The efficacy of noble gases in the attenuation of ischemia reperfusion injury: a systematic review and meta-analyses

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Abbreviations:

CI: confidence interval

IH: injury/histology

IRI: ischemia reperfusion injury

LAD: left anterior descending artery

NF: neurological function

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SES: standardized effect sizes

tPA: tissue-type plasminogen activator

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Abstract

Objective: Noble gases have been attributed organ protective effects in ischemia reperfusion injury (IRI) in a variety of medical conditions, including cerebral and cardiac ischemia, acute kidney injury, and transplantation. The aim of this study was to appraise the available evidence by systematically reviewing the literature and performing meta-analyses.

Data Sources: PubMed, EMBASE, and the Cochrane Library.

Study Selection: Inclusion criteria specified any articles on noble gases and either IRI or transplantation. *In vitro* studies, publications without full text, review articles and letters were excluded.

Data Extraction: Information on noble gas, organ, species, model, length of ischemia, conditioning and noble gas dose, duration of administration of the gas, endpoints and effects was extracted from 79 eligible articles. Study quality was evaluated using the Jadad scale. Effect sizes were extracted from the articles or retrieved from the authors to allow meta-analyses using the random-effects approach.

Data Synthesis: Argon has been investigated in cerebral, myocardial, and renal IRI; helium and xenon have additionally been tested in hepatic IRI; while neon was only explored in myocardial IRI. The majority of studies show a protective effect of these noble gases on IRI across a broad range of experimental conditions, organs and species. Overall study quality was low. Meta-analysis for argon was only possible in cerebral IRI and did not show neuroprotective effects. Helium proved neuroprotective in rodents and cardioprotective in rabbits, there were too few data on renal IRI. Xenon had the most consistent effects, being neuroprotective in rodents, cardioprotective in rodents and pigs and renoprotective in rodents.

Conclusion: Helium and xenon show organ protective effects mostly in small animal IRI models. Additional information on timing, dosing and comparative efficacy of the different noble gases as well as confirmation in large animal models is needed before designing clinical trials.

Introduction

Ischemia reperfusion injury (IRI) is a major contributor to morbidity and mortality in a variety of medical conditions, including cerebral, cardiac, and intestinal ischemia, acute kidney injury, and solid organ transplantation. Tissue hypoperfusion and ischemia are also frequently encountered in critically ill patients and significantly contribute to multi-organ failure and perioperative death. An effective treatment of IRI is currently not available (1) but the use of inhalational drugs, including volatile anesthetics (2, 3) and noble gases, to attenuate IRI is increasingly explored. Of the six noble gases (helium, neon, argon, krypton, xenon, and radon), two are used medically. While helium is occasionally used to ventilate patients with chronic obstructive pulmonary disease (4), xenon exhibits anesthetic properties under normobaric conditions, provides the fastest onset and recovery from anesthesia of all known anesthetics, and has a remarkably safe cardiovascular profile (5-7).

The use of noble gases to treat IRI has been investigated since the early 1970s, but no published comprehensive reviews are available. The aim of this study was to appraise the current evidence by systematically reviewing the literature and performing meta-analyses.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). It has been registered with the National Institute for Health Research (PROSPERO) (CRD42015021934).

Data sources, search details, and eligibility criteria

PubMed, EMBASE, and the Cochrane Library were searched for 'ischemia reperfusion injury' or 'transplantation' and 'noble gases' March 2nd, 2014 (Fig.S1). Relevant synonyms and subcategories were included. The search strategy was set up in conjunction with experienced librarians. No limits were specified. To identify potentially relevant studies, title and abstract of all articles were screened

by two independent reviewers (with discrepancies resolved by a third reviewer). Next, the full texts of the pertinent articles were assessed for eligibility. Additionally, reference lists of all included articles were checked for any relevant papers that were not identified in the primary search. *In vivo* and *ex vivo* studies (animal and human) evaluating the effects of noble gases on IRI or organ function post-transplantation were included. Exclusion criteria were: *in vitro* studies, publication without full text, review articles, letters, and language other than English, French, Dutch, German or Spanish. The Supplement Digital Content gives additional information on the search strategy.

Data extraction and meta-analyses

Abstracted information from included articles included but was not limited to: type of noble gas, administration method, concentration, duration of administration, organ, species, gender, number of animals, endpoints and duration of follow-up. Quantitative data on the effect size of a single noble gas compared to control were extracted for primary and secondary endpoints to perform meta-analyses. Effect sizes were grouped as a function of type of organ (brain, heart, kidney, liver), species (rat/mouse, rabbit, pig) and endpoint. Endpoints were clustered as either referring to organ injury (infarct size, histological changes,...) or function (neurological function, kidney function,...). Standardized effect sizes (SES) were calculated with a positive value referring to a better outcome in the treatment group. The random-effects approach was used to combine SESs (9). The Supplemental Digital Content details the meta-analytical strategy. Analyses were performed using SAS software, version 9.2 for Windows.

Quality assessment

The quality of the reported experiments was scored using the Jadad-scale which considers randomization, double blinding, methods of blinding/randomisation, and whether all participants were included in the analysis (10). Although the Jadad-scale was not developed for preclinical research, there are no alternatives (11). We therefore additionally report whether the sample size

was calculated, animal characteristics were given and if the optimal time window and dose-response were investigated (11).

Defining the 'conditioning' setting

The time at which the gas is given relative to IRI determines the 'conditioning' setting. In preconditioning, gas administration is started before the onset of ischemia; in reconditioning it is administered during ongoing ischemia; and in postconditioning after reperfusion.

Results

Study selection and data extraction

The search identified 2108 articles (PubMed: 987, EMBASE: 1093, Cochrane Library: 28) (Fig. 1) of which 59 were found eligible. An additional 386 potential articles were identified from the references of which 20 were eligible. In total, 79 articles were included in the qualitative analysis. Of these, 7 investigated argon, 22 helium, 56 xenon, and 1 neon. Five articles compared noble gases. All but 3 were animal studies. Quantitative data for meta-analyses could be extracted from 50 papers resulting in 244 effect sizes.

Quality Assessment

Randomisation was performed in 71% (56/79) of studies. Only 5% (4/79) of the experiments were performed double blind, meaning that, for animal studies, both the investigators performing the experiments and the investigators assessing the outcome were blinded. In contrast 49% (39/79) were single blinded studies. Nearly all studies (78/79) mention animal characteristics but only 61% (48/79) provide details on animal drop-out. 20% (16/79) of studies describe sample size calculation. 23% investigated dose-response relationships (18/79) and 16% the most effective window of opportunity (13/79). 41% (32/79) received 2/5 on the Jadad-scale. 16% (13/79) scored 3/5 on the Jadad-scale and were the highest scoring articles (Tables 1, S2-4).

Data synthesis

Tables S5-7 give an overview of the studies included in the systematic review. They summarize the animal model used, the type of injury inflicted, the duration, timing and dose of noble gas administration, the endpoints and effects. Table S8 shows the individual SESs of all endpoints included in the different meta-analyses.

Argon (Table S5)

Brain

Individual studies with argon *postconditioning* in experiments of brain ischemia in rodents report improved neuron survival and neurological function (12-15). A dose-response experiment showed better results for higher doses: neurological outcome in rats after 7 min of cardiac arrest was best when 70% argon was inhaled (14). Notably, the meta-analysis did not show a beneficial effect of argon in this setting (Fig. 2, Table 1).

No experiments on argon *preconditioning* are available.

Heart

One report showed a reduction in myocardial infarct size after *preconditioning* with argon 70% using three intermittent 5 min exposures (16).

Kidney

Reconditioning rat kidneys by preserving them in an argon-saturated perfusion solution showed higher creatinine clearance post-transplantation when compared to controls (17).

Helium (Table S6)

Brain

Late *preconditioning* with 3x5 min of 70% helium significantly reduced the infarct ratio (area of infarcted brain tissue/area at risk) in rodents. Furthermore, it increased the number of viable neurons and improved sensorimotor function 5 weeks later (18).

Helium was also investigated during *postconditioning* with only high doses being effective, as 70% helium (but not 30%) inhaled during 1h immediately postreperfusion reduced infarct size and neurologic deficit. The protective effect disappeared when helium was started 30 or 60 min postreperfusion (19). On the other hand, some studies show that helium is protective even when started later after reperfusion: 3h of 75% helium started 1h after reperfusion reduced infarct volume and neurologic deficit (20). Helium also improved neurological function but was unable to decrease infarct volume when administered 2h after reperfusion (12).

Starting 70% helium during ischemia and continuing it during postreperfusion decreased infarct volume and neurological deficit as well (21).

Meta-analyses summarizing these various findings showed that helium improves neurological function but has no effect on infarct size (Fig. 3, Table 1).

Endothelium

In human volunteers, 3x5 min cycles of *preconditioning* with 79% helium 24h or 5 min before forearm ischemia, induced by inflating a blood pressure cuff, preserved the endothelial response to the vasodilator acetylcholine on venous occlusion plethysmography, while this response was blunted in controls (22). In a different setting with continuous inhalation of 50% helium from 15 min before to 5 min after IRI, inflammatory and pro-coagulant markers were reduced in human volunteers but endothelial function did not improve (23).

Heart

Individual rodent and rabbit studies show that 3x5 min of 70% helium *preconditioning* significantly reduced infarct ratios (16, 24-31). In rabbits, one cycle of 5 min reduced infarct ratio, but 3 cycles were more potent with no added benefit of 5 cycles (28). However, Pagel found a reduced infarct ratio after 1 cycle of helium combined with morphine, but not after 1 cycle of helium (25).

Late preconditioning with 30, 50, or 70% helium significantly reduced infarct ratios in a rodent model of cardiac ischemia (32). Repeated helium exposure at 48 or 72h before ischemia did not reduce infarct ratio further (32).

Similarly, 15 min of *postconditioning* reduced infarct ratio, but no additive effect was found when postconditioning was supplemented with preconditioning (33).

Interestingly, the efficacy of helium pre- and postconditioning seems to depend upon the absence of obesity (31). When lean and obese Zucker rats with 25 min of left coronary artery ligation received pre- or postconditioning, infarct ratio was only reduced in lean rats. This was likely caused by a reduced effect of helium on mitochondrial respiration (31).

Reconditioning (15 min pre- until 3h post-IRI) with 70% helium had no effect (34).

Combining these data in meta-analyses showed a significant effect of helium on infarct size in rabbits and a positive, non-significant effect in rodents (Fig. 3, Table 1).

Kidney

Reconditioning rabbit kidney grafts with hyperbaric helium at different pressures during cold storage did not improve outcomes compared with hyperbaric oxygen (35). However, dog kidneys transplanted after 12 days of cold storage at -32°C had improved creatinine clearance when hyperbaric helium was added to the storage solution (36).

Liver

In contrast to ischemic preconditioning, *preconditioning* with 70% helium before partial hepatic ischemia in a rat model did not change levels of serum transaminases (37).

Xenon (Table S7)

Brain

Preconditioning

In rats, xenon preconditioning 2h before injury had no effects on ischemic brain injury, while preconditioning 4, 8 or 24h before ischemia reduced infarct volumes and neurologic deficit, the latter only tested for preconditioning at 4h (38). Late preconditioning with 70% xenon for 2h decreased infarct size and focal neurological deficit in mice of both genders (39). In a rat model of neonatal asphyxia, a dose-response study found higher xenon-doses to be more efficient as 75% xenon but not 30% reduced infarct size. Interestingly, the combination of 20% xenon and 0.75% sevoflurane also protected the brain, although neither was effective individually (40). Rat pups exposed to intrauterine perinatal asphyxia 4h after treatment of the mother with 35% xenon showed less neurological deficit, neural loss, cellular disorganization and cell shrinkage (41).

Reconditioning

Rodent experiments on xenon reconditioning have repeatedly demonstrated decrease of infarct volume and neurological deficit (42-44). In dose-response studies, 70% xenon was found to be most effective with respect to histological findings and neurologic function, but positive results were already observed with concentrations as low as 35-40% (42, 43). 60% xenon during cardiopulmonary bypass ameliorated bypass-induced neurocognitive damage in rats (44).

Xenon reconditioning during cardiac arrest in pigs showed decreased brain injury markers (glycerol, lactate) (45).

Postconditioning

All included rodent experiments showed that xenon-postconditioning improved neurologic outcome, reduced infarct size and histological injury (12, 43, 46-55). One study observed long-term neurological improvement at 10 weeks follow-up (50). In two studies, xenon was delivered via echogenic liposomes encapsulating the gas in a hydrophilic core surrounded by a phospholipid bilayer. Ultrasound exposure triggered the release of the gas from the liposome at the target location, resulting in a reduction in infarct size and significantly better neurologic outcomes (46, 51).

The protective effects of xenon were most pronounced when administered soon after the ischemic insult, preferably within 8h (43, 47, 51). Of note, xenon combined additively with hypothermia to

provide neuroprotection, even when administered asynchronously (43, 50, 54, 56). In rats, the co-administration of 3h of hypothermia together with 60 min of xenon improved histology and behavioral testing compared with hypothermia alone. Interestingly, female rats receiving any combination of hypothermia and xenon performed significantly better at the motor test, while no gender-related differences could be found on histology (54).

In a rat model of thromboembolic stroke, administration of 50% xenon after 45 min of cerebral ischemia and subsequent injection of tissue plasminogen activator (tPA) reduced infarct volumes and suppressed cerebral hemorrhage. Notably, the simultaneous intra-ischemic co-administration of xenon and tPA led to an increased infarct volume (53). Several in vitro, ex vivo and in vivo studies have shown that noble gases are tPA-inhibitors.(53, 57-59)

Dose-dependent protective effects of xenon were shown in a perinatal focal ischemia model in which neuroprotection was demonstrated with xenon concentrations $\geq 60\%$ (43). Paradoxically, decreased neurological deficit and infarct volume were shown with xenon 30%, but not with 15% or 45%. The effect of 30% xenon was no longer apparent 28 days post-injury (52).

The ideal duration of xenon administration was also investigated and 8, 20 and 44h of 30% xenon all demonstrated improved neurological function 7 days after injury (52).

Low dose xenon (20%) in combination with hypothermia (35°C) administered 4h after the insult decreased neuronal injury and neurological deficit while neither did so individually (43).

These promising results in rodent models could only be partly reproduced in porcine models. Fries performed three studies in which pigs were exposed to 8 or 10 min of cardiac arrest followed by resuscitation and postconditioning with 70% xenon (60-62). Xenon administered 1h after resuscitation improved short-term neurocognitive function and histology, with animals receiving only 1h of xenon performing slightly (albeit not significantly) better than those receiving xenon during 5h (60). When xenon administration was started earlier, at 10 min after resuscitation, only a non-significant trend towards improved neurologic recovery was seen (61). These findings were corroborated by Derwall, who, in a similar model, found the same positive effect of delaying

postconditioning for 1h and a slight but non-significantly better result of 1h of xenon compared to 5h (63). The combination of either a short (1h) or long (18-24h) period of xenon administration and mild hypothermia immediately after resuscitation improved functional recovery and histologic injury (62, 64, 65). But not all studies reported an added benefit of the combined treatment over hypothermia alone (65).

Meta-analyses

The meta-analysis of xenon administration in rodent models of brain ischemia showed neuroprotection as assessed by infarct size, histological changes, and neurological function. Summarizing the various finding in pigs could not show a significant effect for xenon when compared to controls (Fig. 4, Table 1).

Spinal cord

Xenon *postconditioning* after spinal ischemia in rats reduced neurologic deficit and increased the number of normal neurons (66, 67). These findings could not be reproduced in a rabbit model using *reconditioning* (68).

Heart

Early xenon *preconditioning* in rat and *ex vivo* rabbit models reduced infarct ratios, improved function and reduced the release of cardiac enzymes (69-73). Weber linked the preconditioning mechanism to the cytoskeleton (74). Late preconditioning reduced the infarct ratio in rats as well (75). In contrast, early xenon preconditioning in pigs did not reduce infarct size (76).

Xenon *postconditioning* has rarely been studied, but beneficial effects on infarct sizes have been reported (77, 78). Schwiebert found a positive effect of xenon postconditioning only for the simultaneous administration of xenon and hypothermia which might be attributed to the use of low xenon concentrations (20%) in this study (78).

Xenon *reconditioning* during ligation of the left anterior descending artery (LAD) reduced cardiac remodeling in a rat model (79). Similar effects were found after LAD ligation in large animals

(pig/dog) in which infarct sizes were reduced (76, 80). This was however less effective than ischemic preconditioning (76). Of note, no effects could be seen with xenon preconditioning (76).

Moreover, in pigs, Baumert did not find a significant difference between xenon combined with isoflurane and isoflurane alone (81). Hein exposed pigs to 70% xenon from 60 min before until 2h after ischemia and found positive effects on both infarct size and hemodynamic stability (82, 83). The same model showed however that xenon reconditioning led to more apoptotic cells in the myocardium when compared to isoflurane anesthesia (84).

Xenon was cardioprotective in both rodent and pig models in meta-analyses (Fig. 4, Table 1).

Kidney

Xenon *preconditioning* exerted beneficial effects on histology and renal function in rodents (85-89). In a rat transplant model, both *pre- and postconditioning* decreased delayed graft function and allograft fibrosis, increasing graft function and survival (85-87).

Xenon *reconditioning* of the kidney during cold storage in canine kidney transplant models in the 1970s showed mixed results (35, 36, 90). More recent studies, where rat kidney grafts were cold-stored in a xenon-saturated preservation solution and then transplanted, showed improved graft function and histology (17, 91).

These findings were confirmed in meta-analysis, showing improved kidney function with xenon administration (Fig.4, Table 1).

Liver

A case series on xenon anesthesia during liver transplantation, found that all 4 patients were hemodynamically stable, no complications occurred perioperatively and hepatic function was satisfactory 7 days postoperatively (92).

Neon

Heart

One study found a reduced infarct ratio of neon preconditioning in myocardial IRI compared to ischemic preconditioning (16).

Studies directly comparing efficacy of noble gases

Brain

Zhuang exposed neonatal rats to 90 min of 70% xenon, helium or argon 2h after hypoxic-ischemic brain injury (12). After 90 min of hypoxia, all three gases significantly increased the number of viable neurons, with only argon being able to restore cell viability to naive levels. Moreover, when 2h of

hypoxia were applied, the infarct volume was reduced only in animals treated with argon or xenon. Neurocognitive outcomes were improved by all.

Heart

Pagel studied the effects of 3x5 min of 70% helium, argon or neon in a model of myocardial ischemia (16). Intermittent exposure to one of these three gases 5 min before ischemic injury reduced infarct ratio with an efficacy comparable to that of ischemic preconditioning. No significant differences between the noble gases could be found (16).

Kidney

Storing dog kidneys in helium or xenon saturated perfusion fluid at -32°C for multiple days showed that although both gases improved kidney function after transplantation, only xenon had a positive effect on histology (35, 36). Irani found the xenon- and argon-saturation of cold storage solutions to protect against IRI in a rat kidney transplantation model, with this effect being significantly more pronounced for argon (17).

Discussion

The majority of original studies included in this systematic review show a protective effect of noble gases on IRI (argon: 6/7; helium: 18/22; xenon: 48/58; neon: 1/1) across a broad range of experimental conditions, organs and species. Protective effects were mostly described for histological endpoints, organ injury and function. Some studies showed equivalence between noble gases and controls, none revealed detrimental effects with noble gas treatment. When summarizing the effect sizes reported in the original articles by meta-analyses, helium was neuroprotective in rodents and cardioprotective in rabbits. Xenon exerted protective effects in cerebral, cardiac, and renal ischemia in rodents. In pigs, neuroprotection by xenon could not be confirmed, although it was cardioprotective. For argon, not enough effect sizes were available to allow meta-analyses for cardiac and renal IRI. Argon postconditioning after cerebral IRI did not reveal significant benefits of argon

over control. This is perhaps a surprising finding as original studies report neuroprotective effects of argon (recently summarized by several authors (93-95)).

The current study is subject to inherent limitations that should be taken into consideration when interpreting the results. First, despite the broad search strategy and searching the reference lists of the articles for additional relevant studies as well, some publications were likely not identified. Second, studies that have been published later than the day of the literature search might reveal information that could change the findings of the meta-analyses. As an example, two papers on neuroprotection by argon postconditioning in rodents have been published since the search (96, 97). Third, although some of the individual articles are of high quality, the vast majority achieve only low Jadad-scores. Fourth, data-extraction for meta-analyses was possible in only 50/79 papers included in the systematic review (Supplementary Methods), possibly omitting relevant findings. Last, the dissimilarity in experimental conditions tested in the various original studies led to a considerable heterogeneity of the meta-analyses. There was a large variability of reported endpoints and a considerable variation in the experimental set-ups with use of different injury models (hypoxia vs. ischemia), degrees of injury (duration of hypoxia/ischemia), timings, concentrations, and durations of noble gas administration. Moreover, different endpoints, durations of ischemia times, and pre-, re- and postconditioning were grouped to be able to perform meta-analyses. As a result, in most settings large and significant values for heterogeneity (I^2 values) were obtained. Therefore, the summary estimates resulting from the random-effects meta-analyses should be interpreted as a mere summary of various findings, rather than referring to an expected effect size in a well-defined homogeneous setting.

Most of the available evidence describes the efficacy of noble gases to protect against warm ischemia of the brain, heart, and kidney in rodent models. Large animal models have only been used occasionally, mainly to investigate the effects of xenon on IRI in brain and heart. Although organ protective effects are quite obvious in rodent studies, they are less obvious in large animals, stressing

the importance of well-designed large animal studies before conducting clinical trials. Human data are even scarcer. The search strategy only identified three human studies. Two investigated the effects of helium preconditioning on endothelial function and produced contradicting results (22, 23). A third study reports 4 cases of xenon anesthesia during liver transplantation (92). Two human trials that were not identified by our search strategy report on the use of xenon. Arola tested the safety and feasibility of mild therapeutic hypothermia in combination with or without xenon inhalation in 33 survivors of out-of-hospital cardiac arrest (98). The incidence of serious adverse reactions was similar in both groups. Interestingly, 72h-post-arrival troponin was significantly less in the xenon+hypothermia group, probably indicating attenuation of myocardial reperfusion injury (98). Dingley performed a feasibility study on xenon administration during hypothermia in 14 infants suffering from periparturient asphyxia. No adverse effects were seen at 18 months follow-up (99). The same group recently published a feasibility report on xenon delivery during ambulance retrieval of 5 neonates (100). To the best of our knowledge there are no other reports on noble gas administration in the clinical setting of IRI.

There are important questions that need to be resolved before large clinical trials can be started. First, the most effective time point of noble gas administration remains largely unknown. Current evidence seems to show that all three windows of protection (i.e., pre-, post-, and preconditioning) can effectively be used, with preconditioning being most frequently investigated. Only three studies have compared the effects of xenon pre- vs. postconditioning in the same model (85-87). Preconditioning might be the ideal setting for surgical procedures with a predictable onset of ischemia (and reperfusion), including cardiovascular surgery, liver resection, partial nephrectomies, and organ procurement. However, in most clinical settings, the onset of ischemia is unexpected and/or even not precisely traceable, e.g. in cerebral ischemia, myocardial infarction. In these cases, postconditioning seems to be the only pragmatic option for noble gases to exert their potentially protective effects. The transplant setting might particularly benefit from preconditioning, allowing the

explanted organ to be treated during the ischemic phase (using cold storage or machine perfusion) (101), possibly followed by postconditioning in the recipient. Second, the duration of noble gas administration to obtain maximal protection is also still largely unknown and might even be organ-specific. Third, very few studies analyzed dose-response relationships for noble gases *in vivo*. It seems that the extent of protection increases with the administered dose. However, it is unknown whether and how the doses that were found to be protective in animals can be translated to the human setting. It is more than probable that different species show different sensitivity to noble gases, as is reflected by the different minimum alveolar concentrations for xenon in rodents, pigs and humans. Last, only a few studies directly compare the efficacy of different noble gases and therefore a network meta-analysis, which combines direct and indirect evidence, was not performed as it would not be reliable. The comparisons between noble gases in a network meta-analysis would be based entirely on the indirect evidence and estimating 'network incoherence' would not be possible. Furthermore, since the performed meta-analyses yield estimates for each noble gas compared with a control condition, the reader might be tempted to use these estimates to compare the noble gases. However, such comparison would ignore the differences between the studies and is therefore not advisable. Nevertheless, the choice of noble gas has important financial and logistical implications. Xenon is extremely costly due to its scarcity (air contains only 87 ppb) and the herewith-associated complexity of purification. Due to its high costs, xenon has to be administered using closed-circuit ventilators to minimize gas losses. These ventilators are currently not ubiquitously available. Moreover, xenon has anesthetic properties, requires administration by anesthesiologists and –in the setting of cerebral ischemia– may complicate neurological monitoring. In contrast, argon is the third most abundant element in our atmosphere (air contains $\pm 1\%$ argon) and therefore up to 100-times more cost-effective than xenon (94).

Although a detailed overview of the mechanisms of action of noble gases in the setting of IRI is beyond the scope of this systematic review, it is worth mentioning that different mechanisms have

been proposed: suppression of apoptosis, activation of pro-survival pathways, preservation of mitochondrial integrity and anti-inflammatory activity. The interested reader can find an overview in Table 2.

Conclusion

Noble gases show promising results as agents for reducing IRI in the brain, heart, and kidney but proper identification of the most effective noble gas, timing, dose and duration of noble gas administration is urgently required. Furthermore, the effects observed in rodents need to be confirmed in preclinical models in larger animals such as the pig. Additionally, noble gases during hepatic IRI are underexplored and unexplored in lung, pancreas, and intestine.

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Figure legends

Fig. 1 Flow diagram of the literature search.

Fig. 2 Forest plot of the efficacy of argon postconditioning after cerebral ischemia in rodents compared to controls.

The diamond represents the summary effect from meta-analysis for each endpoint (IH or NF). The summary SES was calculated by random-effects meta-analysis; a value above 0 favours argon. Horizontal bars and values in parentheses represent 95%-confidence intervals.

CI, confidence interval; IH, injury/histology; NF, neurological function; SES, standardized effect size

Fig. 3 Forest plot of the efficacy of helium administration in the setting of cerebral and myocardial ischemia in rodents and rabbits compared to controls.

The diamond represents the summary effect from meta-analysis for each endpoint (IH or NF). The summary SES was calculated by random-effects meta-analysis; a value above 0 favours helium. Horizontal bars and values in parentheses represent 95%-confidence intervals.

CI, confidence interval; IH, injury/histology; NF, neurological function; SES, standardized effect size

Fig. 4 Forest plot of the efficacy of xenon administration in the setting of cerebral, myocardial, and renal ischemia in rodents and pigs compared to controls.

The diamond represents the summary effect from meta-analysis for each endpoint (IH or NF). The summary SES was calculated by random-effects meta-analysis; a value above 0 favours xenon. Horizontal bars and values in parentheses represent 95%-confidence intervals.

CI, confidence interval; IH, injury/histology; NF, neurological function; SES, standardized effect size

Table 1 Overview of the meta-analyses performed. A random-effects approach was used.

Organ	Species	Endpoint	Gas	SES	Evaluation between-study heterogeneity				
					95% CI		I ²	Cochran's Q	p-value
Brain	Rat-Mouse	Infarct-Histology	Argon	1.58	-1.31	4.47	73.12	37.2	<0.0001
Brain	Rat-Mouse	Infarct-Histology	Helium	1.90	-0.06	3.86	65.9	17.6	0.007
Brain	Rat-Mouse	Infarct-Histology	Xenon	1.18	0.70	1.65	78.8	2050.4	<0.0001
Brain	Rat-Mouse	Neurological function	Argon	2.31	-0.25	4.86	71.6	77.6	<0.0001
Brain	Rat-Mouse	Neurological function	Helium	1.87	0.86	2.89	70.0	23.3	0.002
Brain	Rat-Mouse	Neurological function	Xenon	0.67	0.33	1.02	82.8	279.2	<0.0001
Brain	Pig	Infarct-Histology	Xenon	0.86	-2.20	3.93	82.1	33.6	<0.0001
Brain	Pig	Neurological function	Xenon	0.63	-0.04	1.29	5.5	25.4	0.38
Heart	Rat-Mouse	Infarct-Histology	Helium	2.04	-0.61	4.69	83.8	117.0	<0.0001
Heart	Rat-Mouse	Infarct-Histology	Xenon	1.83	0.47	3.20	74.7	19.9	0.001
Heart	Rabbit	Infarct-Histology	Helium	4.23	1.93	6.52	80.5	41.0	<0.0001
Heart	Pig	Infarct-Histology	Xenon	1.42	0.38	2.47	36.6	4.7	0.2
Kidney	Rat-Mouse	Kidney function	Xenon	3.26	1.39	5.12	79.0	57.1	<0.0001

SES, standardized effect size

Significant SESs are marked in red

Table 2 Overview of proposed mechanisms of action of noble gases in the setting of ischemia reperfusion injury

	Apoptosis	Survival & Growth	Inflammation & Immunity	Mitochondrial Function & Stability
Upregulation	-	Ref (16, 38, 39, 51, 72, 74, 86-89, 91)	Ref (32, 75)	Ref (14, 16, 24, 26-28, 30, 31, 69-71)
No effect	Ref (84)	Ref (72)	Ref (22, 23, 32, 37, 75, 84, 89)	Ref (32)
Downregulation	Ref (12, 16-18, 26, 28, 38, 39, 41, 43, 51, 65-67, 69, 70, 72, 79, 84-87, 89, 91)	-	Ref (23, 37, 82, 85-87, 91)	-

Supplemental Digital Content

Additional supplemental Information can be found in the online version of this article

Fig.S1: Search strategies used to search PubMed, EMBASE, and the Cochrane Library.

Table S1: Overview of the classifications used in the meta-analyses.

Table S2: Quality assessment of articles on argon treatment in ischemia reperfusion injury.

Table S3: Quality assessment of articles on helium treatment in ischemia reperfusion injury.

Table S4: Quality assessment of articles on xenon treatment in ischemia reperfusion injury.

Table S5: Studies on argon treatment in ischemia reperfusion injury included in the systematic review.

Table S6: Studies on helium treatment in ischemia reperfusion injury included in the systematic review.

Table S7: Studies on xenon treatment in ischemia reperfusion injury included in the systematic review.

Table S8: Overview of individual sizes used in meta-analyses.