A method for calculating the gas volume proportions and inhalation temperature of inert gas mixtures allowing reaching normothermic or hypothermic target body temperature in the awake rat

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Abstract

The noble gases xenon (Xe) and helium (He) are known to possess neuroprotective properties. Xe is considered the golden standard neuroprotective gas. However, Xe has a higher molecular weight and lower thermal conductivity and specific heat than those of nitrogen, the main diluent of oxygen (O_2) in air, conditions that could impair or at least reduce the intrinsic neuroprotective properties of Xe by increasing the critical care patient's respiratory workload and body temperature. In contrast, He has a lower molecular weight and higher thermal conductivity and specific heat than those of nitrogen, but is unfortunately far less potent than Xe at providing neuroprotection. Therefore, combining Xe with He could allow obtaining, depending on the gas inhalation temperature and composition, gas mixtures with neutral or hypothermic properties, the latter being advantageous in term of neuroprotection. However, calculating the thermal properties of a mixture, whatever the substances – gases, metals, rubbers, *etc*. – is not trivial. To answer this question, we provide a graphical method to assess the volume proportions of Xe, He and O_2 that a gas mixture should contain, and the inhalation temperature to which it should be administered to allow a clinician to maintain the patient at a target body temperature.

Key words: xenon; helium; inert gases; gas composition; inhalation temperature; body temperature; hypothermia; hyperthermia; normothermia

INTRODUCTION

Previous research has shown that the chemically and metabolically inert gases xenon (Xe) and helium (He) have neuroprotective properties in models of hypoxic-ischemic, brain ischemia, and traumatic brain insults.[1-18] In line with the critical role played by the N-methyl-D-aspartate (NMDA) receptor in the mechanisms of neuronal death induced by these types of brain insults,[19-22] Xe that is thought to provide neuroprotection by inhibiting the NMDA receptor[23-25] is considered to be the golden standard neuroprotective gas.

However, Xe has a molecular weight of 131 g/mol that is higher than that of nitrogen, the main diluent of oxygen in air which molecular weight is 28 g/mol, and further possesses a thermal conductivity of 5.5 mW/m/K and specific heat of 0.16 kJ/kg•K (at 298°K or 25°C) that are lower than those of nitrogen, which thermal conductivity and specific heat are 25.8 mW/m/K and 1.04 kJ/kg•K, respectively,[26] conditions that could impair or at least reduce the intrinsic neuroprotective properties of Xe by increasing the critical care patient's respiratory workload[27,28] and body temperature. In addition,

in line with its scarcity, Xe suffers an excessive cost of production that is a major obstacle to its clinical development. In contrast, He has a molecular weight of 4 g/mol, which is lower than that of nitrogen, and a thermal conductivity of 155.3 mW/m/K and specific heat of 5.19 kJ/kg•K,[26] which are higher than those of nitrogen, but unfortunately it is far less neuroprotectant than Xe.

As expected from these physical characteristics of Xe, here we show that depending on the temperature at which Xe is inhaled, breathing Xe can induce hyperthermia, a condition that could impair or at least reduce the intrinsic neuroprotective properties of Xe, so that neuroprotection provided by Xe could be less effective than it could be if body temperature would be maintained at 37°C or below. In contrast, as also expected from the physical characteristics of He, we and others have previously have demonstrated that, depending on the temperature at which He is inhaled, breathing He can induce hypothermia.[16,18,29] In line with this finding and the fact that hypothermia is neuroprotective by itself,[30,31] He has been shown to provide inhalation temperature-dependent neuroprotection.[16,18] These hypothermic effects of He are well known in humans in conditions where He is used instead of nitrogen to reduce respiratory workload and avoid nitrogen narcosis during deep dives at atmosphere pressures ranging of 6–61 atm (1 atm = 0.1 MPa). One disadvantage of gas mixtures containing He is the heat loss due to the high conductivitiy of He, which requires the gas inhalation temperature to be increased to about 30°C and more.[31-33]

Mixing Xe and He would allow obtaining a gas mixture with reduced molecular weight and increased thermal conductivity as compared to Xe alone, and furthermore benefiting from the antagonistic properties of Xe at the NMDA receptors and from the hypothermic properties of He depending on the inhalation temperature of such a Xe-He gas mixture. This could be of real interest, since combining Xe with moderate mechanical hypothermia has been demonstrated to induce synergistic neuroprotective effects in models of hypoxia/ischemia.[34,35] However, calculating the thermal properties of a mixture, whatever the substances – metals, rubbers, and even gases, is not trivial and constitutes a complex problem due to the fact that the thermal properties of the elements that constitute the mixture do not vary in a similar fashion when temperature varies and to the presence, in mammals, of thermoregulatory processes.

To answer this question so far the noble gases are concerned, we provide an evidence-based graphical method that allows assessing the volume proportions of Xe, He and oxygen (O_2) that a gas mixture should contain and the inhalation temperature to which it should be administered

to allow a clinician to maintain the patient's body temperature at a target value. To illustrate the method, we provide examples of calculations for gas mixtures containing Xe, He, and O_2 in volume proportions allowing (1) maintaining body temperature at 37°C, or (2) reducing body temperature at 34°C, a temperature shown to provide maximal neuroprotection compared to other hypothermic temperatures.[34]

MATERIALS AND METHODS
Animals
Male adult Sprague-Dawley rats ($n = 25$) weighing 250–280 g were obtained from Janvier (Le Genest Saint-Isle, France). All animal use procedures were approved by the local ethic committee in accordance within the framework of the French legislation for the use of animals in biomedical experimentation, and the European Communities Council Directive issued on 24 November 1986 (86/609/EEC). Before being used, rats were housed at 21 ± 0.5°C in Perspex home cages with free access to food and water for at least one week. Light was maintained on a light/dark reverse cycle with lights on from 8:00 p.m. to 8:00 a.m.

Protocol
Experimental data were obtained as follows. Rats were placed in a closed chamber of 10 L volume, fitted with a viewing window. The effects on the rats' body temperature of a 3-hour treatment with Xe-O_2 or He-O_2 gas mixtures containing 25% O_2 at various gas inhalation temperatures were investigated ($n = 3$–4 per group). The gas flow rate was 6 L/min, a condition that allows maintaining carbon dioxide at a concentration below 0.03%.[16] The temperature at which the gas mixtures were administered was controlled using a heating/cooling system and a temperature probe placed into the closed chamber, as detailed previously.[16] Immediately before and after the 3-hour period of exposure to the above mentioned gas mixtures, the rats' body temperature was measured.

Gas mixtures
Xe, He and O_2 of medicinal grade were obtained from Air Liquide Santé (Paris, France). Gas mixtures containing Xe or He at 75% with the remainder being 25% O_2, were obtained using computer-driven gas mass flowmeters (Aalborg, Orangeburg, NY, USA) of 1% absolute accuracy and an oxygen analyzer to double check that the gas mixture was not hypoxic or did not contain more than 25% O_2.

RESULTS
Experimental data
The effects on body temperature of the inhalation tempera-

ture at which the gas mixtures containing Xe or He at 75%, with the remainder being 25% O_2, are shown in **Figure 1**. Based on these data, we provide an evidence-based graphical method that allows assessing the volume proportions of Xe, He, and O_2 that a gas mixture should contain, and the inhalation temperature to which it should be a delivered, to allow a clinician to maintain the patient's body temperature at a desired target value.

Evidence-based graphical method for modeling and calculating the composition of gas mixtures with defined thermal properties
General principles

The steps of the method are as follows:

1) The experimental effects on body temperature of the gas mixtures containing Xe-O_2 or He-O_2 are fit according to linear regression as shown in **Figures 1, 2**.

2) For a given inhalation temperature, the theoretical body temperatures, labelled Ya for Xe-O_2 and Yb for He-O_2, are calculated using Equation 1 and Equation 2 indicated in **Figure 1**, respectively, and then drawn on the graph.

3) A horizontal line and a vertical line are drawn on the graph respectively from the target body temperature (Y-axis) and gas inhalation temperature (X-axis) values; intersection point between horizontal line and vertical line is labelled Yc.

4) Then, for the given gas inhalation temperature, the respective concentrations of Xe and He required to obtain a target body temperature (T°) are calculated as follows:

% $Xe_{(T°)}$ = ((% Xe + % He + % O_2) – % O_2) × ((Ya – Yb) – (Ya – Yc)) / (Ya – Yb)

% $He_{(T°)}$ = ((% Xe + % He + % O_2) – % O_2) × ((Ya – Yb) – (Yc – Yb)) / (Ya – Yb)

Example n°1

If one considers, as illustrated in **Figure 1**, conditions in which target body temperature is 37°C, gas inhalation temperature is 21°C, and gas mixture's oxygen volume proportion is 25%, then the volume proportions of Xe and He in a gas mixture containing Xe, He and O_2 will be as follows. Particularly for Xe:

% $Xe_{(37)}$ = (100 – 25) × (Yc – Yb) / (Ya – Yb)
% $Xe_{(37)}$ = (75) × (Yc – Yb) / (Ya – Yb)
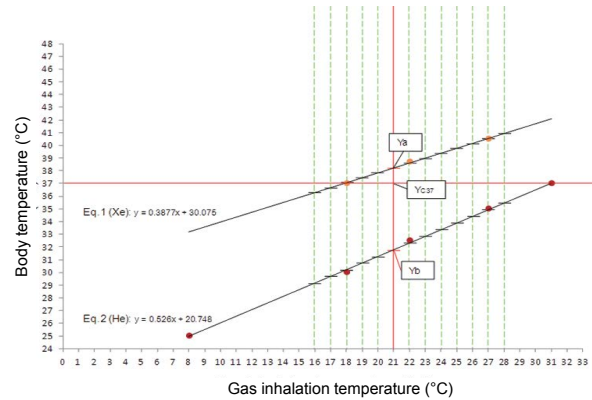% $Xe_{(37)}$ = 75 × (37 – 31.794) / (38.2167 – 31.794)
% $He_{(37)}$ = 75 × 5.206 / 6.4227
% $He_{(37)}$ = 60.79 ≈ 61

All things remaining equal, the concentration of He can be calculated in a similar fashion as follows:

% $He_{(37)}$ = (100 – 25) × (Ya – Yc) / (Ya – Yb)
% $He_{(37)}$ = (75) × (Ya – Yc) / (Ya – Yb)

Figure 1: Estimation of the volume proportions of Xe and He in a Xe-He-O_2 gas mixture containing 25% O_2 with an inhalation temperature of 21°C, and a target body temperature of 37°C, using the experimental effects on body temperature of gas mixtures containing 75% He (brown circles) or 75% Xe (orange circles) in combination with 25% O_2.
Note: Eq: Equation; O_2: oxygen; He: helium; Xe: xenon.

% $He_{(37)}$ = 75 × (38.2167 – 37) / (38.2167 – 31.794)
% $He_{(37)}$ = 75 × 1.2167 / 6.4227
% $He_{(37)}$ = 14.21 ≈ 14
or more simply:
% $He_{(T°)}$ = % Total – (% O_2 + % Xe)
% $He_{(37)}$ = 100 – (25 + 61)
% $He_{(37)}$ = 14

This means that to obtain a target body temperature of 37°C, a gas mixture containing 25% O_2 should be composed of 61% Xe and 14% He if gas mixture inhalation temperature is 21°C.

Example n°2

If one considers conditions illustrated in **Figure 2** in which the target body temperature is 34°C, the gas inhalation temperature is 21°C, and gas mixture's oxygen volume proportion is 25%, then the volume proportions of Xe and He in a gas mixture containing Xe, He and O_2 will be as follows. Particularly for Xe:

% $Xe_{(34)}$ = (100 – 25) × (Yc – Yb) / (Ya – Yb)
% $Xe_{(34)}$ = (75) × (Yc – Yb) / (Ya – Yb)
% $Xe_{(34)}$ = 75 × (34 – 31.794) / (38.2167 – 31.794)
% $Xe_{(34)}$ = 75 × 2.206 / 6.4227
% $Xe_{(34)}$ = 25.76 ≈ 26

All things remaining equal, the concentration of He can be calculated in a similar fashion as follows:
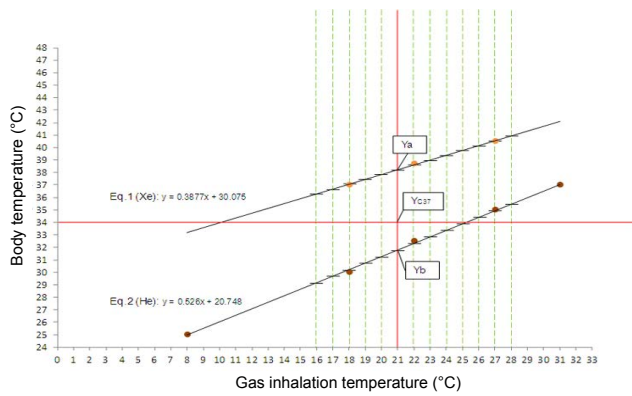
% $He_{(34)}$ = (100 – 25) × (Ya – Yc) / (Ya – Yb)
% $He_{(34)}$ = (75) × (Ya – Yc) / (Ya – Yb)
% $He_{(34)}$ = 75 × (38.2167 – 34) / (38.2167 – 31.794)
% $He_{(34)}$ = 75 × 4.2167 / 6.4227
% $He_{(34)}$ = 49.24 ≈ 49
or more simply:

Figure 2: Estimation of the volume proportions of Xe and He in a Xe-He-O$_2$ gas mixture containing 25% O$_2$ with an inhalation temperature of 21°C, and a target body temperature of 34°C, using the experimental effects on body temperature of gas mixtures containing 75% He (brown circles) or 75% Xe (orange circles) in combination with 25% O$_2$.
Note: Eq: Equation; O$_2$: oxygen; He: helium; Xe: xenon.

% He$_{(T°)}$ = % Total – (% O$_2$ + % He)
% He$_{(34)}$ = 100 – (25 + 26)
% He$_{(34)}$ = 49

This means that to obtain a target body temperature of 34°C, a gas mixture containing 25% O$_2$ should be composed of 26% Xe and 49% He if the gas mixture inhalation temperature is 21°C.

Table 1 shows what the volume proportions of He and Xe should be in a Xe-He-O$_2$ gas mixture containing 25% O$_2$, for a target body temperature set at a value between 32°C and 35°C and inhalation temperature set at a value between 16°C and 24°C.

In practice

Whether a gas mixture containing Xe and He would be developed for clinical use, the volume proportions of such an approved medical gas mixture would be predetermined. In such conditions, **Table 1** indicates to the clinician the temperature range to which the gas mixture should be inhaled by the patient in order to maintain the patient's body temperature at the target value desired by the clinician.

For instance, if one supposes a patient treated with a gas mixture containing 55% He, 20% Xe, and 25% O$_2$ and whose target body temperature is 34°C as decided by the clinician, then the inhalation temperature to which the gas mixture should be administered by the clinician should be typically 22°C. If target body temperature is considered acceptable as being 34 ± 1°C, then the gas inhalation temperature should be maintained between 20°C and 24°C. If target body temperature is considered acceptable as being only 34 ± 0.5°C, then the gas inhalation temperature should be maintained between 21°C and 23°C.

DISCUSSION

In the present report, we investigate the inhalation temperature-dependent effects of Xe and He on body temperature in rats breathing gas mixtures containing Xe or He at 75%, with the remainder being 25% O$_2$. As expected from the molecular weight, thermal conductivity and specific heat of Xe, we found that breathing Xe-O$_2$ gas mixture increases

Table 1: Relationships between gas mixture composition, gas mixture inhalation temperature, and patient's target body temperature (TBT)

Gas inhalation temperature (°C)	TBT = 37°C		TBT = 36°C		TBT = 35°C		TBT = 34°C		TBT = 33°C	
	% He	% Xe	% He	% Xe	% He	% Xe	% He	% Xe	% He	% Xe
16			3	72	13	62	24	51	35	40
17			7	68	18	57	29	46	39	36
18	1	74	12	63	23	52	33	42	44	31
19	5	70	16	59	27	48	39	36	50	25
20	9	66	21	54	32	43	44	31	55	20
21	14	61	26	49	38	37	49	26	61	14
22	19	56	31	44	43	32	55	20	67	8
23	24	51	37	38	49	26	61	14	73	2
24	30	45	42	33	55	20	67	8		
25	35	40	48	27	61	14	74	1		
26	41	34	54	21	67	8				
27	48	27	61	14	74	1				

Note: As an example, if one supposes a patient treated with a gas mixture containing 55% helium (He), 20% xenon (Xe), and 25% oxygen (O$_2$) and whose TBT is 34°C as decided by the clinician, then the inhalation temperature to which the gas mixture should be administered by the clinician should be typically 22°C. If TBT is considered acceptable as being 34 ± 1°C, then the gas inhalation temperature should be maintained between 20°C and 24°C. If target body temperature is considered acceptable as being only 34 ± 0.5°C, then the gas inhalation temperature should be maintained between 21°C and 23°C, approximately (data extrapolated, but can be easily calculated).

body temperature when given at inhalation temperatures above 18°C. Since hyperthermia is a condition well known to be avoided in many human diseases, this increase in body temperature could theoretically impair or at least reduce the intrinsic neuroprotective properties of Xe, so that neuroprotection provided by Xe could be less than it could be expected if body temperature would be maintained at 37°C or below. In contrast, as expected from the molecular weight, thermal conductivity and specific heat of He, He at inhalation temperatures below 31°C produces hypothermia, a condition known to be neuroprotective by itself when mediated either by helium[16,18] or mechanically.[30,31]

Given the thermal properties of Xe and He, mixing Xe with He could allow obtaining gas mixtures with thermally neutral or hypothermic properties, depending on the respective concentration of each gas in the breathing mixture and the inhalation temperature at which the gas mixture would be inhaled. Combining Xe with He in volume proportions allowing to obtain a gas mixture with hypothermic effects could be particularly advantageous in term of neuroprotection, since combining Xe with mechanical hypothermia has been reported to provide synergistic neuroprotective effects in models of hypoxia/ischemia.[34,35] In addition, He-containing gas mixtures – which are expected with little doubt to diffuse homogeneously within all parts of the body – could further allow advantageously avoiding or at least reducing temperature gradients within the body compared to mechanical techniques of hypothermia.

In the present report, we provide an evidence-based graphical method, which resulting equations are applicable within normal range of atmospheric pressure, to allow assessing the volume proportions of Xe, He, and O_2 that a gas mixture should contain, and the inhalation temperature to which it should be administered, to allow a clinician to maintain the patient's body temperature at a target value. Interestingly, as illustrated in **Figure 1** and **Figure 2** and further reported in **Table 1** and as expected from the molecular weight, thermal conductivity, and specific heat of Xe and He, we found that the highest the gas inhalation temperature is, the highest the volume proportion of He should be in order to maintain body temperature at a given target value. As a result, the highest is the volume proportion of He (Ya-Yc), the lowest is the volume proportion of Xe (Yc-Yb) in the gas mixture. This clearly supports reliability of the method. However, whether body temperature as measured in rats after breathing Xe-He gas mixture would be consistent with the predictive results shown in **Table 1** remains to be investigated. Also, translation to humans could need establishing new regression lines regarding the effects of Xe-O_2 and He-O_2 gas mixtures on body temperature. However, once done, the same principles should apply.

In conclusion and alternatively, the method reported in the present study could also be applied for gas mixtures containing He and argon (Ar), another noble gas with neuroprotective and organprotective properties[36-39] that also exhibits, to a lesser extent than Xe however, a molecular weight of 40 g/mol that is higher than that of nitrogen and a thermal conductivity of 17.75 mW/m/K and specific heat of 0.52 kJ/kg•K that are lower than those of nitrogen.[26] As well, the method could also be used for Xe-He-O_2 or Ar-He-O_2 gas mixtures containing O_2 concentration lower or higher than 25% (the O_2 value used in the present study). Indeed, although no experiments were performed in such conditions of O_2 concentration, it can be easily assumed that increasing O_2 up to 50% would have only little effect on the thermal properties of such Xe-He-O_2 or Ar-He-O_2 gas mixtures since O_2 has molecular weight, thermal conductivity and specific heat values that are not far from those of nitrogen, the reference gas and main diluent of O_2 in air.

REFERENCES

1. Ma D, Wilhelm S, Maze M, Franks NP. Neuroprotective and neurotoxic properties of the 'inert' gas, xenon. *Br J Anaesth*. 2002;89:739-746.
2. Wilhelm S, Ma D, Maze M, Franks NP. Effects of xenon on in vitro and in vivo models of neuronal injury. *Anesthesiology*. 2002;96:1485-1491.
3. Petzelt C, Blom P, Schmehl W, Muller J, Kox WJ. Prevention of neurotoxicity in hypoxic cortical neurons by the noble gas xenon. *Life Sci*. 2003;72:1909-1918.

4.   David HN, Leveille F, Chazalviel L, et al. Reduction of isch-emic brain damage by nitrous oxide and xenon. *J Cereb Blood Flow Metab*. 2003;23:1168-1173.

5.   Petzelt C, Blom P, Schmehl W, Muller J, Kox WJ. Xenon pre-vents cellular damage in differentiated PC-12 cells exposed to hypoxia. *BMC Neurosci*. 2004;5:55.

6.   Homi HM, Yokoo N, Ma D, et al. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. *Anesthesiology*. 2003;99:876-881.

7.   Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP. Xe-non attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. *Anesthesiology*. 2003;98:690-698.

8.   Abraini JH, David HN, Lemaire M. Potentially neuroprotective and therapeutic properties of nitrous oxide and xenon. *Ann N Y Acad Sci*. 2005;1053:289-300.

9.   Dingley J, Tooley J, Porter H, Thoresen M. Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. *Stroke*. 2006;37:501-506.

10. Ma D, Hossain M, Pettet GK, et al. Xenon preconditioning re-duces brain damage from neonatal asphyxia in rats. *J Cereb Blood Flow Metab*. 2006;26:199-208.

11. David HN, Haelewyn B, Rouillon C, et al. Neuroprotective effects of xenon: a therapeutic window of opportunity in rats subjected to transient cerebral ischemia. *FASEB J*. 2008;22:1275-1286.

12. Harris K, Armstrong SP, Campos-Pires R, Kiru L, Franks NP, Dickinson R. Neuroprotection against traumatic brain injury by xenon, but not argon, is mediated by inhibition at the N-methyl-D-aspartate receptor glycine site. *Anesthesiology*. 2013;119:1137-1148.

13. Campos-Pires R, Armstrong SP, Sebastiani A, et al. Xenon im-proves neurologic outcome and reduces secondary injury fol-lowing trauma in an in vivo model of traumatic brain injury. *Crit Care Med*. 2015;43:149-158.

14. Pan Y, Zhang H, VanDeripe DR, Cruz-Flores S, Panneton WM. Heliox and oxygen reduce infarct volume in a rat model of fo-cal ischemia. *Exp Neurol*. 2007;205:587-590.

15. Coburn M, Maze M, Franks NP. The neuroprotective effects of xenon and helium in an in vitro model of traumatic brain injury. *Crit Care Med*. 2008;36:588-595.

16. David HN, Haelewyn B, Chazalviel L, et al. Post-ischemic helium provides neuroprotection in rats subjected to middle cerebral artery occlusion-induced ischemia by producing hypo-thermia. *J Cereb Blood Flow Metab*. 2009;29:1159-1165.

17. Pan Y, Zhang H, Acharya AB, Cruz-Flores S, Panneton WM. The effect of heliox treatment in a rat model of focal transient cerebral ischemia. *Neurosci Lett*. 2011;497:144-147.

18. Haelewyn B, David HN, Blatteau JE, et al. Modulation by the noble gas helium of tissue plasminogen activator: effects in a rat model of thromboembolic stroke. *Crit Care Med*. 2016;44:e383-389.

19. Parsons CG, Danysz W, Quack G. Glutamate in CNS disorders as a target for drug development: an update. *Drug News Per-spect*. 1998;11:523-569.

20. Palmer GC, Widzowski D. Low affinity use-dependent NMDA receptor antagonists show promise for clinical development. *Amino Acids*. 2000;19:151-155.

21. Priestley T, Horne AL, McKernan RM, Kemp JA. The effect of NMDA receptor glycine site antagonists on hypoxia-induced neurodegeneration of rat cortical cell cultures. *Brain Res*. 1990;531:183-188.

22. Rogawski MA. Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines. *Trends Pharmacol Sci*. 1993;14:325-331.

23. Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR. How does xenon produce anaesthesia? *Nature*. 1998;396:324.

24. Yamakura T, Harris RA. Effects of gaseous anesthetics nitrous oxide and xenon on ligand-gated ion channels. Comparison with isoflurane and ethanol. *Anesthesiology*. 2000;93:1095-1101.

25. David HN, Ansseau M, Lemaire M, Abraini JH. Nitrous oxide and xenon prevent amphetamine-induced carrier-mediated do-pamine release in a memantine-like fashion and protect against behavioral sensitization. *Biol Psychiatry*. 2006;60:49-57.

26. Encyclopédie des gaz Air liquide. https://encyclopediaairliq-uidecom/fr.

27. Rueckoldt H, Vangerow B, Marx G, et al. Xenon inhalation in-creases airway pressure in ventilated patients. *Acta Anaesthe-siol Scand*. 1999;43:1060-1064.

28. Baumert JH, Reyle-Hahn M, Hecker K, Tenbrinck R, Kuhlen R, Rossaint R. Increased airway resistance during xenon anaes-thesia in pigs is attributed to physical properties of the gas. *Br J Anaesth*. 2002;88:540-545.

29. Tapper D, Arensman R, Johnson C, Folkman J. The effect of helium-oxygen mixtures on body temperature. *J Pediatr Surg*. 1974;9:597-603.

30. Konstas AA, Choi JH, Pile-Spellman J. Neuroprotection for ischemic stroke using hypothermia. *Neurocrit Care*. 2006;4:168-178.

31. Kollmar R, Blank T, Han JL, Georgiadis D, Schwab S. Dif-ferent degrees of hypothermia after experimental stroke: short- and long-term outcome. *Stroke*. 2007;38:1585-1589.

32. Raymond LW, Thalmann E, Lindgren G, et al. Thermal homeo-stasis of resting man in helium-oxygen at 1-50 atmospheres absolute. *Undersea Biomed Res*. 1975;2:51-67.

33. Abraini JH, Gardette-Chauffour MC, Martinez E, Rostain JC, Lemaire C. Psychophysiological reactions in humans during an open sea dive to 500 m with a hydrogen-helium-oxygen mix-ture. *J Appl Physiol (1985)*. 1994;76:1113-1118.

34. Ma D, Hossain M, Chow A, et al. Xenon and hypothermia com-bine to provide neuroprotection from neonatal asphyxia. *Ann Neurol*. 2005;58:182-193.

35. Martin JL, Ma D, Hossain M, et al. Asynchronous administra-tion of xenon and hypothermia significantly reduces brain in-farction in the neonatal rat. *Br J Anaesth*. 2007;98:236-240.

36. Höllig A, Schug A, Fahlenkamp AV, Rossaint R, Coburn M; Argon Organo-Protective Network (AON). Argon: systematic review on neuro- and organoprotective properties of an "Inert" gas. *Int J Mol Sci*. 2014;15:18175-18196.

37. Ulbrich F, Goebel U. The Molecular Pathway of Argon-Medi-ated Neuroprotection. Int J Mol Sci. 2016;17:E1816.

38. Lemoine S, Blanchart K, Souplis M, et al. Argon exposure in-duces postconditioning in myocardial ischemia-reperfusion. *J Cardiovasc Pharmacol Ther*. 2017:1074248417702891.

39. David HN, Dhilly M, Degoulet M, et al. Argon blocks the ex-pression of locomotor sensitization to amphetamine through antagonism at the vesicular monoamine transporter-2 and mu-opioid receptor in the nucleus accumbens. *Transl Psychiatry*. 2015;5:e594.