The purpose of this investigation was to evaluate the pulmonary clearance rate of $^{99m}$technetium-diethylenetriaminepentaacetic acid ($^{99m}$Tc-DTPA) through the use of continuous positive airway pressure (CPAP) in different postures. It was a quasi-experimental study involving 36 healthy individuals with normal spirometry. $^{99m}$Tc-DTPA, as aerosol, was nebulized for 3 min with the individual in a sitting position. The pulmonary clearance rate was assessed through pulmonary scintigraphy under spontaneous breathing and under 20 and 10 cmH$_2$O CPAP in the sitting and supine positions. The clearance rate was expressed as the half-time ($T_{1/2}$), that is, the time for the activity to decrease to 50% of the peak value. 20 cmH$_2$O CPAP produced significant reduction of the $T_{1/2}$ of $^{99m}$Tc-DTPA in the supine position ($P = 0.009$) and in the sitting position ($P = 0.005$). However, 10 cmH$_2$O CPAP did not alter the $T_{1/2}$ of DTPA in both positions. The postural variation from supine to the sitting position with 10 cmH$_2$O CPAP ($P = 0.01$) and 20 cmH$_2$O ($P = 0.02$) also reduced the $T_{1/2}$ of $^{99m}$Tc-DTPA. High levels of positive pressure in normal lungs resulted in faster $^{99m}$Tc-DTPA clearance. Moreover, the sitting position further increased the clearance rate of the $^{99m}$Tc radioaerosol imaging in the two pressure levels studied.

**Key words:** Continuous positive airway pressure, $^{99m}$Tc-DTPA, scintigraphy, posture.

**INTRODUCTION**

The application of continuous positive airway pressure (CPAP) produces important hemodynamic alterations, which can influence breathing pattern and heart rate variability and it has been used as supplementary therapy in the clinical treatment of various types of acute respiratory failure, demonstrating effectiveness in chronic
obstructive pulmonary disease (COPD) exacerbations and acute cardiogenic pulmonary edema (ACPE) (Keenan and Mehta, 2009; Nava and Hill, 2009; Mariani et al., 2011; Chaturvedi and Zidulka, 2011). CPAP provides an additional therapy between conventional oxygen therapy and controlled ventilation. It helps to prevent atelectasis, reduce the work of breathing and eliminate or reduce hypoxia (Ashurst, 1995). It allows normalization of the functional residual capacity (Romand and Donald, 1995; Place, 1997). In the management of pulmonary edema, it can improve cardiac output (Baratz et al., 1992) although in normal volunteers without cardiac, edema performance is reduced (Perkins et al. 1989).

The rate at which inhaled aerosol of 99mTc-diethylenetriamine pentaacetate (DTPA) leaves the lung by diffusion into the vascular space can be measured with a gamma camera or simple probe. Many acute and chronic conditions that alter the integrity of the pulmonary epithelium cause an increased clearance rate. Thus, cigarette smoking (Nery et al., 1988; Schmekel et al., 1992), alveolitis from a variety of causes (Uh et al., 1994), adult respiratory distress syndrome (ARDS) (Braude et al., 1986; Tennenberg et al., 1987; Royston et al., 1987), and hyaline membrane disease (HMD) in the infant have all been shown to be associated with rapid pulmonary clearance of 99mTc-DTPA (Jefferies et al., 1984; O’Brodovich and Coates, 1988). Rapid clearance is also promoted by increased lung volume and decreased surfactant activity. Although the mechanism of increased clearance in pathological states is not known, the 99mTc-DTPA lung-clearance technique has great potential clinically, particularly in patients at risk from ARDS and in the diagnosis and follow-up of alveolitis (Coates and O’Brodovich, 1986).

Some authors have evaluated the effect of positive airway pressure on technetium-99m-labeled diethyleneetriaminepentaacetic acid (99mTc-DTPA) aerosol clearance (Cooper et al., 1987; Bishai et al., 2007; O’Brodovich et al., 1986). Positive pressure is responsible for the increase of 99mTc-DTPA clearance, probably due to the increase of the pulmonary volume (Marks et al., 1985; Rinderknecht et al., 1980) and the alveolar area (Bishai et al., 2007; Nolop et al., 1987), as well as changes in the permeability of the intraepithelial junction (Barrowcliffe et al., 1989) or the disruption of the by the pulmonary clearance rate of 99mTc-DTPA. After deposition in the peripheral airways, the tracer seems to cross the alveolar-capillary barrier that comprises the surfactant layer, the alveolar epithelium, the basement membrane, and the capillary endothelium (West, 2003; alveolar surface (West, 2003; Maina and West, 2005).

Body position is also used as therapeutic intervention. Previous studies have reported the influence of the posture and regional pulmonary blood flow on macro aggregates, as well as the behavior of the regional distribution of the pulmonary blood flow in the orthostatic position (Kosuda et al., 2000; Johansson et al., 2004; Richter et al., 2010).

The pulmonary epithelial permeability can be evaluated Coates and O’Brodovich, 1986; Barrowcliffe and Jones, 1987; Oberdorster et al., 1984; Bajic and Jonson, 2011. Due to the importance of the use of the CPAP and the body position in a clinical practice, this investigation aimed to evaluate the pattern of 99mTc-DTPA clearance in healthy subjects using 10 cmH2O and 20 cmH2O CPAP in the sitting and supine positions.

MATERIALS AND METHODS

Subjects
Thirty six (36) healthy volunteers (12 males and 24 females) with an average age of 26 years old were included in the present study. The subjects were nonsmokers, healthy, with no history of cardiovascular, respiratory or neuromuscular dysfunction. None of the women were pregnant. All subjects had normal pulmonary function under clinical medical evaluation. This investigation was conducted by the Serviço de Pneumologia and the Serviço de Medicina Nuclear of the Hospital de Clínicas de Porto Alegre (HCPA). This research was approved by the Ethical Committee (Comissões Científicas e de Ética em Pesquisa e de Radioproteção do HCPA) under the protocol number 02009.

Procedures

An initial clinical assessment was performed, consisting of anamnesis and spirometry. Spirometric tests were performed to assess the normality of the pulmonary function. The forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC relation were evaluated (Collins Survey II Spirometer - Collins, Inc., Boston, USA) and results were expressed according to the norms provided by the American Thoracic Society (Miller et al., 2005).

All volunteers were submitted to lung scintigraphy with a radioaerosol of 99mTc-DTPA in two stages. Firstly, a scintigraphy under spontaneous breathing was performed and after a period of time of one week, another scintigraphy under non-invasive ventilatory support with CPAP (BiPAP® STD/30 Respironics Inc., Pennsylvania, USA) in the same volunteer was carried out. A comparison between these two scintigraphies was performed.

Aerosol lung scintigraphy

99mTc was chelated by adding 99mTc-sodium pertechnetate (740 MBq - 20 mCi) (Instituto de Pesquisas Energéticas e Nucleares, Comissão Nacional de Energia Nuclear, São Paulo, Brazil) to DTPA (DTPATEC-S, Sorin Biomedica S.p.A., Saluggia, Italy) in 5 ml of normal saline (NaCl 0.9% solution) to obtain the radiopharmaceutical 99mTc-DTPA. The radiochemical control
showed a labeling efficiency >95%. The radiopharmaceutical was placed in the nebulizer reservoir (Aerogama, Medical, Porto Alegre, Brazil) with an oxygen flow of 9 l/min, which was inhaled by the volunteers for 3 min at their normal tidal volume while seated. This system produced particles with a mass median aerodynamic diameter of 0.86 µm and a geometric standard deviation of 0.89 (Dalcin et al., 2002). Radioactivity was measured immediately after 32 inhalation in the supine and seated position over a gamma camera (Starcam 4000i, GE, USA) under spontaneous breathing or under CPAP and images were obtained every 20 s for a 30 min period of time. Two regions of interest were defined. Left and right lungs were computer drawn, and a time-activity curve was obtained. The negative inclination of each curve was defined as the clearance of each lung, by using the maximum and minimum values of the clearance. The clearance rate was expressed as the half-life ($T_{1/2}$), which is the time for a 50% reduction of the peak value.

### Lung clearance rate of $^{99m}$Tc-DTPA with continuous positive airway pressure

By a computer-generated randomization scheme, the volunteers were allocated in group 1 (n = 8) (supine 20 cmH$_2$O CPAP); group 2 (n = 8) (sitting 20 cmH$_2$O CPAP); group 3 (n = 11) (supine 10 cmH$_2$O CPAP) and finally, group 4 (n = 9) (sitting 10 cmH$_2$O CPAP).

The noninvasive ventilator supplied gas to the airways through a facial mask fit snugly to the face, providing a perfect fit without causing discomfort. The equipment allowed for adjusting the pressure levels at 10 and 20 cmH$_2$O, respectively (Figure 1). Upon correlating the variables of age, weight, height, and BMI with the clearance rate of DTPA ($T_{1/2}$) radioaerosol, a significant correlation (Pearson and Spearman’s rank correlation) was seen between the height and the $T_{1/2}$ $^{99m}$Tc-DTPA ($r = -0.482$; $P = 0.003$).

Once the interference of height on the pulmonary clearance rate of $^{99m}$Tc-DTPA was evidenced, the ANOVA test for multiple factors was used, followed by the minimum significant differences test in order to evaluate the behavior of the $T_{1/2}$ $^{99m}$Tc-DTPA compound with the use of CPAP in different postures.

### $^{99m}$Tc-DTPA lung clearance

The analysis of the results related to $^{99m}$Tc-DTPA clearance was performed considering the mean clearance of the right and left lung, since no statistical difference was found between the two lungs in the four groups analyzed.

**Table 1. Anthropometric data in the groups studied.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 8)</th>
<th>Group 2 (n = 8)</th>
<th>Group 3 (n = 11)</th>
<th>Group 4 (n = 9)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.25 ± 4.83</td>
<td>25.25 ± 3.69</td>
<td>26.92 ± 9.17</td>
<td>23.88 ± 4.97</td>
<td>0.417</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.66 ± 4.01</td>
<td>75.31 ± 9.68</td>
<td>55.96 ± 4.62</td>
<td>69.75 ± 3.72</td>
<td>0.055</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 ± 0.10</td>
<td>1.76 ± 0.08</td>
<td>1.63 ± 0.06</td>
<td>1.68 ± 0.06</td>
<td>0.004*</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>22.92 ± 2.49</td>
<td>24.11 ± 1.46</td>
<td>21.01 ± 2.14</td>
<td>24.42 ± 7.21</td>
<td>0.379</td>
</tr>
</tbody>
</table>

BMI, Body mass index. Age, weight, height and BMI are reported as means ± SD. The ANOVA test was used to control co-variables (age, height, weight and body mass index – BMI). *The Tukey test detected a height alteration between Groups 2 and 3. *Significance level at $P \leq 0.05$.

**Statistical analysis**

All statistical analyses were performed using a SPSS 15.0 for windows (SPSS Inc. Illinois, USA). All data are presented as mean ± standard deviation (SD). $^{99m}$Tc-DTPA clearance under spontaneous breathing condition and positive pressure was compared to student test. Qualitative data were analyzed by the Chi-square test. Correlations were assessed using Pearson and Spearman’s rank correlation. The analysis of variance (ANOVA) test was used to control co-variables (age, height, weight and body mass index – BMI). A two-tailed $P$ value of 0.05 was considered as significant.

Table 1 shows the anthropometric and spirometric parameters. The anthropometric analysis only revealed a significant difference in height between the two groups ($P = 0.004$). The sample consisted of 12 Caucasian men and 24 Caucasian women, and it has to be mentioned that the gender of the individuals did not interfere in the $T_{1/2}$ of $^{99m}$Tc-DTPA ($P = 0.074$).

Upon correlating the variables of age, weight, height, and BMI with the clearance rate of DTPA ($T_{1/2}$) radioaerosol, a significant correlation (Pearson and Spearman’s rank correlation) was seen between the height and the $T_{1/2}$ $^{99m}$Tc-DTPA ($r = -0.482$; $P = 0.003$).

Once the interference of height on the pulmonary clearance rate of $^{99m}$Tc-DTPA was evidenced, the ANOVA test for multiple factors was used, followed by the minimum significant differences test in order to evaluate the behavior of the $T_{1/2}$ $^{99m}$Tc-DTPA compound with the use of CPAP in different postures.
influence of the variation from the supine to the sitting position on the $T_{1/2}$ $^{99m}$Tc-DTPA aerosol in spontaneous breathing, it was observed that there was a significant reduction from supine to sitting position ($P = 0.009$). In this case, the $T_{1/2}$ varied from 71.80 ± 14.36 to 67.44 ± 24.77, respectively (Figure 1).

**DISCUSSION**

The aim of this investigation was to assess the pattern of $^{99m}$Tc-DTPA clearance in healthy subjects using 10 and 20 cmH$_2$O CPAP in the sitting and supine positions. The results show that 20 cmH$_2$O CPAP applied both in the supine position and in the sitting position, produced an increase in the pulmonary $^{99m}$Tc-DTPA clearance. However, 10 cmH$_2$O CPAP did not considerably improved the clearance rate.

Marks et al. (1985) evaluated the effect of pulmonary insufflation on the $^{99m}$Tc-DTPA clearance in healthy individuals and showed that the clearance accelerates exponentially with the increase of the CPAP levels between 6 and 18 cmH$_2$O. According to Suzuki et al. (1995), the increase in DTPA clearance occurs due to the distension of the intraepithelial junctions and is neither related to the increase of the area nor to the thickness of the alveolar surface.

According to Egan (1982), accentuated pulmonary hyperdistension is necessary for acceleration for the clearance of intra-alveolar solutes to take place. Some reports suggest that the increase in the DTPA clearance rate occurs in relation to the increase of the pulmonary volume (Chadda et al., 2002; Wright et al., 1997). The mechanisms by which the pulmonary insufflates at elevated volumes causes a $^{99m}$Tc-DTPA clearance increase which is still controversial. Some authors attribute this effect to the increase of the diffusion area of the alveolar surface (Jones et al., 1982), whereas others to the increase of the epithelial permeability (Mason et al., 1984), to the functional changes undergone in the pulmonary surfactant layer (Oberdorster et al., 1984), or to the distension of the intercellular junctions of the alveolar epithelium (West, 2003; Suzuki et al., 1995).

Pulmonary insufflation at high volumes or the use of elevated levels of PEEP can result in microlesions to the alveolar-capillary barrier. In these cases, discontinuity of the endothelial or epithelial layer was seen, but the basal membrane remained intact, possibly because it is formed by type IV collagen, which gives it high tensile resistance. Whether these microlesions occur at the level of the intercellular junctions is still under discussion. These lesions are quickly reversible once the transmural pressure is reduced (West, 2003; Maina and West, 2005; Elliott et al., 1992).

Mechanisms that are generally accepted for increasing airways clearance using non invasive positive pressure such as collateral ventilation or as spontaneously breathing individuals will force breath out harder against resistance causing some degree of active expiration. In both, airway clearance may however enhance the mechanisms responsible for this effect which are not readily apparent. Our results show that there was a significant variation in $T_{1/2}$ $^{99m}$Tc-DTPA radioaerosol in spontaneous breathing when changing from supine to sitting position. The sitting position increased the clearance rate of the DTPA compound in relation to the supine position, probably due to the increase in residual functional capacity (RFC) (Petersson et al., 2009). When evaluating the effect of the postural change with the use of 20 cmH$_2$O and 10 cmH$_2$O CPAP, it was observed that the change in posture from supine to sitting produced an increase in the clearance rate of the $^{99m}$Tc-DTPA.
radioaerosol with the two levels of pressure studied. The distribution of ventilation and pulmonary perfusion varies according to the body's position (Kaneko et al., 1966; Petersson et al., 2009). Previous study demonstrated that RFC lowers considerably from sitting to supine position, because, in the latter position, the gravitational force pushes the relaxed diaphragm cranially (Scott et al., 2006).

However, upon investigating if the positive pressure variation interfered in the $T_{1/2}$ on the DTPA compound, in the sitting position no statistical difference was observed. This is, it is probably because in the sitting position, there is a natural increase in the RFC and optimization of the diaphragmatic mechanics (West, 2003). It is also worth pointing out that as the 99mTc-DTPA compound was limited by diffusion, the increase of the regional blood flow in the sitting position possibly produced a reduction effect on the $T_{1/2}$ of the 99mTc-DTPA aerosol (O'Brodovich et al., 1986).

It is therefore possible that the variation of positive pressure from 20 cmH2O to 10 cmH2O did not produce changes on the $T_{1/2}$ of the 99mTc-DTPA aerosol in the sitting position because of the alveoli units in this position, as they are already too stretched, do not allow variations in the positive pressure to change to any great extent the 99mTc-DTPA clearance (O'Brodovich et al., 1986; Rindenknecht et al., 1980).

The traditional theory which attributes to gravitational force, cause the greater perfusion in dependent lung regions, regardless of the anatomic region, has been questioned (Johansson et al., 2004; Glenny et al., 1991; Mure et al., 2001). The lung is an elastic structure and gravity causes lung parenchyma to stretch at the top and compress at the bottom. Consequently, blood flow will appear to be greater toward the lung bases because of the increased density of blood vessels within the parenchyma and the pioneering studies that formed the basis of the gravitational model did not account for tissue compression down the lung (Hopkins et al., 2007; Glenny, 2008).

The reasons for the increase in the clearance rate of the 99mTc-DTPA with the use of positive pressure are still not totally clear. The present study had some limitations. Firstly, few pressures were tried (only 10 and 20 cmH2O CPAP), so we must take care in attempting to extrapolate our findings to other pressures. Secondly, critical closing pressures of the upper airway were not assessed. Thirdly, the anthropometric analysis revealed a difference in height between the two groups.

In conclusion, considering the conditions of our investigation, we demonstrated that moderate levels of CPAP had minor effect on the pulmonary clearance of 99mTc-DTPA. Moreover, high levels, like 20 cmH2O, resulted in substantial 99mTc-DTPA depuration. Furthermore, the sitting position also increased the clearance rate of the 99mTc radioaerosol expressed by reduction of the $T_{1/2}$ of this compound, both in spontaneous breathing and under positive pressure in the two levels that were evaluated. The physiological importance of our findings is related to the fact that the use of a high level of CPAP and the sitting position seem to increase effectively the alveolar permeability.

Although, these findings are important and these results are of particular clinical relevance for the clearing of radioactive aerosols from the lungs, further investigations are necessary to clarify the physiological bases of the effects of positive pressure on dependent postural lung permeability.

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