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 (O2) 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 O2 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

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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 receptor23-25 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 workload27,28 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, 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. In line with this finding and the fact that hypothermia is neuroprotective by itself, He has been shown to provide inhalation temperature-dependent neuroprotection. 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 conductivity of He, which requires the gas inhalation temperature to be increased to about 30°C and more.

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. 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 (O₂) 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 O₂ 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.

**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-O₂ or He-O₂ gas mixtures containing 25% O₂ 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%. 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. 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 O₂ of medicinal grade were obtained from Air Liquide Santé (Paris, France). Gas mixtures containing Xe or He at 75% with the remainder being 25% O₂, 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% O₂.

**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% O₂, 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 O₂ that a gas mixture should contain, and the inhalation temperature to which it should be 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-O₂, or He-O₂ 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-O₂ and Y_b for He-O₂, 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 Y_c.

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

\[
\text{% Xe (T°)} = \left(\frac{Y_c - Y_b}{Y_a - Y_c}\right) \times \left(\% Xe + \% He + \% O_2\right) - \% O_2
\]

\[
\text{% He (T°)} = \left(\frac{Y_c - Y_b}{Y_a - Y_c}\right) \times \left(\% Xe + \% He + \% O_2\right) - \% O_2
\]

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 O₂ will be as follows. Particularly for Xe:

\[
\text{% Xe (37)} = \frac{(100 - 25) \times (Y_c - Y_b)}{Y_a - Y_b}
\]

\[
\text{% Xe (37)} = \frac{(100 - 25) \times (Y_c - Y_b)}{Y_a - Y_b}
\]

\[
\text{% Xe (37)} = \frac{(75 \times (Y_c - Y_b))}{(Y_a - Y_b)}
\]

\[
\text{% Xe (37)} = 75 \times \frac{3.206}{6.4227}
\]

\[
\text{% Xe (37)} = 25.76 \approx 26
\]

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

\[
\text{% He (37)} = \frac{(100 - 25) \times (Y_a - Y_c)}{Y_a - Y_b}
\]

\[
\text{% He (37)} = 60.79 \approx 61
\]

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 O₂ will be as follows. Particularly for Xe:

\[
\text{% Xe (34)} = \frac{(100 - 25) \times (Y_c - Y_b)}{Y_a - Y_b}
\]

\[
\text{% Xe (34)} = \frac{(100 - 25) \times (Y_c - Y_b)}{Y_a - Y_b}
\]

\[
\text{% Xe (34)} = \frac{(75 \times (Y_c - Y_b))}{(Y_a - Y_b)}
\]

\[
\text{% Xe (34)} = 75 \times \frac{3.206}{6.4227}
\]

\[
\text{% Xe (34)} = 25.76 \approx 26
\]

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

\[
\text{% He (34)} = \frac{(100 - 25) \times (Y_a - Y_c)}{Y_a - Y_b}
\]

\[
\text{% He (34)} = \frac{(100 - 25) \times (Y_a - Y_c)}{Y_a - Y_b}
\]

\[
\text{% He (34)} = \frac{(75 \times (Y_a - Y_c))}{(Y_a - Y_b)}
\]

\[
\text{% He (34)} = 49.24 \approx 49
\]

or more simply:
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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% O₂ 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% O₂. As expected from the molecular weight, thermal conductivity and specific heat of Xe, we found that breathing Xe-O₂ gas mixture increases

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**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  | 29  | 46  |
| 17                              | 7   | 68  | 18  | 57  | 33  | 42  | 44  | 31  | 36  | 39  |
| 18                              | 1   | 74  | 12  | 63  | 23  | 52  | 39  | 36  | 50  | 25  |
| 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   | 74  | 1   |
| 25                              | 35  | 40  | 48  | 27  | 61  | 14  | 74  | 1   | 74  | 1   |
| 26                              | 41  | 34  | 54  | 21  | 67  | 8   | 74  | 1   | 74  | 1   |
| 27                              | 48  | 27  | 61  | 14  | 74  | 1   | 74  | 1   | 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 (O₂) 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 or mechanically.

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. 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 O2 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-O2 and He-O2 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 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. As well, the method could also be used for Xe-He-O2 or Ar-He-O2 gas mixtures containing O2 concentration lower or higher than 25% (the O2 value used in the present study). Indeed, although no experiments were performed in such conditions of O2 concentration, it can be easily assumed that increasing O2 up to 50% would have only little effect on the thermal properties of such Xe-He-O2 or Ar-He-O2 gas mixtures since O2 has molecular weight, thermal conductivity and specific heat values that are not far from those of nitrogen, the reference gas and main diluent of O2 in air.

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**Author contributions**

HND performed the experiments, JHA, HND, JJR developed the graphic model, and JHA, NV, JEB, and JJR wrote the manuscript.

**Conflicts of interest**

Monatomics Technology SAS (Paris, France) has patent applications on this work. HND is a shareholder in Monatomics Technology SAS. All other authors declare no competing interest.

**Research ethics**

The study protocol was approved by the local ethic committee at Toulon, France.

**Data sharing statement**

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

**Peer review**

Externally peer reviewed.

**Open access statement**

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