cell survival/growth (mRNA and tissue protein quantification) as well as animal survival were determined. The researchers concluded that argon postconditioning did not improve kidney graft function in this experimental model. The peak plasma creatinine concentration was similar in the control and argon groups. The intervention did not affect any other secondary outcome parameters, including animal survival.

Irani Y. et al. [69] showed that cold storage solution saturated with noble gas (xenon or argon) limits ischemia-reperfusion damage after cold ischemia. Creatinine clearance was significantly higher and urinary albumin level was significantly lower in the argon and xenon groups than in the other groups on days 7 and 14 (P<0.05). These effects were significantly more pronounced for argon than for xenon. In addition, argon-treated kidneys and, to a lesser extent, xenon-treated kidneys exhibited intact architecture as well as higher CD10 expression and lower caspase-3 activity compared with the other groups (P<0.05).

Cardioprotective properties

In addition to the neuroprotective properties of argon, much attention is paid to the study of its cardioprotective effects [70].

Previous studies demonstrated that preconditioning with argon provided a remarkable decrease in inflammation and apoptosis and increased myocardial contractility in acute ischemia-reperfusion (IR). Rats were anesthetized, ventilated, and divided into the control and argon groups, the latter receiving 3 sessions of argon (50% argon, 21% oxygen, and 29% nitrogen). Cold ischemia (4°C) for 60 minutes was induced by histidine-tryptophan-ketoglutarate cardioplegia followed by 40-minute reperfusion. The functional parameters of the heart were evaluated. The expression of extracellularly regulated kinase (ERK1/2), AKT serine/threonine kinase (Akt), jun N-terminal kinase (JNK), endothelial nitric oxide synthase (eNOS), and HMGB1 protein was studied in left ventricular tissue samples. At the end of reperfusion, argon preconditioned rats showed better recovery of cardiac output (101±6% versus 87±11%; P<0.01), stroke volume (94±4% versus 80±11%; P=0.001), and coronary blood flow (90±13% versus 125±21%; P<0.01) compared with controls. In addition, argon preconditioning significantly reduced JNK activation (0.11±0.01 versus 0.25±0.03; P=0.005) and HMGB1 protein expression (0.52±0.04 versus 1.5±0.10; P<0.001) after reperfusion. These results suggest a potentially new cardioprotective approach in cardiac surgery.

Lemoine S. et al. [4] investigated the role of MPTP induction (pore of nonspecific mitochondrial permeability, PNMP) in the mechanism of argon action (Fig. 2). This nonselective channel of the inner mitochondrial membrane opens during ischemia-reperfusion following the calcium overload of cardiac cells [71–78]. In rats, ischemia-reperfusion was induced *in vivo* using temporary coronary artery ligation, and cardiac function was assessed

by magnetic resonance imaging. Hypoxia-reoxygenation (HR)-induced arrhythmias were assessed *in vitro* using intracellular microelectrodes on both an isolated rat ventricle and a guinea pig ventricular borderline model. Loss of contractility during hypoxia-reoxygenation was evaluated in human atrial auricles. In these models, post-conditioning was induced by a 5-minute administration of argon during reperfusion. In the *in vivo* model, ischemia-reperfusion (IR) led to a decrease in left ventricular ejection fraction (24%) and an increase in wall motion index (36%), which was prevented by argon during post-conditioning. Post-conditioning with argon *in vitro* eliminated the IR-induced rhythm disturbances, such as early post-depolarizations, conduction blocks, and re-entry arrhythmias. Recovery of contractility in human atrial auricles after HR was better in the argon group, increasing from 51±2% in the unconditioned group to 83%±7% in the group using argon (P<0.001). In the experiment on the atrial auricle model, the use of PNMP activator prevented the cardioprotective effect of argon. This may indicate that argon acts directly or indirectly by inhibiting PNMP opening, thereby protecting the mitochondria. However, PNMP is also known to be controlled by the RISK pathway, the activation of which prevents PNMP opening [79–81]. Researchers have shown that inhibition of PI3K-Akt and MEK/ERK1/2 signaling kinases of the RISK pathway suppresses the cardioprotective effect of argon, which may suggest that the RISK pathway is involved in the inhibitory effect of argon on PNMP opening. In addition, inert gases including argon have been hypothesized to act by disrupting the structure and dynamics of lipid membranes and thereby indirectly altering protein function as an alternative or additional way of modulating the activity of ion channels.

Mayer B. et al. [5] observed the induction of HSP27 gene transcription during argon exposure in an *in vitro* model study [82–84]. The argon-mediated increase in HSP27 mRNA was hypothesized to contribute to delayed cardioprotection by enhancing protein folding, abnormal protein degradation, apoptosis inhibition, and cytoskeleton stabilization. In this study, isolated cardiomyocytes from rats were exposed to 50% argon for 1 h and then subjected to sublethal hypoxia (<1% O_2) for 5 h during either the first (0–3 h) or second window (24–48 h) of preconditioning. Subsequently, cell viability and proliferation were measured. Argon preconditioning significantly increased mRNA expression of heat shock protein (HSP) B1 (HSP27) (P=0.048), superoxide dismutase 2 (SOD_2) (P=0.001), vascular endothelial growth factor (VEGF) (P<0.001) and inducible nitric oxide synthase (iNOS) (P=0.001). These results provide the first evidence for the effect of argon on cardiomyocyte survival during the second preconditioning window, which may be mediated by the induction of HSP27, SOD_2, VEGF, and iNOS.

Qi H. et al. [24] confirmed in their study the action of argon through ERK1/2, JNK, and Akt pathways. The study showed that myocardial protection against oxidative stress-related damage by preconditioning with argon is at least partially mediated by phosphoactivation of MAPK and Akt pathways. Argon rapidly activates JNK phosphorylation within 15 minutes and then dephosphorylates the protein again to below baseline. Interestingly, the JNK inhibitor SP600125 reduces the protective effect of argon on cardiomyocytes, although to a lesser extent than the MEK1 inhibitor U0126. Downstream effectors of MAPkinase activation were also identified. The c-Jun, a member of the activator protein-1 (AP-1) family of transcription factors, is activated by the ERK1/2 and JNK pathways and is involved in cell cycle proliferation and progression with its activity being highly enhanced upon argon exposure [85–87]. Akt activation occurred through Ser473 phosphorylation, and the Akt inhibitor MK2206 could completely abolish the protective effect of argon.

Possible additional protective properties of argon have been studied in several studies. For example, in a study by David H. et al. [14] argon was suggested to affect the thrombolytic efficacy of tPA (tissue plasminogen activator). Previous data clearly demonstrated the inhibitory effect of xenon on enzymatic and thrombolytic efficiency of tPA and the critical importance of the time of xenon administration (during or after ischemia in order to prevent thrombolysis inhibition for better neuroprotective effect). The study showed that argon has a concentration-dependent dual effect on the enzymatic and thrombolytic efficacy of tPA. Low and high concentrations of argon (25 and 75 vol%) block and enhance respectively enzymatic and thrombolytic efficacy of tPA. The possible use of argon at low and high concentrations in the treatment of acute ischemic stroke during or after tPA-induced reperfusion with respect to its neuroprotective effects and its inhibitory and facilitation effects has been considered.

The same authors have recently obtained other important results [25]. Argon blocked the expression of motor sensitization to amphetamine by inhibiting the mu-opioid receptor and the vesicular transporter monoamine-2, which plays a critical role in drug addiction.

Ulbrich F. et al. [19] studied the effect of argon on retinal ischemia and reperfusion. Retinal ischemia and reperfusion are known to cause significant damage and apoptosis of the retina, measured by the decrease in the number of vital retinal ganglion cells and caspase cleavage [88]. Argon inhalation

suppressed endogenous cell defense mechanisms, such as the expression of HSP-70, HSP-90, and HO-1 [89,90]. At the same time, argon inhalation differentially induced stress kinases, as evidenced by increased phosphorylation of p38 and ERK-1/2, but not JNK MAP kinase. Inhibition of ERK-1/2 regulated argon-mediated HSP expression in this lesion model because inhibition of ERK-1/2 partially counteracted argon-mediated suppression of HO-1. Argon exposure resulted in a distinct suppression of various heat shock proteins after retinal ischemia reperfusion injury, leading to additional cytoprotective effects. Thus, the study confirmed the hypothesis that argon exerts neuroprotection through the ERK-1/2-dependent pathway.

Faure A. et al. [21] observed an increased Hsp27 expression after air/argon exposure in a pig liver transplant model. However, two days after reperfusion, the expression continued to rise only when argon was used during storage. These data suggest that argon exerts its protective effect, at least in part, by increasing the expression of Hsp27 [91]. These results are consistent with previous reports, which showed that Hsp27 expression provides a significant survival advantage under conditions of redox stress and inflammation, in particular by stimulating the antioxidant defense of the cell.

Clinical applications. Argon has been already used in various areas of science and medicine [92–100] where its safety has been demonstrated, including the study of hemodynamic parameters (cardiac output) and lung volume using the assessment of inert soluble gas absorption from lungs as well as the operation of respiratory mass spectrometer [101–103]. In contrast to argon, another noble gas, xenon, was already approved for clinical use as a general anesthetic and demonstrated neuroprotective properties in numerous *in vitro* and *in vivo* studies [108–112].

However, its use in routine clinical practice is still challenging due to its high cost and narcotic effect, which complicates the neurological assessment of patients.

Conclusion

Discussed studies show the neuroprotective effectiveness of argon. Argon is inexpensive to produce and does not require a closed breathing circuit. It has no sedative properties and, therefore, does not affect the neurological status. The simplicity of administration (via a face mask), absence of toxicity and influence on the cerebral blood flow enable argon administration starting from the moment of hospital admission. The results of preclinical studies of argon showed safety and organoprotective properties of the gas in *in vitro* and *in vivo* models using different animal species. All of the above provides a rationale for initiating clinical studies of argon, which could significantly improve the outcomes of patients after cerebral accidents, in particular, ischemic strokes.

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