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Full Length Research Paper

Continuous positive airway pressure and body position alter lung clearance of the radiopharmaceutical 99mtechnetium-diethylenetriaminepentaacetic acid (99mTc-DTPA)

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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_2O 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_2O 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_2O 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_2O CPAP ($P = 0.01$) and 20 cmH_2O ($P = 0.02$) 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 normalisation 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 ^{99m}Tc-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 ^{99}mTc-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 ^{99m}Tc-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 diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) aerosol clearance (Cooper et al., 1987; Bishai et al., 2007; O'Brodovich et al., 1986). Positive pressure is responsible for the increase of ^{99m}Tc-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 ^{99m}Tc-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; Bajc 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 ^{99m}Tc-DTPA clearance in healthy subjects using 10 cmH_2O and 20 cmH_2O 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 by 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 (FEV_1), forced vital capacity (FVC), and FEV_1/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 ^{99m}Tc-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

^{99m}Tc was chelated by adding ^{99m}Tc-sodim 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 ^{99m}Tc-DTPA. The radiochemical control

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Abbreviations: ^{99m}Tc-DTPA, ^{99m}Technetium-diethylenetriaminepentaacetic acid; **CPAP,** continuous positive airway pressure.

Table 1. Anthropometric data in the groups studied.

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

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 ≤ 0.05.

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_2O CPAP); group 2 (n = 8) (sitting 20 cmH_2O CPAP); Group 3 (n = 11) (supine 10 cmH_2O CPAP) and finally, group 4 (n = 9) (sitting 10 cmH_2O CPAP).

The noninvasive ventilator supplied gas to the airways through a facial mask fit snuggly to the face, providing a perfect fit without causing discomfort. The equipment allowed for adjusting the pressure levels at 10 and 20 cmH_2O. The passage of the flow to the subject took place by means of a 2 m long flexible, corrugated hose made of non-toxic PVC, fitted to the siliconized facial mask, which contains unidirectional valves (inhaling/exhaling) and a cephalic device for mask adjustment.

All the individuals performed lung scintigraphy under spontaneous breathing (baseline), where individuals of the groups 1 and 3 were in supine position and the individuals of the groups 2 and 4 in sitting position. On a week later, scintigraphies were performed in the same individuals with CPAP. The individuals of groups 1 and 3 were in supine position and the pressures (CPAP) were 20 and 10 cmH_2O, respectively while, the individuals of the groups 2 and 4 were in sitting position and the pressures (CPAP) were 20 and 10 cmH_2O, respectively.

The ^{99m}Tc-DTPA radioactivity measurement was taken with the collimator positioned about 1.5 cm in front of the chest. The scoring of the thorax radioactivity was performed at every 20 s during a total examination period of 30 min. After the examination, the noninvasive ventilator was turned off and the facial mask was carefully removed, allowing the subject to breathe normally in ambient air. This protocol was previously described by Coates and O'Brodovich (1986) and Dalcin et al. (2002). All investigators were kept masked to outcome measurements and trial results. Moreover, the participants were blinded just to the pressure level used.

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.

^{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.

Group 1 showed significant reduction in $T_{1/2}$ from 75.05 ± 19.18 to 48.69 ± 20.76 min (P = 0.009). In group 2 there was a reduction in $T_{1/2}$ from 75.03 ± 30.25 to 39.76 ± 9.95 min (P = 0.005). Group 3 did not present any alteration in $T_{1/2}$ (from 67.69 ± 11.28 to 67.39 ± 20.04 min) (P = 0.374) nor did group 4 (from 66.29 ± 20.69 to 54.98 ± 15.99 min) (P = 0.608). The change from a supine position to a sitting one reduced the $T_{1/2}$ with 20 cmH_2O CPAP from 48.69 ± 20.76 to 39.76 ± 9.95 min (P = 0.002) and with 10 cmH_2O CPAP from 67.39 ± 20.04 to 54.98 ± 15.99 min (P = 0.016) (Figure 1).

Upon analyzing the effect of the positive pressure variation in one position only, it was observed that in the supine position, there was significant variation in $T_{1/2}$ from 67.39 ± 20.04 to 48.69 ± 20.76 min with the application of 10 cmH_2O and 20 cmH_2O CPAP, respectively (P = 0.022). In the seated position, there was no significant variation with the changes of the CPAP levels from 10 cmH_2O to 20 cmH_2O (P = 0.572), where the $T_{1/2}$ varied from 54.98 ± 15.98 to 39.76 ± 9.95, respectively (Figure 1). Upon analyzing the

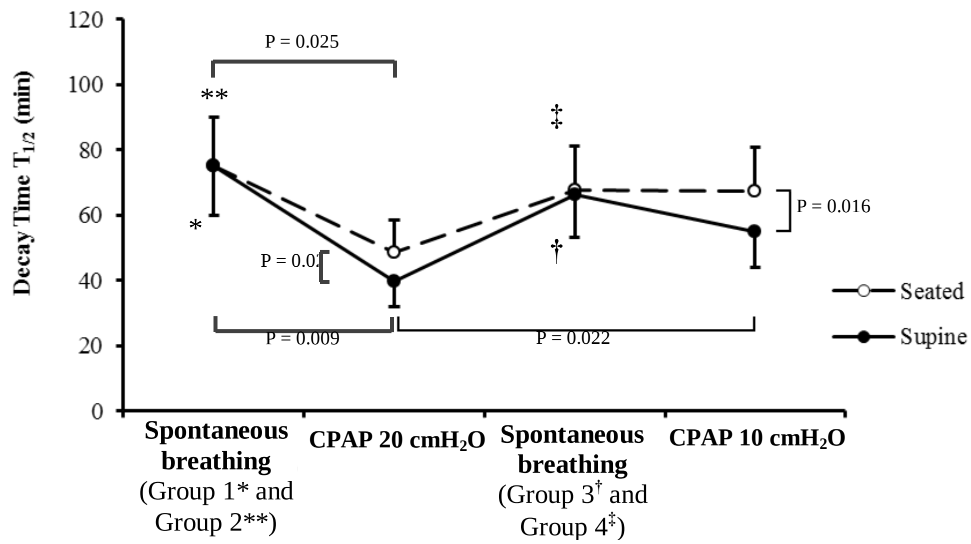

Figure 1. Intragroup and intergroup variation of the time of the transfer half-life of ^{99m}Tc-DTPA ($T_{1/2}$) with 20 cmH_2O CPAP and 10 cmH_2O CPAP in a sitting and supine position.

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_2O CPAP in the sitting and supine positions. The results show that 20 cmH_2O 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_2O 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_2O. 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_2O and 10 cmH_2O 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. In this case, 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 ^{99m}Tc-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 ^{99m}Tc-DTPA aerosol (O'Brodovich et al., 1986).

It is therefore possible that the variation of positive pressure from 20 cmH_2O to 10 cmH_2O did not produce changes on the $T_{1/2}$ of the ^{99m}Tc-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 ^{99m}Tc-DTPA clearance (O'Brodovich et al., 1986; Rinderknecht 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 ^{99m}Tc-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 cmH_2O 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 ^{99m}Tc-DTPA. Moreover, high levels, like 20 cmH_2O, resulted in substantial ^{99m}Tc-DTPA depuration. Furthermore, the sitting position also increased the clearance rate of the ^{99m}Tc 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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