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Title page

Title: Nebulization during spontaneous breathing, CPAP and Bilevel: a randomized analysis of pulmonary radioaerosol deposition.

Running title: Nebulization during spontaneous breathing, nonivansive ventilation, aerosol therapy

Authors

Juçara Gasparetto Maccari MD[a,b]

Cassiano Teixeira MD, PhD[b,c]

Augusto Savi PT, PhD[b]

Roselaine Pinheiro de Oliveira MD, PhD[b,c]

André Sant'Ana Machado MD[b]

Tulio Frederico Tonietto MD[b]

Eduardo Ludwig[d]

Paulo José Zimermann Teixeira MD, PhD[a]

Marli Maria Knorst MD, PhD[a]

Institutions

Graduate Program in Pneumology, Department of Pulmonary Medicine, Federal University of Rio Grande do Sul School of Medicine, Brazil[a]

Department of Intensive Care, *Moinhos de Vento* Hospital, Porto Alegre, Brazil[b]

Federal University of Health Sciences School of Medicine, Porto Alegre[c]

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Department of Nuclear Medicine, *Moinhos de Vento* Hospital, Porto Alegre, Brazil[d]

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Address for correspondence

Juçara Gasparetto Maccari

Ramiro Barcelos, 910 / CTI-Adulto

Porto Alegre, RS – Brasil

Zip-Code: 90035-001

Phone: +55 (51) 3314.3387 / +55 (51) 8426 4286

E-mail: ju.maccari@hotmail.com

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ABSTRACT

Rationale: There have been few reports of factors affecting aerosol delivery during noninvasive ventilation (NIV). Nebulization is a standard practice and our objective was to determine the effect of spontaneous breathing and NIV mode on 99m-Technetium (Tc) lung deposition in subjects with normal lung.

Methods: Thirteen healthcare volunteers were submitted to a randomized radioaerosol nebulization with 99m-Tc during spontaneous breathing (SB), continuous positive airway pressure – CPAP (10 cmH_2O) and bilevel positive pressure ventilation – Bilevel (Inspiratory/Expiratory pressures of 15/5 cmH_2O). NIV was performed by a ResMed VPAP II ST-A. The radioaerosol deposition was evaluated by pulmonary scintigraphy after 10 minutes of inhalation. Regions of interest (ROI) were outlined on left lung (LL) and right lung (RL) and trachea (TRQ). The average number of counts per pixel in each ROI was determined and the ratio of lung and trachea was calculated.

Measurements and Main Results: The three techniques showed comparable lung deposition. Analysis of radioaerosol deposition in the lungs showed a mean count at RL of 108.7±40 with CPAP, 111.5±15 with Bilevel, and 196.6±167 with SB. At LL, the finding values were 92.7±15 with CPAP, 98.4±14 with Bilevel and 225.0±293 with SB. There was no difference between the means of radioaerosol deposition in the RL, LL or TRQ, as well as the lung calculated ratio [LCR = (RL + LL) / TRQ], which was similar comparing ventilatory strategies.

Conclusions: Based on our data, there is an equivalent deposition of inhaled substances in individuals with healthy lungs, when spontaneous breathing, CPAP and Bilevel are compared.

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INTRODUCTION

Many patients suffering from acute respiratory failure (ARF) due to exacerbation of chronic obstructive pulmonary disease (COPD) require some form of ventilatory support [1, 2]. The ventilatory strategy employed in such patients has evolved over the last few years, and noninvasive ventilation (NIV) is now considered as a first-line modality of ventilatory support for patients with exacerbations of COPD [2-6]. NIV has been successfully used to improve gas exchange and avoid intubation [2, 3, 6]. NIV also reduces the work of breathing (WOB) and averts the circle leading to ARF by counterbalancing intrinsic positive end-expiratory pressure (PEEP) with extrinsic PEEP, by unloading respiratory muscles and by augmenting tidal volume (V_T) [5].

Despite the amount of therapies used to treat respiratory diseases, inhalation therapy is usually focused on our clinical practice using metered-dose inhaler (MDI), dry powder inhaler (DPI) or nebulizers [7]. COPD patients receiving NIV also require inhaled bronchodilators for relief of airway obstruction [5, 8]. Nebulization associated with NIV is used in emergency services and intensive care units (ICUs), not only as a form of reverting bronchial obstruction but also of reducing WOB; in fact, the efficiency of nebulized drug during nebulization with NIV depends on the effectiveness of the drug deposition in the lungs [8, 9]. The deposition of an aerosol in the lung may widely vary according to many parameters including the type of nebulizer and the type of compressor used to produce the aerosol, the nebulizer fill, the injected flow and the breathing pattern [9, 10]. Unfortunately, there is a paucity of information regarding the use of aerosol therapy in patients receiving NIV, and the development of guidelines needs better understanding of the factors influencing aerosol drug delivery during this mode of ventilation [7–14]. Thus, heterogeneous drug deposition has been demonstrated *in-vitro* [9, 12, 14, 15] and *in-vivo,* such as healthy [11, 16], cystic fibrosis [17], asthma [8, 18, 19], and COPD individuals [13, 20].

Scintigraphy has been used to analyze peripheral deposition of aerosol during NIV compared with spontaneous breathing (SB) [19]. Previous studies have compared bilevel positive pressure ventilation (Bilevel) with SB [7, 11, 19, 20], and continuous positive airway pressure (CPAP) with SB [12], but the

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comparison of the three methods has not been carried out until now. Therefore, the objective of this study was to analyze the pulmonary regional deposition of radioaerosol administered by nebulization to healthy individuals, during SB and during two modes of NIV (CPAP and Bilevel).

METHODS

Subjects

Thirteen healthy volunteers (10 men and 3 women) were studied. Their mean age was 30.8±4 years and their body mass index (BMI) was 23.3±2.9 kg/m^2. Exclusion criteria were: < 18 or > 60 years, history of smoking or respiratory diseases (COPD, asthma or tuberculosis), cardiac disease, pregnancy, conditions requiring systemic corticosteroids, forced expiratory volume in one second (VEF_1) < 2 L, peak expiratory flow < 300 Liters/min, body mass index > 30 Kg/m^2, neuromuscular disease diagnosis or maximal inspiratory pressure (MIP) > -30 cmH_2O.

Measurements and procedures

Volunteers were enquired about their age, history of smoking and any previous pulmonary illness. Anthropometric data (weight, height and BMI) were collected and cardiopulmonary assessment was then carried out. MIP was obtained using a manometer (Support Famabra, Brazil); forced vital capacity (FVC) and FEV_1 were measured using a spirometer (Satellite, Subminiature ad Jones Spirometer, Windsor, England).

All volunteers were randomly submitted (at least 1 week apart) to Bilevel (Inspiratory/Expiratory pressures of 15/5 cmH_2O), CPAP (pressure of 10 cmH_2O) and SB. The NIV was performed by a ResMed VPAP II ST-A (ResMed Ltd – Sydney, Australia). In both phases, the radioaerosol used was the 99m-Technetium (Tc), generated by jet nebulizer (micronebulizer, NS – São Paulo, Brasil), diluted in 0.9% saline solution to a volume of 3 mL and placed in a leaded box. Aerosol flow was set at 7 L/min coming from an oxygen tank. The tests were all performed in the nuclear medicine department (*Moinhos de*

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Vento Hospital). Radioaerosol inhalation was carried out with subjects using a facemask (Anesthesia Air Cushion Mask), attached by straps on volunteers' head, in seated position. All volunteers were previously trained for mask adaptation and breathing pattern. The circuit is shown schematically in Figure 1.

The 99m-Tc deposition was evaluated with pulmonary scintigraphy after 10 minutes of inhalation. Regions of interest (ROI) were outlined on left (LL) and right lung (RL), trachea (TRQ), mouth and stomach. The average number of counts per pixel in each ROI was determined and the ratio of RL, LL and TRQ was calculated by: lung calculated ratio (LCR) = (RL + LL) / TRQ. The ratio of lung deposition (LL and RL) and number of counts per pixel in mouth, stomach and all sites (TRQ, mouth and stomach) were also calculated.

The study protocol was approved by the institutional ethics committee. All volunteers gave informed consent.

Statistical analysis

Data were presented as mean±SD or median [minimum-maximum]. Lung deposition was analyzed using the Friedman test (repeated measures), with a level of significance of $p<0.05$, for the comparisons of scintigraphic parameters. We used Wilcoxon to compare the lung deposition between Bilevel and CPAP, SB and CPAP, SB and Bilevel. Each subject was his/her own control. The statistical analysis was performed using the program SPSS 16.0.

RESULTS

All 13 subjects were able to perform measurements without problems. The clinical status remained stable during inhalation in all subjects. Table 1 shows the baseline data of subjects. All volunteers had normal spirometric values. Figure 2 represents an example of lung scan obtained at the end of the inhalation (subject #5).

The three techniques showed comparable lung deposition. Analysis of radioaerosol deposition in the lungs showed a mean count at RL of 108.7±40 with CPAP, 111.5±15 with Bilevel and 196.6±167 with SB. At left lung, the finding values were 92.7±15 with CPAP, 98.4±14 with Bilevel and 225.0±293

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with SB. The trachea deposition was also similar: 29.8±25 in CPAP, 28.3±19 in Bilevel, and 39.8±26 in SB. Table 2 shows no differences in radioaerosol deposition when the lung calculated ratio and its comparison with mouth and stomach are evaluated.

Table 3 shows that the LCR was similar in all comparisons and that there was more deposition of radioaerosol in the stomach (ratio [RL + LL]/stomach) when Bilevel ventilatory strategy was compared with CPAP ($p=0.03$).

DISCUSSION

There was no difference in lung regional deposition of radioaerosol delivered via nebulization to healthy individuals, during SB, Bilevel and CPAP. Previous studies have compared Bilevel with SB [8, 11, 20], and CPAP with SB [12], but this is the first study that compares the three ventilatory methods, each subject being his/her own control.

A small number of papers have been published about the treatment of patients who need NIV and bronchodilators, and some authors demonstrated that the delivery of aerosol was enhanced by intermittent positive pressure respiration [18] while other investigators did not [20]. França *et al.* [11] studied the pulmonary radioaerosol deposition during jet nebulization in thirteen healthy volunteers and demonstrated a decrease in deposition during Bilevel ventilation when compared to SB nebulization. This study has an important standardization bias, because the absolute count was used in scintigraphy. We believe that the use of a ratio between lung and trachea deposition is more reliable, because there is no influence of little variations on radioisotope amount.

Dolovich *et al.* [20] studied the distribution of saline technetium-99m pertechnetate in a group of stable COPD patients. In this study, the positive pressure implied a rapid initial flow rate during inspiration with subsequent increased impaction of aerosol against tubing, mouth and proximal airway and overall reduced deposition in the distal bronchi. Our study also evaluated the deposition of aerosol in trachea, mouth and stomach, and the Bilevel strategy increased the deposition of radioaerosol in stomach (based on ratio [RL + LL] / stomach), when compared with CPAP. However, we believe that this difference is not clinically significant because there was no difference between groups

(CPAP, Bilevel or SB) when the ratio of deposition in right and left lung over trachea was compared.

Some authors evaluated the lung drug deposition. Pollack *et al.* [8] proved a significantly increase in peak expiratory flow rate with Bilevel ventilation versus SB during the administration of beta-agonist aerosol, in wheezing patients in the emergency department. Whether aerosol particles were penetrating more deeply with Bilevel ventilatory support could not be determined. In the absence of data on drug deposition, they were unable to discriminate whether the effect was due to NIV itself or to a synergistic action of NIV and beta-adrenergic drug delivery. According to the results of our study, we could assume that there was no difference in aerosol deposition.

Parkes *et al.* [12] evaluated how CPAP delivered by facemask at a flow of 50 L/min and at a pressure of 10 cm/H_2O could influence aerosol kinetics and bronchodilator efficacy in a group of stable asthmatic subjects. They found that in the CPAP-treated group the availability of aerosolized drug was significantly reduced compared to what happened to the same patients inhaling bronchodilators through the same mask without CPAP. Nevertheless, the bronchodilator response was identical in the two groups as far as the dose-response curve and the amelioration of forced expired volume were concerned, and the authors concluded that nebulized beta-agonists were effectively administered by CPAP. Our study included healthy volunteers with normal lung function, making it impossible to evaluate the improvement of peak expiratory flow rate. Despite the equal distribution of radioaerosol suggests the same clinical response, clinical studies in subjects with increased bronchial reactivity are needed to confirm this hypothesis.

Recently, Galindo-Filho *et al.* [19] studied 21 adults with moderate to severe asthma attack who were randomized to a control group (nebulization, n=11) or experimental group (noninvasive ventilation + nebulization, n=10). All patients inhaled bronchodilators for nine minutes, and then particles were counted with a gamma camera to analyze regions of interest and pulmonary clearance at 0, 15, 30, 45 and 60 minutes. The authors conclude that coupling nebulization with NIV during asthma exacerbation did not improve radioaerosol pulmonary deposition, but did improve pulmonary function in patients.

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In addition, there are few studies that evaluate the delivery of MDI in patients on NIV. Nava *et al.* [13] compared the bronchodilator response of salbutamol administered by MDI compared to placebo in a group of stable COPD patients in NIV and SB, and salbutamol was equally effective, whatever the mode of ventilation. Our study evaluates the distribution of radioisotopes delivered via nebulization and is not valid for MDI.

It is known that multiple factors can influence the efficiency of aerosol delivery during NIV, including the type of ventilator, mode of ventilator, ventilator circuit, type of interface, placement of nebulizer in the circuit, drug related factors, breathing parameters and patient-related factors [7, 21]. The results of our study were not influenced by other parameters, since the only variable that changed was the ventilation mode. High inspiratory flows employed during NIV increase turbulence and the associated high inertial forces cause greater particle impaction on central airways [22]. However, this result was not observed in our study. The relationship between the central and peripheral distribution was equal in the three ventilatory modes.

On the other hand, application of positive pressure reduces aerosol particle size, increases tidal volume and reduces respiratory rate, all of which tend to enhance aerosol delivery [23, 24, 25, 26]. Moreover, an increase in expiratory time due to a slower respiratory rate could enhance particle sedimentation and alter the pattern of drug deposition during exhalation [24].

Our study has some limitations. The first is the small sample; however, since all volunteers were their own control, this limitation becomes less important. Secondly, we evaluated subjects with normal lung, and the results cannot be used on patients with sick lung. However, this allows us to better assess the effect of ventilation on distribution of radioaerosol without the influence of structural lung disease. Since the inhalation study was a radioisotope study, masks with exhalation were not used. Therefore, the results are valid for the use of NIV closed system, without regard to loss of contents. Moreover, conclusions about the different positions of exhalation port and mask design cannot be drawn.

Delivery of aerosols to patients receiving NIV is complex. We believe that our study has important clinical and research implications, considering that the use of aerosol during NIV could be effective in the delivery of drugs into lower airways. In our view, this knowledge is necessary to safely study the use of aerosol with NIV on patients with sick lung. Surely, further studies are needed to assess the efficacy of aerosol delivered on NIV in these patients.

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Figure 1: Schematic representation of the circuit of inhalation. a. Facemask; b. T connector, c. Jet nebulizer (connected to an oxygen tank); d. Exhalation valve; e. Inspiration tube; f. NIV machine; g. Passive exhalation (with tubing going to a collection chamber for the radioaerosol particles) .

Figure 2: Image obtained by lung scintigraphy of subject #5.

Figure 3: schematic representation of right (RL) and left (LL) lung areas and of trachea (TQB) for radiation counting.

Table 1: Data of age, body mass index (BMI), maximal expiratory pressure (MEP), maximal inspiratory pressure (MIP), forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), peak expiratory flow rate (PEFR) for the group of subjects.

Subject	Aged (years)	BMI (Kg/m^2)	MEP (cmH_2O)	MIP (cmH_2O)	FVC (L)	FVC (%)	FEV_1 (L)	FEV_1 (%)	FEV_1/ FVC (%)	PEFR (L/min)
1	27	21.3	85	80	3.54	87.4	2.88	83.4	82	400
2	34	23.8	150	125	5.2	107.8	4.62	114.9	88	820
3	27	21.4	150	125	4.2	92.3	3.52	90.2	84	660
4	30	25.3	145	150	4.87	97.9	4.16	100	85	700
5	39	29	150	130	4.11	73.6	3.74	99	90	630
6	26	19.8	110	100	5.03	89	4.25	91	83	600
7	32	21	90	100	4.2	120	3.8	120	90	850
8	30	23.5	150	120	5.6	98.4	4.86	104.5	86	730
9	34	24.9	110	80	4.99	110.3	3.83	100.5	76	900
10	30	20.5	100	90	5.4	92.7	4.44	93.9	82	595
11	30	22.8	120	110	4.99	100.4	4.25	104.1	85	700
12	39	23.3	150	150	5.91	105.1	4.59	101.5	78	800
13	31	25.2	140	140	4.87	95.8	4	96.3	82	700
Mean	31.46	23.36	126.92	115.38	4.83	97.75	4.07	100.56	83.9	698.8
SD	4.14	2.91	25.21	24.28	0.66	11.69	0.52	10.04	4.1	130.8

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Table 2: Data of lung calculated ratio (LCR) and ratio between lung and stomach, mouth and all values using Friedman test (repeated measures).

	SB	Bilevel	CPAP	
	Median (Min – Max)	Median (Min – Max)	Median (Min – Max)	p*
LCR	11.0 (3.9 – 35.9)	9.8 (2.4 – 19.4)	6.0 (1.9 – 12.2)	0.6
LL + RL / stomach	14.7 (2.8 – 258)	4.9 (0.8 – 11.3)	16.6 (2.7 – 267)	0.6
LL + RL / mouth	0.9 (0.4 – 2.3)	1.3 (0.7 – 5.0)	1.0 (0.4 – 10.1)	0.6
LL + RL / (TRQ + stomach + mouth)	0.6 (0.4 – 2.0)	0.8 (0.5 – 2.1)	0.6 (0.4 – 1.9)	0.6

*Friedman test

SB, spontaneous breathing; Bilevel, bilevel positive pressure ventilation; CPAP, continuous positive airway pressure; LCR, lung calculated ratio ([right lung + left lung] / trachea); LL, left lung; RL, right lung.

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Table 3: Data of lung calculated ratio (LCR) and the ratio between lung and stomach, mouth and all values using Wilcoxon test (paired samples).

	p* SB vs. Bilevel	p* SB vs. CPAP	p* Bilevel vs. CPAP
LCR	0.17	0.26	0.4
LL + RL / stomach	0.06	0.89	*0.03*
LL + RL / mouth	0.09	0.57	0.33
LL + RL / trachea + stomach + mouth	0.86	0.89	0.48

*Wilcoxon test

SB, spontaneous breathing; NPPV, noninvasive positive pressure ventilation; CPAP, continuous positive airway pressure; LCR, lung calculated ratio ((right lung + left lung) / trachea); LL, left lung; RL, right lung.

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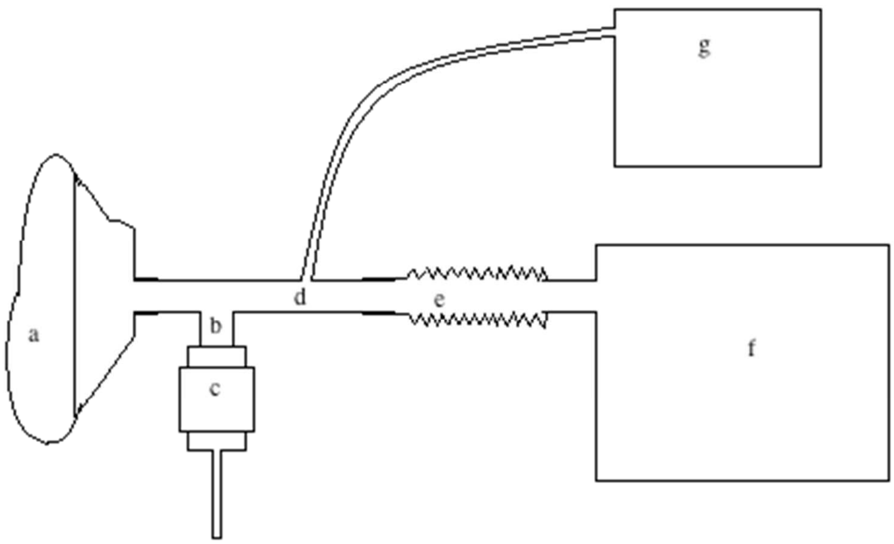

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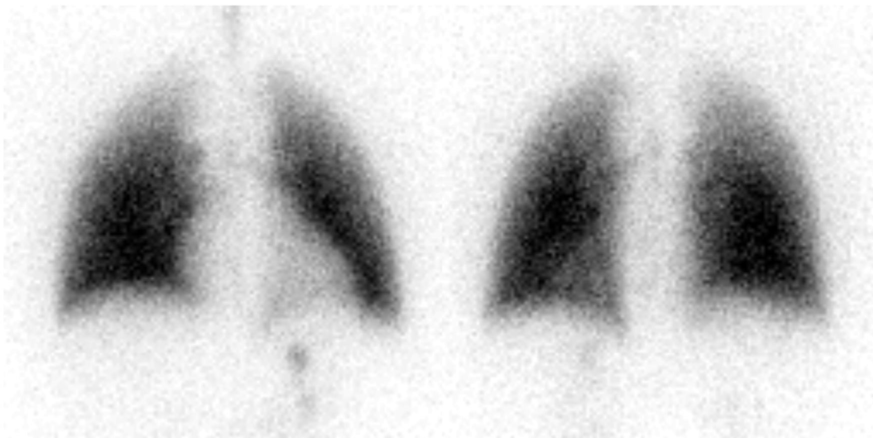

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