NOTE

The effect of perfluorocarbon vapour on the measurement of respiratory tidal volume during partial liquid ventilation

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Abstract. During partial liquid ventilation perfluorocarbon vapour is present in the exhaled gases. The volumes of these gases are measured by pneumotachometers. Error in measuring tidal volumes will give erroneous measurement of lung compliance during partial liquid ventilation. We aim to compare measured tidal volumes with and without perfluorocarbon vapour using tidal volumes suitable for use in neonates.

Tidal volumes were produced with a 100 ml calibration syringe from 20 to 100 ml and with a calibrated Harvard rodent ventilator from 2.5 to 20 ml. Control tidal volumes were drawn from a humidifier chamber containing water vapour and the PFC tidal volumes were drawn from a humidifier chamber containing water and perfluorocarbon (PC-77) vapour. Tidal volumes were measured by a fixed orifice, target, differential pressure flowmeter (VentTrek) or a hot-wire anemometer (Bear Cub) placed between the calibration syringe or ventilator and the humidifier chamber.

All tidal volumes measured with perfluorocarbon vapour were increased compared with control (ANOVA $p < 0.001$ and post $t$-test $p < 0.0001$). Measured tidal volume increased from 7 to 16% with the fixed orifice type flow-meter, and from 35 to 41% with the hot-wire type. In conclusion, perfluorocarbon vapour flowing through pneumotachometers gives falsely high tidal volume measurements. Calculation of lung compliance must take into account the effect of perfluorocarbon vapour on the measurement of tidal volume.

Keywords: fluorocarbons, partial liquid ventilation, pneumotachometer, tidal volume, lung compliance, measurement error

1. Introduction

Liquid assisted ventilation with perfluorocarbon liquids promises to provide an alternative mode of assisted ventilation for severe lung disease. The technique of partial liquid ventilation was introduced by Fujiwara et al (1991) where perfluorocarbons were instilled into the lungs, at volumes approximating the functional residual capacity, whilst continuing with conventional mechanical ventilation. Partial liquid ventilation has been shown to improve gas exchange and lung function, with decreased secondary lung injury, in animal models of acute lung injury and surfactant deficiency (Titiucic et al 1993, Smith et al 1997, Foust et al 1996, Leach et al 1993, 1995). The majority of the research to date has taken place in the animal laboratory although there are limited results from the use of partial liquid ventilation in

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humans. Human studies have included uncontrolled studies in neonates (Leach et al 1996, Pranikoff et al 1996) and adults (Hirsch et al 1996) and a randomized controlled trial in paediatric patients (Fuhrman et al 1998) with acute respiratory distress syndrome. The majority of studies on humans have used perfluoroctyl bromide (perflubron), although a variety of other perfluorocarbons have been used in humans and animals, including FC-77 (3M Pharmaceuticals, St Paul, MN, USA) (Davies et al 1999, Kuo et al 1998, Dickson et al 1998, Stewart et al 1998a, b). All perfluorocarbons have similar physical properties but also important differences (such as density, vapour pressure, viscosity and surface tension) (Wolfson et al 1998, Lowe 1997). Research into the use of partial liquid ventilation often includes measurement of lung compliance (Davis et al 1996) with pneumotachometers placed between the endo-tracheal tube and ventilator circuit (Tüttinçü et al 1993, Foust et al 1996, Leach et al 1993, 1995, 1996, Pranikoff et al 1996). Pneumotachometers measure the flow of inspiratory and expiratory gases and the volume of gases flowing through them can be calculated from this. These measurements are dependent on the composition of gases flowing through the pneumotachometer (Jaffe 1996, Plak et al 1998, Sullivan et al 1984, Bear Medical Systems Inc, 1997). Perfluorocarbon liquid in the lungs is heated to 37°C and perfluorocarbon vapour is present in the expiratory gases. The effect of perfluoro carbon vapour on tidal volumes measured by pneumotachometers has only been studied with large tidal volumes, that might be used in children or adults, using perflubron (Devabhaktuni et al 1999). We hypothesized that the presence of perfluoro carbon vapour in the gas flowing through pneumotachometers would give inaccurate tidal volume measurements. This study aimed to compare measured tidal volumes with and without perfluorocarbon vapour with tidal volumes suitable for use in neonates using FC-77. We also aimed to determine the correction factor needed to calculate tidal volumes measured with FC-77 vapour.

2. Methods

In the first experiment tidal volumes were produced with a 100 ml calibration syringe (5510 series, Hans Rudolph Inc., Kansas City, MO, USA) from 20 to 100 ml and with a calibrated Harvard rodent ventilator (model 683, Harvard Apparatus, Southnatick, MA, USA) from 2.5 to 20 ml. Control tidal volumes were drawn from a humidifier chamber containing water only. The perfluorocarbon tidal volumes were drawn from the humidifier chamber containing water and FC-77. The humidifier chamber was placed on a Fisher and Paykel MR6-series humidifier (Fisher and Paykel Healthcare Pty Ltd, Ringwood, Australia) set at 37°C with 51 min^-1 O2 bias flow (figure 1). Therefore the control tidal volumes were drawn from a humidifier chamber containing pure (100%) oxygen and water vapour, and the perfluorocarbon tidal volumes were drawn from a humidifier chamber containing pure (100%) oxygen, water vapour and perfluorocarbon vapour. Tidal volumes were measured by a VenTrak respiratory mechanics monitor with a neonatal flow sensor (Novametrix Medical Systems Inc, Wallingford, CT, USA)—a fixed orifice, target flow-meter which calculates flow from the differential pressure across a fixed orifice—placed between the calibration syringe or ventilator and the humidifier chamber. From a pilot sample of 20 tidal volumes with a mean (SD) of 109.9 (0.97) ml a sample size of 30 in each group would give a power of 95% to show a difference of 1 ml ($\alpha = 0.05, \beta = 0.05$).

In the second experiment, the calibration syringe was used to study tidal volumes from 20 to 100 ml with the same set-up as in the first experiment. Measurements were made with a Bear Cub flow sensor (a hot-wire anemometer) attached to the Bear Cub 750vs infant ventilator. From a pilot sample of 20 tidal volumes with a mean (SD) of 93.9 (0.92) ml, a sample size of 20 in each group would give a power of 90% to show a difference of 1 ml ($\alpha = 0.05, \beta = 0.1$).
Figure 1. Experimental set-up for measurement of tidal volumes. B—bias flow, C—humidifier chamber, H—humidifier, L—liquid, M—respiratory function monitor, P—pneumotachometer, R—vapour reservoir, S/RV—calibration syringe or rodent ventilator, T—temperature probe.

3. Results

The control and perfluorocarbon tidal volumes and the percentage difference between them for each set tidal volume are shown in table 1. All tidal volumes measured with perfluorocarbon vapour were increased compared with control. With the VenTrak, the increase in tidal volume measured varied between 7 and 16%. The increase was considerably greater with the hot-wire pneumotachometer with an increase from 35 to 41%.

In order to be able to calculate the true tidal volume from the measured tidal volume in the presence of FC-77 vapour the mean control tidal volume was plotted against the mean perfluorocarbon tidal volume. These regression plots are shown in figure 2. Regression equations for mean control tidal volumes (response, Y) versus mean perfluorocarbon tidal volumes (predictor, X) are:

VenTrak \[ Y = 0.675 + (0.879X) \] \[ r^2 = 0.998 \] \[ p < 0.0001 \]

Bear 750 \[ Y = -1.943 + (0.751X) \] \[ r^2 = 0.999 \] \[ p < 0.0001 \]

4. Discussion

Partial liquid ventilation is a novel technique for providing assisted ventilation to patients with severe lung disease. Perfluorocarbon liquids are a group of chemicals derived from the
Table 1. Tidal volumes measured by two pneumotachometers with 100% oxygen and water vapour (control tidal volumes) and 100% oxygen, water vapour and FC-77 (PFC tidal volumes).

<table>
<thead>
<tr>
<th></th>
<th>VenTrak fixed-orifice pneumotachometer mean (SD) tidal volumes [ml]</th>
<th>Bear Cub hot-wire anemometer mean (SD) tidal volumes [ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control</td>
<td>PFC</td>
</tr>
<tr>
<td>N = 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>120.7 (0.83)</td>
<td>140.1 (1.04)*</td>
</tr>
<tr>
<td>PFC</td>
<td>102.4 (0.82)</td>
<td>111.5 (1.14)*</td>
</tr>
<tr>
<td></td>
<td>79.4 (0.94)</td>
<td>90.9 (2.26)*</td>
</tr>
<tr>
<td></td>
<td>55.8 (0.70)</td>
<td>60.1 (0.59)*</td>
</tr>
<tr>
<td></td>
<td>31.3 (0.44)</td>
<td>34.0 (0.65)*</td>
</tr>
<tr>
<td></td>
<td>20.2 (0.22)</td>
<td>23.0 (0.13)*</td>
</tr>
<tr>
<td></td>
<td>10.4 (0.08)</td>
<td>11.9 (0.10)*</td>
</tr>
<tr>
<td></td>
<td>5.3 (0.06)</td>
<td>6.6 (0.06)*</td>
</tr>
<tr>
<td></td>
<td>2.7 (0.10)</td>
<td>3.1 (0.19)*</td>
</tr>
</tbody>
</table>

* ANOVA p < 0.001 and post t-test p < 0.0001.

Figure 2. Regression plots for control tidal volumes versus perfluorocarbon vapour tidal volumes for the two pneumotachometers.

Fluorination of organic compounds with a carbon chain backbone or ring. Perfluorocarbons are colourless, odourless liquids that are chemically and biologically inert. The properties of perfluorocarbons determine the beneficial effects of partial liquid ventilation (Wolfson et al 1998). Perfluorocarbons have a high oxygen carrying capacity and solubility for CO$_2$—they can dissolve approximately 20 times more O$_2$ and three times more CO$_2$ than water. Whilst during gas ventilation nitrogen is the inert carrier of respiratory gases, during liquid ventilation nitrogen is replaced by perfluorocarbon as the inert carrier of O$_2$ and CO$_2$. The perfluorocarbon is oxygenated and CO$_2$ removed by means of tidal gas movement provided by the gas ventilator. Perfluorocarbons are more dense than water and soft tissue and will mechanically recruit collapsed alveoli. This will happen preferentially in the dependent portions of the lung therefore improving ventilation/perfusion matching and decreasing intra-pulmonary shunting. Perfluorocarbons have a low viscosity that facilitates movement of perfluorocarbon in small peripheral airways. They have low surface tension and when instilled into the lung the air/liquid alveolar interface (which in the surfactant deficient lung has a high surface tension) is abolished, thereby lowering surface tension, increasing compliance and increasing alveolar recruitment. This allows lower ventilator pressures to be used, decreasing ventilator induced lung injury. The physical properties of FC-77 are summarized in table 2 (3M Chemicals 1998, 1999).

The vapour pressure of a liquid determines the amount of substance, near the liquid-gas interface, present as vapour at any given temperature. The majority of perfluorocarbons
Perfluorocarbon vapour and measured lung tidal volume


<table>
<thead>
<tr>
<th></th>
<th>FC-77</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical composition</td>
<td>C₆F₁₄</td>
<td>H₂O</td>
</tr>
<tr>
<td>Molecular weight (g)</td>
<td>415</td>
<td>18</td>
</tr>
<tr>
<td>Boiling point (°C) at 101.3 kPa</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Density (kg m⁻³ x 10⁵) at 25°C</td>
<td>1.78</td>
<td>1.00</td>
</tr>
<tr>
<td>Kinematic viscosity (m² s⁻¹ x 10⁻⁶) at 25°C</td>
<td>0.80</td>
<td>0.89</td>
</tr>
<tr>
<td>Vapour pressure (kPa) at 25°C</td>
<td>5.6</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>at 37°C</td>
<td>11.3</td>
</tr>
<tr>
<td>Surface tension (N m⁻¹ x 10⁻³) at 25°C</td>
<td>15</td>
<td>73³</td>
</tr>
<tr>
<td>O₂ solubility (ml/100 ml) at 25°C</td>
<td>50</td>
<td>2.5</td>
</tr>
<tr>
<td>CO₂ solubility (ml/100 ml) at 37°C</td>
<td>198</td>
<td>65⁹</td>
</tr>
<tr>
<td>Vapour density (air = 1) at 20°C</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

³ at 20°C.
⁹ at 25°C.

being used in partial liquid ventilation research have high vapour pressures, as does FC-77. Therefore, during partial liquid ventilation there will be large amounts of perfluorocarbon vapour in the expired gases passing through the pneumotachometers measuring tidal volume. This study has shown that the presence of perfluorocarbon vapour in the gas flowing through pneumotachometers leads to inaccurate measurement of tidal volumes. This effect has been demonstrated with two different types of pneumotachometer—a fixed orifice, differential pressure flow-meter and a hot-wire anemometer. The degree of inaccuracy of the measured tidal volume is different for the two pneumotachometers.

The only published study on the effects of perfluorocarbon vapour on tidal volumes measured by pneumotachometers found that perfluoron vapour had little effect on tidal volume measurement (Devabhaktuni et al 1999). However, only one type of pneumotachometer was studied (a Lilly type pneumotachometer) using large tidal volumes (100 and 500 ml). Also the experimental set-up used in their study may not have ensured that the gas flowing through the pneumotachometer was fully saturated with perfluoron vapour. The vapour entered the tubing, in which the tidal volumes were measured, via a side arm. In our study tidal volumes were drawn directly from the humidifier chamber to ensure maximal saturation with the perfluorocarbon vapour. Also to more closely mimic the clinical situation we added water to the humidifier chamber to achieve water vapour levels similar to expired air.

The VenTrak pneumotachometer is of the fixed orifice target type, where the target generates a pressure difference across the sensor. The differential pressure is proportional to the square of the flow, although the measured flow is corrected by use of empirically determined coefficients due to variations from this relationship (Jaffe 1996). There is turbulent flow through the sensor and changes in the density of the gas mixture will have a greater effect on this kind of sensor than will changes in the viscosity of the gas (Sullivan et al 1984).

The Bear CUB 750vs pneumotachometer is of the hot-wire anemometer type (Bear Medical Systems Inc. 1997). The flow sensing element consists of two platinum wires maintained at a constant temperature. Gas flow cools the wires, increasing the current needed to maintain the wires at constant temperature. Two wires are required in order to determine the direction of flow—the upstream wire cooling more and requiring more current to maintain constant temperature. Hot-wire anemometers are sensitive to changes in gas composition. The viscosity, density and specific heat capacity of the gas all influence the measured flow (Plakk et al 1998).
All pneumotachometers require correction of the measured flow for gas temperature and composition. The VenTrak allows the gas composition to be manually entered, whereas the Bear Cub 750vs is calibrated to 37°C, ambient pressure and 100% humidity (Bear Medical Systems Inc. 1997). Failure to compensate for the gas composition can lead to large errors in measured flow. For the VenTrak, anaesthetic gases cause measured flow to differ from actual flow by up to 28% and helium can cause errors of 81% (Jaffe 1996). Separate corrections are needed for inspiratory and expiratory phases as the gas composition and temperature are different. This effect will be significant during partial liquid ventilation, as there will be perfluorocarbon vapour present in the expired gas but not in the fresh gas supply. Table 2 shows that the physical properties of the exhaled gas during partial liquid ventilation will be significantly different from that exhaled during conventional ventilation due to the presence of perfluorocarbon vapour.

The use of heat and moisture exchangers is common in paediatric and adult intensive care units. They are placed at the end of the endotracheal tube and are designed to trap exhaled water vapour so that this trapped water vapour can moisturize the inhaled gases. They are not used routinely in neonatal intensive care units because they add an unacceptable amount of dead space—undesirable when ventilating infants with small tidal volumes. As these experiments were designed to investigate the effects of perfluorocarbon vapour on tidal volumes used in neonates we did not study the effect of heat and moisture exchangers placed between the endotracheal tube and the pneumotachometer. The effect of heat and moisture exchangers when used in conjunction with partial liquid ventilation is unknown and warrants further study.

The compliance of the lung \( (C_L) \) is equal to the change in volume \( (ΔV) \) per unit change in pressure \( (ΔP) \) (Davis et al 1996):

\[
C_L = \frac{ΔV}{ΔP}
\]

The higher the compliance the easier it is to inflate the lung with lower pressure (or effort). In parenchymal lung disease such as infant respiratory distress syndrome or acute respiratory distress syndrome the compliance is greatly reduced with higher inspiratory pressures required to inflate the lung. Because the measurement of compliance is proportional to the measured tidal volume the presence of perfluorocarbon vapour causing the tidal volume to be overestimated must be taken into account when calculating compliance in lungs ventilated with perfluorocarbon liquids. A falsely high tidal volume will give a falsely low compliance and suggest improvement in the underlying function of the lung. This improvement may not all be due to the perfluorocarbon per se but in part due to the error resulting from how the lung function is measured.

5. Conclusion

The presence of perfluorocarbon vapour in the gas flowing through pneumotachometers gives falsely high tidal volume measurements. The effect is more marked with the Bear Cub pneumotachometer. An estimate of the true tidal volume allowing for the presence of FC-77 vapour can be made from regression equations. Any calculation of lung compliance must take into account the effect of perfluorocarbon vapour on the measurement of tidal volume.

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Perfluorocarbon vapour and measured lung tidal volume

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