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Short communication

Theoretical and experimental evaluation of the effects of an argon gas mixture on the pressure drop through adult tracheobronchial airway replicas

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ABSTRACT

Argon has the potential to be a novel inhaled therapeutic agent, owing to the neuroprotective and organoprotective properties demonstrated in preclinical studies. Before human trials are performed, an understanding of varying gas properties on airway resistance during inhalation is essential. This study predicts the effect of an 80% argon/20% oxygen gas mixture on the pressure drop through conducting airways, and by extension the airway resistance, and then verifies these predictions experimentally using 3-D printed adult tracheobronchial airway replicas.

The predicted pressure drop was calculated using established analytical models of airway resistance, incorporating the change in viscosity and density of the 80% argon/20% oxygen mixture versus that of air. Predicted pressure drop for the argon mixture increased by approximately 29% compared to that for air. The experimental results were consistent with this prediction for inspiratory flows ranging from 15 to 90 slpm. These results indicate that established analytical models may be used to predict increases in conducting airway resistance for argon/oxygen mixtures, compared with air. Such predictions are valuable in predicting average patient response to breathing argon/oxygen mixtures, and in selecting or designing delivery systems for use in administration of argon/oxygen mixtures to critically ill or injured patients.

1. Introduction

Recently there has been an increased interest in the biological effects of the noble gases: helium, neon, argon, krypton, and xenon (Růzicka et al., 2007; Jawad et al., 2009; Rizvi et al., 2010; Zhuang et al., 2012; Smit et al., 2015). Xenon has been shown to have neuroprotective (Ma et al., 2002, 2006; Wilhelm et al., 2002; Homi et al., 2003; David et al., 2007), cardioprotective (Preckel et al., 2000; Dingley et al., 2001; Schroth et al., 2002) and hepatoprotective (Dabbagh and Rajaei, 2012) properties. Neuroprotective properties have also been identified for helium (David et al., 2009; Oei et al., 2010; Berganza and Zhang, 2013).

Similarly, argon has been found to be neuroprotective and organoprotective (Yarin et al., 2005; Pagel et al., 2007; Jawad et al., 2009; Loetscher et al., 2009; Sanders et al., 2010; Irani et al., 2011; Ryang et al., 2011; David et al., 2012, 2013, 2014; Zhuang et al., 2012; Harris et al., 2013; Brücken et al., 2013). In previous studies the argon concentration ranged from 15% argon in combination with varying concentrations of carbon dioxide, nitrogen and oxygen to 80% argon/ 20% oxygen; administration times varied from 2 to 72 h after a hypoxic-ischemic insult in vitro and in animal models; while treatment times ranged from 2 to 96 h. The exact argon concentration for maximum effect and optimal timing and duration of therapy has not yet been determined. However, based on the promising results of studies utilizing argon, recent investigators have concluded that commencement of clinical investigation in humans appears to be justified (Alderliesten et al., 2014). Argon would potentially be administered via inhalation in combination with oxygen and possibly other medical gases to critically ill or injured patients, ranging from those spontaneously breathing to those mechanically ventilated, hence a range of patient interfaces and respiratory support devices may be required. Therefore, investigating the effects of argon/oxygen

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mixtures on airway resistance is an important step in defining appropriate delivery modalities.

Two noble gases are currently used as inhaled therapeutic agents, xenon and helium. It is known that xenon, which has a density 4.55 times that of air (Katz et al., 2011a), increases airway resistance in a dog model (Zhang et al., 1995) and in human subjects (Rueckoldt et al., 1999) and this effect in vivo is solely due to its physical properties, i.e. its density and viscosity (Baumert et al., 2002). Helium, with a density one-quarter that of nitrogen, reduces airway resistance and the work of breathing when inhaled in mixtures with oxygen (Barach and Eckman, 1935, 1936; Hess et al., 2006; Martin et al., 2012).

The objectives of this study were to determine the effect on pressure drop across hollow adult airway replicas when air is replaced with an 80% argon and 20% oxygen mixture. The hypothesis was that the change in pressure drop measured experimentally across airway replicas for a mixture of 80% argon/20% oxygen versus that for air could be predicted, using established analytic models, based on the change in viscosity and density of the gas mixture.

2. Methodology

To predict the degree of difference in airway resistance when using an 80% argon/20% oxygen gas mixture versus air the following was proposed: the equation for pressure drop (ΔP) in an airway segment developed by Pedley et al. (1970b) and subsequently modified by van Ertbruggen et al. (2005) is:

$$\Delta P_{Modifed\ Pedley} = \gamma\sqrt{Re\frac{D}{L}}\frac{32\mu LU}{D^2} \tag{1}$$

where D is the diameter of the airway segment, L is the length of the airway segment, μ is the dynamic gas viscosity, U is mean velocity of the gas flow, Re is the Reynolds number and γ is a coefficient proposed by van Ertbruggen et al. (2005) to improve agreement between the original Pedley model and their own results obtained using computational fluid dynamics simulation of airflow through an anatomically-based model of the tracheobronchial airways. Values for γ for airway generations 0–3 are 0.162, 0.239, 0.244 and 0.295 respectively.

Given that the values for γ, D, and L would not change between different gas mixtures for any characteristic flow velocity (U) in a particular airway segment, the pertinent determinants of ΔP for the present analysis are the Reynolds number (Re) and the viscosity (μ) of the gas mixture. Therefore, the ratio of the difference in pressure drop across the airway when using 80% argon/20% oxygen versus air can be represented as shown below.

$$\frac{\Delta P_{Ar/O_2}}{\Delta P_{Air}} = \frac{\sqrt{Re_{Ar/O_2}}\times\mu_{Ar/O_2}}{\sqrt{Re_{Air}}\times\mu_{Air}} \tag{2}$$

where:

$$Re = \frac{UD}{\nu} \tag{3}$$

and where ν is the kinematic gas viscosity. Again, assuming consistent values for D, and U between gases, the kinematic viscosity is the sole variable determining variation in the Reynolds number between gases. Therefore, Eq. (2) becomes:

$$\frac{\Delta P_{Ar/O_2}}{\Delta P_{Air}} = \frac{\sqrt{\nu_{Air}}\times\mu_{Ar/O_2}}{\sqrt{\nu_{Ar/O_2}}\times\mu_{Air}} \tag{4}$$

The value of ν, the kinematic viscosity, is equal to the dynamic viscosity divided by the density,

$$\nu = \frac{\mu}{\rho} \tag{5}$$

Thus, Eq. (4) can also be written as:

$$\frac{\Delta P_{Ar/O_2}}{\Delta P_{Air}} = \sqrt{\frac{\rho_{Ar/O_2}\times\mu_{Ar/O_2}}{\rho_{Air}\times\mu_{Air}}} \tag{6}$$

Eq. (6) allows for prediction of the change in pressure drop through an airway when substituting an 80% argon/20% oxygen gas mixture in place of air.

Following the methodology of Katz et al. (2011a) the density and dynamic viscosity for pure argon at 20 °C were calculated based on molecular and Lennard-Jones potential parameters. Density and viscosity of the argon/oxygen mixture were then calculated to be 1.595 kg/m^3 and 2.253×10^{-5} kg/s·m respectively following models described in Katz et al. (2011a).

Inserting the values for the density and viscosity of air and the 80% argon/20% oxygen gas mixture into Eq. (6) gives the following:

$$\frac{\Delta P_{Ar/O_2}}{\Delta P_{Air}} = \sqrt{\frac{1.595\times(2.253\times10^{-5})}{1.200\times(1.806\times10^{-5})}} = 1.288 \tag{7}$$

The prediction was therefore to expect a value for the pressure drop across each hollow adult airway replica to be approximately 29% greater when using the 80% argon/20% oxygen gas mixture compared with the result when air was utilized, when all other conditions remain the same.

The predicted effect of argon on the pressure drop across an airway was verified by performing experiments with five adult tracheobronchial airway replicas, consisting on average of airway generations 0–3, previously fabricated and described by Borojeni et al. (2014, 2015).

The experimental set-up is shown in Fig. 1. Cylinders of a certified standard gas mixture comprising 80/20 vol% of argon/oxygen and cylinders of compressed air were obtained from Praxair Canada. Flow rates of 15, 30, 45, 60, 75, and 90 standard litres per minute (slpm) were delivered to the proximal inlet, i.e. the trachea, of each of the five conducting airway replicas using a gas mass flow controller (MCR 100 slpm; Alicat Scientific, Tucson, AZ). Calibration of the mass flow controller was adjusted for the dynamic viscosity of the argon/oxygen mixture. A length of TYGON® tubing (115 cm × 19 mm ID) was placed between the mass flow meter and the inlet of the airway replicas to allow the flow to develop before entering the replicas. The distal outlets of the airway replicas were open to room atmosphere. The pressures immediately upstream from the airway replicas' inlets were monitored using a digital manometer (HHP-103; OMEGA Engineering, Stamford, CT) with low range 0–498 Pa, high range 0–2590 Pa, and an accuracy of ±0.2% full scale. Each experiment was repeated in triplicate for each airway replica at each flow rate. As the digital manometer reading fluctuated slightly for constant flow rate, for every experiment, maximum and minimum values of the pressure drop

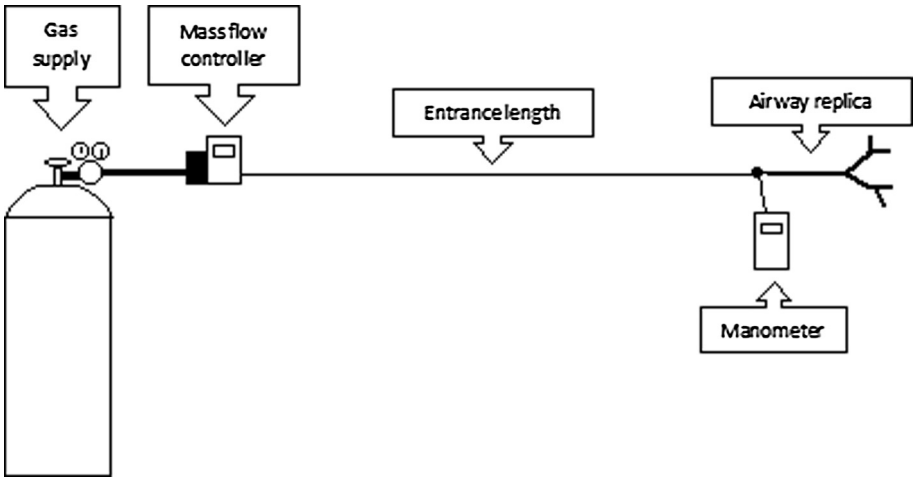

Fig. 1. Experimental equipment set-up to measure pressure drop in conducting airway replicas.