

Cellular Effects of Helium in Different Organs

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ABSTRACT

Experimental research in cardiac and neuronal tissue has shown that besides volatile anesthetics and xenon, the non-anesthetic noble gas helium also reduces ischemia–reperfusion damage. Even though the distinct mechanisms of helium-induced organ protection are not completely unraveled, several signaling pathways have been identified. Beside the protective effects on heart and brain that are mainly obtained by different pre- and postconditioning protocols, helium also exerts effects in the lungs, the immune system, and the blood vessels. Obviously, this noble gas is biochemically not inert and exerts biologic effects, although until today the question remains open on how these changes are mediated. Because of its favorable characteristics and the lack of hemodynamic side effects, helium is suitable for use also in critically ill patients. This review covers the cellular effects of helium, which may lead to new clinical strategies of tissue salvage in ischemia–reperfusion situations, both within and outside the perioperative setting.

HELIUM is an odorless, tasteless, colorless monatomic element. It belongs to the family of noble gases, characterized by filled valence orbitals, meaning that a maximum amount of electrons is carried in the outer shell of the atom. This fact suggests that noble gases are “inert,” thus less capable of interacting with other compounds. In contrast to the noble gas xenon, helium lacks anesthetic properties¹ and the application of 80–90 atmospheres of helium pressure even increased the mini-

mum alveolar concentration for volatile anesthetics. Therefore, helium is categorized as a “nonimmobilizer,” a gas that is not able to induce anesthesia (immobilize) but that might have other behavioral effects.² Experimental research has convincingly shown that, although “inert” and nonanesthetic, helium exerts cellular effects *in vitro* and *in vivo*, it reduces ischemia–reperfusion damage in cardiac and brain tissue. Organ protective properties of helium gas might also become relevant for clinical practice. This review summarizes the current knowledge on the cellular effects of helium in various organs.

Physical and Chemical Properties of Helium

Helium is the lightest noble gas (molecular weight 4 g/mol) and has the lowest melting and boiling points of all elements.³ It has a lower density (0.179 g/m³) compared with oxygen (1.43 g/m³) and nitrogen (1.25 g/m³), and its absolute viscosity is 201.8 μ poise (oxygen: 211.4 μ poise; normal air: 188.5 μ poise). As flow depends on the density and viscosity of each element within a gas mixture, the physical properties of helium reduce airway resistance, thereby promoting airflow through the lungs.

Helium has a high thermal conductivity, and heat loss of the body may occur when it is completely surrounded by helium. Because lower body temperature may result in reduced metabolism, embedding of a body in a helium environment could result in lower energy expenditure.⁴ In rats, extended breathing of 75% helium induced hypothermia.⁵ However, in humans, hypothermia during helium breathing, at least for short episodes, has not been reported yet.⁶

Possible Mechanisms of Action Underlying Biologic Effects of Helium

As anesthetic potency is nearly linearly correlated with the oil–water partition coefficient (known as the “Meyer–Overton rule”),⁷ it can be predicted that noble gases with lower solubility in fat and water have negligible anesthetic effects. This holds true for helium, in contrast to xenon and krypton, which can produce the full state of general anesthesia.^{8,9}

The low fat solubility of helium can be overcome by the increase in partial pressure above the atmospheric level, de-

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livering a sufficient amount of the gas into the central nervous system. However, in rats exposed to 84.6 ± 22.2 atmospheres of helium, tremors and convulsions have been observed, resembling activation of the central nervous system rather than depression of neural cell activity.^{2,10} This marked helium as a nonimmobilizer, a compound producing convulsions near the estimated partial pressures needed to produce anesthesia as predicted by the Meyer–Overton rule. In addition, the counteracting antagonism of pressure itself, proven by reversal of general anesthesia in newts and mice after exposure to hydrostatic or gas pressure,¹¹ makes a depressive effect of helium at high pressures unlikely. However, only a direct comparison between high pressures of helium and high pressure *per se* could completely elucidate this matter. In fact, helium pressure could actually reduce duration and frequency of convulsions.

The biologic effects of gases were once attributed to both indirect and direct actions on cytosolic and membrane bound (specific) proteins. The exact mechanism behind the biologic effects or the possible role for pressure in this matter is currently still not understood. The same holds true for helium and its effect on brain tissue or its biologic effects in general.

Helium-induced Organ Protection

Heart

Myocardial tissue can be protected against ischemia–reperfusion injury by subjecting it to one or more short ischemic episodes according to a specific protocol; early preconditioning (EPC) or late preconditioning before ischemia or post-conditioning after myocardial ischemia.¹² In addition to ischemia, pharmacologic compounds can also trigger the signaling cascades of ischemic conditioning, thereby inducing organ protection. Activation of adenosine, muscarinic, α -adrenergic, opioid, or bradykinin receptors by ischemic preconditioning is known to trigger subsequent transduction pathways,¹³ and therefore drugs that act directly on these receptors contribute to organ protection.

Halogenated fluorocarbons such as isoflurane, desflurane, and sevoflurane, as well as the noble gas xenon are also known to exert cardioprotective effects.^{14–17} In rabbits that underwent three cycles of 5 min inhalation of 70% helium, neon, or argon with 30% oxygen, interspersed with 5-min washout of the respective noble gas or three cycles of brief ischemia interspersed with 5 min of reperfusion, before the index ischemia of 30 min and 3 h of reperfusion, a reduction in infarct size was observed after ischemic- and noble gas-induced preconditioning.¹⁸

Volatile anesthetics activate multiple pathways in which reactive oxygen species, protein kinase C, and various mitochondrial channels play a crucial role (for a detailed overview see Weber and Schlack¹³). For an overview of currently discussed signaling kinases and targets involved in helium-induced conditioning, see figure 1. In helium-induced EPC,

the use of selective inhibitors of phosphatidylinositol 3-kinase, extracellular signal-regulated kinase, and 70-kDa ribosomal protein s6 kinase abolished cardioprotection.¹⁸ Blockade of glycogen synthase kinase or the apoptotic protein p53 lowers the threshold of helium EPC, as the combination of only one cycle of helium preconditioning with a glycogen synthase kinase- or apoptotic protein p53-inhibitor provided an infarct size reduction comparable to three cycles of helium alone.¹⁹ Not only inhibition of glycogen synthase kinase and apoptotic protein p53 pathways were shown to lower the threshold of helium EPC but also administration of morphine lowered the threshold of helium; the combination of one 5-min cycle of helium administration along with morphine resulted in an infarct size reduction equal to three cycles of helium.²⁰ In contrast to a previous study,¹⁹ one cycle of helium alone did not reduce infarct size in comparison with controls. Use of a nonselective opioid receptor antagonist prevented the infarct size reduction.²⁰ The above described data imply involvement of the so-called reperfusion injury signaling kinase pathways and an opioid receptor-mediated mechanism in helium-induced preconditioning.

It has been suggested that preconditioning affects cardiac mitochondrial function by regulation of extracellular signal-regulated kinase 1/2, phosphatidylinositol 3-kinase/Akt, and glycogen synthase kinase-3 β .^{21,22} Opening of the mitochondrial permeability transition pore (mPTP) can lead to mitochondrial dysfunction.²¹ Pagel *et al.*¹⁹ showed in an *in vivo* study in rabbits that application of a selective mPTP opener abolished helium EPC, suggesting a role for the mPTP in helium-induced EPC. Opening of the mPTP during reperfusion is enhanced by normalization of acidic pH after restoration of blood flow.²³ Thus, helium EPC may reduce infarct size by maintaining modest intracellular acidosis during early reperfusion, which keeps the mPTP closed. This is supported by data showing that helium preconditioning is not cardioprotective in rabbits that underwent transient metabolic alkalosis during reperfusion. In these experiments, myocardial protection could be restored after coadministration of cyclosporin A, an mPTP inhibitor.²⁴ Next to the mPTP, the mitochondrial adenosine triphosphate-regulated potassium channel has been demonstrated to be involved in helium preconditioning: administration of the adenosine triphosphate-regulated potassium channel antagonist 5-hydroxydecanoate blocked helium-induced infarct size reduction.²⁴

In rats subjected to 25 min of regional myocardial ischemia and 2 h of reperfusion, cardiac mitochondrial function was analyzed by the rate of oxygen consumption by isolated mitochondria after administration of a complex 2 substrate (state 2), adenosine diphosphate (state 3), and after complete phosphorylation of adenosine diphosphate to adenosine triphosphate (state 4).²⁵ The respiratory control index, calculated as state 3/state 4, represents mitochondrial coupling between respiration and oxidative phosphorylation. The re-

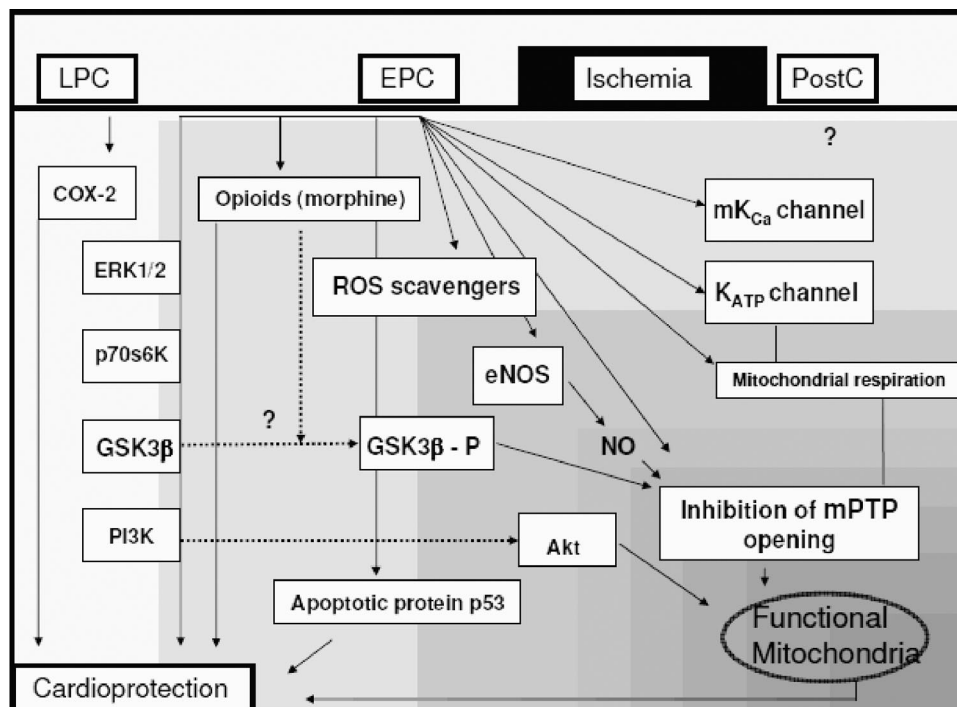


Fig. 1. Signaling kinases and targets that are currently considered to be involved in helium preconditioning. Evidence from experimental studies mainly focuses on signaling cascades induced by early preconditioning; regarding late preconditioning and postconditioning, we have only little data and this needs further investigation. COX-2 = cyclooxygenase-2; eNOS = endothelial NO synthase; EPC = early preconditioning; ERK = extracellular signal-regulated kinase; GSK3 β = glycogen synthase kinase 3 β ; K_{ATP} = mitochondrial adenosine triphosphate-regulated potassium channel; LPC = late preconditioning; mK_{Ca} = mitochondrial calcium-sensitive potassium channel; mPTP = mitochondrial permeability transition pore; p70s6K = 70-kDa ribosomal protein s6 kinase; PI3K = phosphatidylinositol 3-kinase; PostC = postconditioning; ROS = reactive oxygen species.

spiratory control index was reduced after helium preconditioning mainly by an increase in state 4 respiration, indicating a mild mitochondrial uncoupling after helium-induced preconditioning.²⁵

Involvement of the mitochondrial calcium-sensitive potassium channel has also been investigated in helium-induced organ protection.²⁵ In rats, infarct size reduction after helium preconditioning and the concomitant reduction of the respiratory control index were abolished by addition of a mitochondrial calcium-sensitive potassium channel blocker. Besides the effects on the mitochondria, other enzymes and mediators might be affected by helium; application of a non-selective blocker of the endothelial nitric oxide synthase abolished infarct size reduction by helium and omitted nitric oxide production.²⁶ In addition, administration of the reactive oxygen species scavengers *N*-acetylcysteine or *N*-2-mercaptopyrionyl-glycine blocked cardioprotection after helium EPC in an *in vivo* study in rabbits, suggesting that a basal amount of reactive oxygen species is necessary for the mediation of the protective effect of helium EPC.²⁷

It has to be noted that although these experimental studies point out the involvement of different kinases and their targets in helium-induced EPC, actual expression and activity of these kinases have not been measured yet or no changes could be demonstrated until now.²⁸

The previously mentioned experimental studies have been conducted in young and healthy animals. However, cardioprotective effects are diminished in disease states such as diabetes or aged subjects.²⁹ A well-known animal model for diabetes type II is the Zucker obese rat.³⁰ These animals display insulin resistance and become hyperlipemic and hyperinsulinemic but are normoglycemic, representing a prediabetic state of type II diabetes. In an *in vivo* study in Zucker obese rats, helium preconditioning did not lead to an infarct size reduction or mild mitochondrial uncoupling in comparison with nondiabetic controls.²⁸

In 22–24-month-old Wistar rats, cardioprotection by helium preconditioning was abolished.²⁵ These findings are in line with findings from anesthetic preconditioning; isoflurane preconditioning was attenuated in aged human atrial cardiomyocytes.³¹ In Langendorff perfused hearts of aged Fischer rats, sevoflurane preconditioning was abolished.³² In the same rat strain, age-related changes in myocardial ischemic tolerance occur during the course of life, represented by an enhanced increase in intracellular Na⁺ content during an ischemic episode.³³ This suggests that changes within the myocardium occur with the progression of age. In fact, several changes in the senescent myocardium have been described that might influence cardioprotection.³⁴ Helium EPC is most likely influenced by age, as infarct size reduction

was abolished in aged rats. In addition, the effects of helium on mitochondrial respiration could not be found in aged animals either.²⁵

Besides EPC, helium also induces late preconditioning: the administration of 30%, 50%, or 70% helium 24 h before the sustained ischemic episode reduced infarct size from 55% in controls to 40%, 34%, and 37%, respectively.³⁵ In contrast, 10% helium was not cardioprotective.³⁵ Repetitive administration of helium on subsequent days within the time window of late preconditioning did not further enhance infarct size reduction.³⁵ Helium-induced late preconditioning was abolished by a cyclooxygenase-2 inhibitor, a mechanism that was previously shown to be involved in xenon late preconditioning as well.³⁶ An effect of helium on mitochondrial function could not be detected outside the early preconditioning window, suggesting that mitochondrial uncoupling is a trigger of helium-induced late preconditioning and not a mediator.

Brain and Neuronal Tissues

The discovery of sustained neuroprotective effects of xenon in various *in vitro* and *in vivo* models^{37–39} caused a shift toward the investigation of helium as a neuroprotectant. Xenon, a low-affinity *N*-methyl-D-aspartate receptor antagonist, causes a reduction in detrimental neurotransmitter presence in the brain. For helium, four studies currently describe its possible role in neuroprotection but can only speculate an underlying mechanism.^{5,40–42}

In an *in vitro* mouse model of traumatic brain injury, brain slices were treated with increased pressures of up to 2 atm of helium (75% helium, 20% oxygen, and 5% carbon dioxide) on top of 1 atm of air (75% nitrogen, 20% oxygen, and 5% carbon dioxide) in a specific gas chamber.⁴⁰ Helium reduced cell damage as measured by a fluorescent technique for cell injury. Despite evidence for protection, a big drawback of this study design is the difficulty to distinguish between the direct pharmacologic effects of helium and the effects of pressure *per se*. In addition, the absence of nitrogen in the helium-oxygen mixture may partly cause the observed differences between helium and control. However, further experiments were conducted with the addition of nitrogen pressure instead of helium pressure. A significantly worse injury outcome was shown under nitrogen pressure in comparison with helium, suggesting that protection was caused by the removal of the detrimental effects of nitrogen.⁴⁰

The detrimental effects of nitrogen and the protective effects of noble gases were also investigated in neuronal cultures from mouse brain tissue.⁴² Cellular injury was provoked by oxygen and glucose deprivation, and cells were subsequently exposed to 90 min of nitrogen hypoxia (95% nitrogen and 5% carbon dioxide) or noble gas hypoxia (75% noble gas, 20% nitrogen, and 5% carbon dioxide), under normobaric conditions. Injured cells in the nitrogen group showed more functional damage in comparison with injured cells in the xenon and argon group,

indicating the protective effects of these gases or the detrimental effects of nitrogen. Although neon and krypton had no effect at all, helium worsened the damage. Interestingly, in uninjured cells, exposure to neon or helium did not have damaging effects, whereas krypton negatively influenced cellular function.⁴² This suggests a difference between healthy and injured cells.

A theory that supports a detrimental role of nitrogen is the “nitrogen-washout theory.”⁴³ This theory hypothesizes that nitrogen obstructs backflow of oxygen to the mitochondria at the time of reperfusion. Normally, oxygen availability is three times that of nitrogen, suggesting oxygen rather than nitrogen uptake in the case of fully functional mitochondria. This is explained by their respective solubility in water (nitrogen 1.6% and oxygen 3.0%) and the delivery rate of oxygen to tissues *via* hemoglobin at 1,000 ml/min. During ischemia, adenosine triphosphate depletion in cells results in swelling and breakdown of the mitochondrial membrane. Because no oxygen is present and the membrane is partially disrupted, mitochondria are limited to nitrogen resorption only. After restoration of blood flow during reperfusion, the nitrogen-filled mitochondria are incapable of quick oxygen reuptake, possibly caused by a delay in the nitrogen outflow along a concentration gradient.

The question is whether any neuroprotective effect at all can be found from helium under normobaric circumstances and how this relates to the amount of nitrogen present. In rat heart, various gas mixtures with or without nitrogen (70% helium/30% oxygen, 50% helium/30% oxygen/20% nitrogen, and 30% helium/30% oxygen/40% nitrogen) were tested and all induced myocardial infarct size reduction.³⁵ This proves a potential beneficial effect of helium itself and not the removal of the detrimental effects of nitrogen. Whether this also holds true for brain tissue is yet to be evaluated.

The effects of helium on the ischemic brain were investigated in rats subjected to 2 h of focal ischemia caused by occlusion of the middle cerebral artery and 1 h of reperfusion. The infarct volume was assessed by 2,3,5-triphenyltetrazolium staining.⁴¹ Three groups (helium, hyperoxia, and control) inhaled the intervention gas during the entire procedure of ischemia and reperfusion. Infarct volume in the 30% oxygen/70% helium group was smaller than that in the 100% oxygen group (hyperoxia), and the 100% oxygen treatment was beneficial compared with the 30% oxygen/70% nitrogen treatment (control). Neurologic scores in the helium-treated group were significantly better compared with controls.⁴¹ The fact that helium at atmospheric pressure levels improves neurologic outcomes suggests a pharmacologic effect of helium itself. On the other hand, the low thermal conductivity of helium might also play a significant role: in the same rat model, 75% helium after reperfusion exerted neuroprotection and improved neurologic outcomes but simultaneously induced hypothermia.⁵

Lung

Barach⁴⁴ first proposed the use of helium in a mix with oxygen as a therapeutic agent in obstructive pulmonary diseases. Nowadays, helium has been implemented in clinical therapies against pulmonary diseases. However, the results from using helium in asthma and chronic obstructive pulmonary disease are inconclusive.^{45,46} Studies focusing on gas behavior in the tracheobronchial system demonstrate a benefit for patients with severe acute asthma, measured as improved peak expiratory flow or forced expiratory volume in 1 s.⁴⁶ In intubated patients with chronic obstructive pulmonary disease, helium reduced the work of breathing and intrinsic positive end-expiratory pressure compared with controls.⁴⁷

The vasodilator effects of nitric oxide on pulmonary vessels were investigated in dogs using either helium or nitrogen as a carrier gas.⁴⁸ This study demonstrated that nitric oxide in combination with helium led to lesser mean pulmonary artery pressure and pulmonary vascular resistance compared with nitric oxide with nitrogen, probably because of enhanced diffusion velocity of nitric oxide in helium.

In asthma and chronic obstructive pulmonary disease, bronchodilators and inhalational corticosteroids are cornerstones of treatment. Theoretically, the low density of helium can lead to an improved aerosol penetration into the lungs. However, no consensus about the use of helium-driven nebulizers exists, as some studies show positive results^{49–52} whereas others failed to show clinical improvement in treated patients.^{53–55} Nawab *et al.* investigated the effect of helium inhalation on lung inflammation and resultant structural alterations. In a neonatal animal model of acute lung injury, animals receiving helium or oxygen showed improved ventilation parameters compared with a control group receiving nitrogen or oxygen. The changes in ventilation parameters were associated with increased alveolar recruitment, lower inspired oxygen requirements, and ultimately an attenuated inflammatory profile.⁵⁶ The authors postulated that this decrease is caused by a reduction in biochemical and physical stress to the lung.⁵⁶ So far, a direct effect of helium on the airways and parenchyma has not been shown.

Immune System

Recent publications showed that the anesthetic technique used in patients with malignant disease undergoing surgery can affect recurrence of malignancy.⁵⁷ The underlying cause is possibly related to the influence of anesthetic agents on cell-mediated immunity and implicates that some agents are more harmful than others. The assumption that a smaller surgical trauma may lead to beneficial changes in the immune response stimulated the development of laparoscopic surgery. However, the notion that a disadvantage of the laparoscopic technique is increased tumor spread during surgery, caused by establishment of pneumoperitoneum, is still not completely ruled out for all types of oncologic surgery.^{58–60} In an *in vivo* study in mice, intraperitoneal tumor distribution was more widespread in groups that underwent pneumoperitoneum

compared with a group of animals that did not undergo insufflation of the abdomen.⁶¹ The authors hypothesized that cancer cells are literally blown through the cavity and therefore easily disseminate. Regarding this effect, the type of gas used for pneumoperitoneum was investigated, and interestingly it was found that tumor weight in helium pneumoperitoneum was smaller than that in the carbon dioxide pneumoperitoneum.⁶¹ In contrast, Gutt *et al.*⁶² could not show any oncologic or immunologic differences between helium or carbon dioxide-induced pneumoperitoneum in rats. In a rat model of peritonitis, a lower incidence of bacteremia was observed using helium compared with carbon dioxide.⁶³

The chemical and physical properties of the used gas might influence tumor implantation and development of malignancies. *In vitro* studies showed differences in cell viability between malignant cell lines that were incubated with carbon dioxide or helium, with lower cell proliferation under helium incubation compared with a control⁶⁴ or compared with a control and carbon dioxide.⁶⁵ The question that specific cellular factors affect tumor growth and dissemination has still to be answered. Incubation of cells in carbon dioxide turns the culture medium acid,⁶⁴ and it was shown that carbon dioxide pneumoperitoneum caused parietal peritoneal acidosis in pigs.⁶⁶ In contrast, helium resulted in an alkalotic parietal peritoneal pH.⁶⁶ Environmental pH may alter macrophage differentiation and function, which in turn affects the ratio of specific collagens in wound healing. *Ex vivo* it was shown that helium increased the collagen 1 to 3 ratio after laparotomy in rats, leading to improved wound healing.⁶⁷ In healthy human volunteers, helium breathing had a modest antiinflammatory effect determined by attenuated expression of inflammatory cell surface markers on leukocytes and platelets in blood.⁶⁸

Blood Vessels

An increase in immune activation may not only be beneficial against tumor spread but also means a higher adherence of circulating cells to vascular endothelium in a site of injury. The latter may play a role in ischemia–reperfusion damage.⁶⁹ In one study in rats, an increased leukocyte–endothelium interaction in tumor and liver vessels was observed after helium application.⁷⁰ In contrast, in healthy human volunteers using an ischemia–reperfusion model of the forearm, no effect of helium on endothelial dysfunction after ischemia was observed.⁶⁸

Clinical Considerations in the Use of Helium

Helium, nonexpensive and easy to administer, has been used in patients with respiratory diseases since 1934.⁴⁴ No (hemodynamic) side effects have been found, making it appealing for a clinician dealing with patients with cardiovascular risk factors or cardiac disease, especially in the anesthetic practice

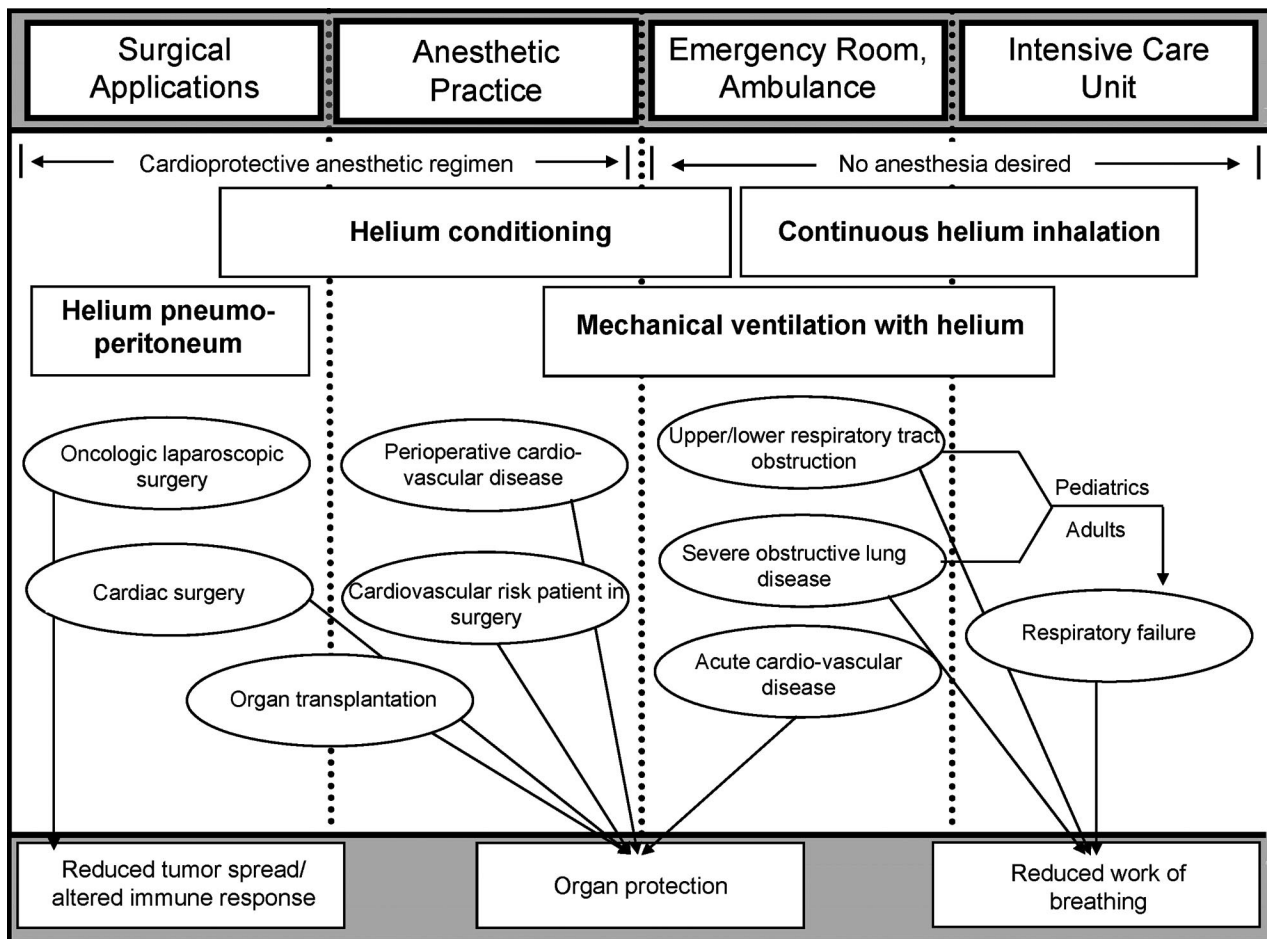


Fig. 2. Potential clinical applications of helium in various medical fields. Current research mainly focuses on conditioning of heart and brain tissue, but in theory any organ in the body can be protected against ischemia–reperfusion injury, such as the lungs, liver, kidney, and intestine. Other clinical applications of helium can be found during invasive and noninvasive ventilation in lung diseases.

in which the prevention of myocardial ischemia in the perioperative period is a daily challenge.

The organ-protective properties of helium gas have been shown mainly in animal studies, and the results of clinical studies are awaited. In humans, anesthetic-induced conditioning depends on the conditioning protocol used.⁷¹ In patients, not only polypharmacy and comorbidity (such as simultaneous presence of diabetes or hypertension) but also age influence the outcome, probably by increasing a “threshold” for a protective agent.^{34,72} For helium-induced EPC, it was shown that coadministration of pharmacologic agents such as morphine and glycogen synthase kinase inhibitors and apoptotic protein p53 inhibitors lowered the threshold for helium preconditioning.^{19,20} Coadministration of these agents in patients who are susceptible for “higher conditioning thresholds” might be a promising strategy in clinical practice to further enhance cardioprotection.

Helium might be used in the perioperative setting together with a protective anesthetic regimen to increase organ protection. Helium is the first nonanesthetic gas inducing organ protection that can also be used safely in patients experiencing ischemic periods but not undergoing anesthesia.

In addition, helium preconditioning could play a role in organ transplantation. For a schematic overview of potential clinical applications of helium, see figure 2. Despite promising results from experimental research, more clinical data are warranted in the specific clinical settings described in this paragraph.

Conclusion

Helium has been used in various clinical settings. The cellular effects of helium leading to cardio- and neuroprotection offer a novel therapeutic approach to protect patients against the detrimental effects of organ ischemia. The effects of helium in humans subjected to organ ischemia should be the subject of future clinical and experimental research.

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