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TITLE PAGE

SCINTIGRAPHIC ASSESSMENT OF RADIOAEROSOL PULMONARY DEPOSITION THROUGH ACAPELLA DEVICE WITH DIFFERENT NEBULISER CONFIGURATIONS

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Fabrício O S Mesquita has no conflicts of interest to disclose. Valdecir Castor Galindo-Filho has no conflicts of interest to disclose. João Luis F Neto has no conflicts of interest to disclose. André M Galvão has no conflicts of interest to disclose. Dr Fink is a consultant to Aerogen, Bayer, Boerhinger Ingleheim, Cubist, Dance Biopharm, Novartis, ONY, Parion, Aridis, and the WHO. Armèle Dornelas-de-Andrade has no conflict of interest to disclose.

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ABSTRACT

Background: Acapella® produces high frequency oscillations and positive expiratory pressure (HFOPEP) for use in bronchial hygiene. However, its performance in aerosol delivery has not been described. The aim of this study was to evaluate the effect of nebulizer configuration in relation to the HFOPEP device on deposition of radiotagged aerosols with healthy subjects. Methods: 10 healthy male subjects (mean age of 24.4±2.2 years) participated in a crossover study that compared pulmonary delivery of 4 mL of Tc99m–DTPA(25mCi) and 0.9% saline solution via jet nebulizer with the following configurations: A–nebulizer attached to the distal end of equipment (distal); B -nebulizer placed between the mouthpiece and the device (proximal); and C -inhalation with the nebulizer alone (control). Scintigraphy was performed to count radioaerosol particles deposited in the regions of interest (ROI) in both lungs in vertical (upper, middle, lower) and horizontal (central, intermediate, peripheral) gradients. Results: Deposition between the right and left lungs was similar, with no significant differences between device configurations. Lung deposition was less with A compared to B (p=.001, for both lungs), and C (p=.003 and p=.001, right and left lungs, respectively). No differences were found between configurations B and C. Vertical gradient demonstrated lower deposition with A in comparison to B (upper, p<.0001; middle, p=.001 and lower regions, p=.003) and configuration C (both upper and middle, p=.001; lower regions, p=.002) with up to a 3 fold difference in the middle lower regions. Horizontal gradient also showed a lower deposition in configuration A when compared to B (central,p<.0001 and peripheral,p=.0002) and C (central and peripheral, p=0.002) differences of 3-4 fold were observed in the central and peripheral regions. Conclusion: Placement of jet nebulizer distal to the HFOPEP devise is recommended by the manufacturer decreased intrapulmonary deposition compared placement of the nebulizer between device and the patient airway or the nebulizer alone.

Keywords: Nebulizer, aerosol, pulmonary scintigraphy, deposition, Acapella, HFO, PEP

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INTRODUCTION

The clearance of pulmonary secretions is directly affected by changes in cross-sectional area of the airways, composition and production of mucus in the respiratory tract, ciliary function and cough reflex[1]. Inflammatory and infectious diseases or dyskinetic syndromes as such asthma, chronic bronchitis and cystic fibrosis can involve hypersecretion and blockage of the airways by mucus[2]. The retention of lung secretions can result in complete or partial obstruction of the airways, which results in atelectasis, lung hyperinflation and increased muscles respiratory load[3].

Inhalation of medical aerosols promotes hydration and reduction of secretions viscosity, optimizing mucociliary clearance[4]. Thus, inhalation of drugs transported as inhalable particles may alter mucus rheology and has become clinically accepted as an adjunct to physiotherapy in the treatment of chronic lung conditions[5]. In addition, inhalation increases mucociliary clearance by influencing ciliary function, increasing osmotic drive, and altering mucus viscoelasticity. This results in reduction of viscosity and augmentation of sputum clearance[6].

Bronchial hygiene therapy involves the use of noninvasive and invasive techniques to assist the mobilization and clearance of secretions[7]. Among the methods of bronchial hygiene reported in the literature include positive expiratory pressure (PEP) and high frequency oscillation of the Airway (HFOA). The principle of PEP is based on generating positive pressure to splint open and stabilize airways preventing bronchial collapse. PEP is also thought to improve collateral ventilation to allow better distribution of gas beyond occluded airways[7]. HFOA may have added benefit over the PEP mask alone in helping to dislodge thick secretions from the airway walls and decrease mucous viscoelasticity[8,9]. High frequency oscillation of both the chest wall and airway have been shown to facilitate secretion clearance[10].

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The Acapellas ® is a high frequency oscillatory positive expiratory (HFOPEP) device in which the oscillations are produced as exhaled air is intermittently occluded by the magnetic attraction effect of an internal adjustable valve system. This device allows changes in frequency, oscillation amplitude, and mean pressure through five levels which are adjusted with a dial located at the distal end of the device. It is suggested that the expectoration can be optimized when the applied pressure frequency coincides with the ciliary movement, approximately 13 Hz[10]. This device can be used in any position, does not depend on the slope or level of PEP, and allows the use of concomitant nebulization[11]. The Acapella® allows concomitant aerosol administration during airway clearance.

We hypothesized that the placement of the nebulizer distal to the HFOPEP device as recommended by the manufacturer would reduce lung delivery compared to more proximal placement (between device and mouthpiece) and the use of the nebulizer alone. The aim of this study was to evaluate the effect of aerosol generator placement in two different positions during use of the HFOPEP device on delivery of radiolabelled aerosol to the lungs of healthy subjects.

MATERIAL AND METHODS

Subjects and study design

This randomized crossover clinical trial received approval from the institutional Ethics and Human Research Committee at the Universidade Federal de Pernambuco and subjects gave written consent to participate. It was registered with *ClinicalTrial.gov* with the registration number NCT01102166.

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Inclusion and exclusion criteria

Inclusion criteria into this study were male volunteers with no history of asthma or other lung disease, between 18 to 30 years of age. Spirometry with normal forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and peak expiratory flow (PEF) as ≥ 80 percent of predicted. Exclusion criteria included history of smoking, signs or symptoms of illness (fever, tachycardia and tachypnea) or respiratory disease.

Procedures

A jet nebulizer, (ST3, NS, São Paulo, Brazil) operated at 7 Lpm of compressed air was used in all configurations. Mass median aerodynamic diameter (MMAD) of 3.6 um and geometric standard deviation (GSD) of 2.2 was previously determined with an Anderson Cascade Impactor using standard USP methods.

Device configurations

Subjects were randomly allocated to receive aerosol with 3 device configurations: A - The nebulizer attached to the distal end of the HFOPEP device (DHD Healthcare, Wampsville, New York, EUA), according to the manufacturer's recommendations (distal); B - The nebulizer connected to a "T" piece between the mouthpiece and the HFOPEP device (proximal).; and C - The nebulizer attached to a standard mouthpiece without the HFOPEP device (control) as shown in Figure 1.

A clinical assessment was performed and data measurements included: age, weight, height, body mass index (BMI), spirometry and maximal inspiratory pressure (MIP). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and peak expiratory

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flow (PEF) were performed with a spirometer (Vitalograph 2110, Kansas, USA) according to ATS standards[12]. MIP was performed using a manuvacuometer (MV-150, Marshal-Town Instrument Industry, New York, USA) with subjects positioned in a seated position and instructed to perform a maximal inspiration during a minimum of 1 second with a nose clip[13]. Three measurements were performed and the highest value was considered for analysis.

Scintigraphy procedures were developed in the Department of Nuclear Medicine. Volunteers performed aerosol inhalation based on the randmizatoin schedule and then underwent scintigraphy. For the analysis of pulmonary deposition Tc99m – DTPA (25mCi) in 0.9% physiologic saline solution to a volume of 4 ml was nebulized over 9 minutes. Radioaerosol inhalation was administered through a mouthpiece with all subjects in a seated upright position. All volunteers were previously trained for deep breathing and inspiratory pause[14].

Immediately after aerosol administration radiation counts were measured with a gamma camera (FORTE, Adac Laboratories, EUA) to obtain the images of both lungs during the period of 300 seconds using a matrix of 256x256x16 in the posterior position.

The lung was divided into regions of interest in both the vertical gradient (upper, middle and lower thirds) and the horizontal gradient (peripheral, intermediate and central) (Figure 2) and the radiation counts in the ROIs were recorded on the computer[15]. For each subject a washout period minimum of 7 days was used between radiolabeled aerosol exposure in order to facilitate the clearance of inhaled radioactive material.

STATISTICAL ANALYSIS

For statistical analysis the Kolmogorov-Smirnov Test was used to analyze normality, followed by ANOVA and Tukey's post-hoc test (SPSS version 18.0). The results were

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expressed as mean ± standard deviation (SD), considering a 95% confidence interval to be statistically significant ($p < 0.05$).

RESULTS

Of the 14 healthy males who met inclusion requirement, only 10 completed the protocol, 2 presented complaints of claustrophobia and 2 declined to participate after inclusion. Antropometric characteristics from subjects were: mean age of 24.4 ± 2.2 years, BMI of 22.6 ± 2.6 kg/m^2, PEF of 583 ± 40.8 Lpm, FEV_1 of 4.3 ± 0.5 L, FVC of 4.7 ± 0.6 L and MIP of 110 ± 16.2 cmH_2O.

Deposition between the right and left lungs was similar, with all configurations studied. Analysis of lung deposition demonstrated less total deposition in configuration A compared to B and C as shown in Figure 3. No differences were found between configuration B and C. Differences in regions of interest we up 3 fold greater with B and C compared to A.

When we analyzed the vertical gradient, all three lung regions (upper, middle and lower thirds) demonstrated lower radiation counts for both lungs during configuration A compared to B and C, as shown in figure 4. The ratio of upper to lower deposition was marginally higher with configuration A (0.70±0.21) than with B or C (0.6±0.11 and 0.58±0.12, respectively). Similarly the horizontal gradients show lower radioaerosol counts during configuration A compared to B and C, as demonstrating in figure 5. The ratio of central to peripheral deposition trended lower with configuration A (0.89±0.11) than B or C (1.05±0.23 and 0.93±0.12, respectively).

The distribution of deposition of radioaerosol inside the Acapella varied with nebulizer placement at the inlet of the Acapella (distal), between the device and the mouthpiece (proximal), as shown in figure 6.

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DISCUSSION

The present study showed that placement of a nebulizer at the distal end of the HFOPEP device resulted in significantly less pulmonary deposition of radioaerosol than nebulizer placement proximal to the patient airway or deposition with the nebulizer alone for both right and left lungs.

The primary reason for the lower pulmonary deposition of radioaerosol with distal nebulizer placement is likely the inertial impaction of larger aerosol particles as they pass through the internal mechanisms of the HFOPEP device making less aerosol available for inhalation by the subjects. Internal mechanisms that create turbulent or transitional flows, in presence of inspiratory flow increases the deposition of larger particles[10].

This is supported by the report of Berlinski and Hayden[16] who evaluated changes in particle size distribution of aerosol from two continuously operated jet nebulizers with a variety of PEP and HFOPEP devices. The mass median aerodynamic diameter (MMAD) of aerosol produced by the Hudson nebulizer of 4.1 µm was reduced to 1.2 µm with both the Acapella Choice and Duet when used as recommended by the manufacturer (distal and inferior, accordingly). This supports our supposition that the internal mechanisms of HFOPEP device act as a line filter for larger aerosol particles, reducing the total dose of aerosol available for inhalation (however this was not reported). This reduction in particle size was associated with an increase of fine particle fraction <5 µm from 59% to >87% which might be expected to have a greater peripheral deposition than the larger MMAD produced by the nebulizer alone. This is consistent greater peripheral deposition, or a lower central to peripheral deposition ratio. In testing of the Pari LC Plus with their proprietary PEP valve at settings of 1.5 to 4.5 , Berlinski and Hayden[16] found no changes is MMAD or GSD. Pari PEP systems did not change nebulized albuterol characteristics.

We did not find the hypothesized difference between proximal nebulizer placement (between the HFOPEP device and the patient) and the nebulizer alone in the normal subjects tested. This suggests that placement of the nebulizer between the HFOPEP device and the mouthpiece did not substantially change the fraction of deposited dose in the lung verses control.

Laube et al[17], compared pulmonary delivery of radiolabeled aerosol delivery from a jet nebulizer (LC Plus, Pari, Germany) with and without PEP in CF patients. They reported reduced pulmonary delivery with PEP, and a modestly lower C/P ratio compared to the nebulizer alone. Our findings are consistent to the point that we also had a modest trend toward lower CP ratio and reduced pulmonary deposition with use of the HFOPEP device when used in configuration a, but not with configuration B or C.

In contrast to Berlinski and Hayden[16], Laube et al[17] reported a reduced MMAD of 3.3 µm with PEP and 4.07 without PEP, with similar GSD at 2.61 and 2.78, respectively. This lower MMAD may account for the difference in both pulmonary deposition and distribution. The authors describe use of a controlled breathing pattern on exhalation with PEP to maintain target during expiration. This may have increased expiratory time and reduced the percent of aerosol inhaled from the continuous nebulization, resulting in the reduction *vs* nebulizer alone. The authors reported that they did not find the expected distribution difference to the periphery or upper ROIs in their population of severe CF patients.

In normal subjects, we also did not find the expected level of increase in peripheral or upper lobe distribution of aerosol with the HFOPEP device in either configuration. This might be due to the nature of the normal condition of the airways such that HFOPEP did not have "floppy" airways to splint or obstructed airways for collateral ventilation to impact distal distribution.

We believe that the lower deposition of radioaerosol found with the manufacturer recommended distal position can be attributed to particles impaction in the membrane and internal components of the Acapella device[11]. This increased impaction is secondary to the design of the equipment, which features several internal ducts with small diameters providing greater impaction of particles.

When we analyzed the deposition of radioaerosol in the upper, middle and lower thirds of the lungs, we observed a higher deposition in the middle and lower thirds compared to upper third in all device configurations tested. This distribution in normal subjects may be attributed mainly to the vertical gradient of the existing pleural pressure between the superior (upper) and dependent (lower) portions of the lungs[18].

According to Alderson and Line[19], other factors also influence the distribution of particles into the lungs, such as minute ventilation, inspiratory pressure and nebulization position during inhalation. Ventilation per unit volume decreases from the base to the lung as a result of regional differences in intrapleural pressure resulting from gravitational influences[18].

In the lung, the gravitational and retractable forces act in the same direction, making the subatmospheric intrapleural pressure more negative in the apex in comparison to the lung base, where the gravitational and retractable forces act in opposite directions. As a result, alveoli from the apex become more expanded and less compliant, with a small change in volume during inspiration. Moreover, alveoli from the base are less expanded and more compliant, with a great variation in volume during the inspiration[18]. In addition to this, our findings corroborate with those published involving radioaerosol deposition coupled to positive pressure through bi-level ventilation in normal subjects[14].

Analysis of radioaerosol deposition across the horizontal regions of interest, we found a larger deposition in the intermediate and peripheral regions than central with all

configurations test, with the flow favors deposition in the large airways, owing to the inertial impact and possibly, the greater radioaerosol deposition in those areas is related to the size of the generated particles[19-22]. Another important consideration is that the intrapleural pressure gradient is relatively uniform in the horizontal direction, consequently there is an absence of horizontal gradient of ventilation per unit alveolar volume in the upright position[18].

Our study design utilized normal subjects so that we could have a homogenous population to determine impact of device configuration on pulmonary deposition, without having to account for differences in disease severity. It was beyond the scope of this study to isolate variables in obstructive pulmonary diseases that might impact distribution of aerosol during HFOPEP. As our objective was to determine differences in distribution in the lungs and across regions of interest, we did not perform a mass balance to express lung deposition as a percentage of nominal dose.

In conclusion, this is the first study to analyze radioaerosol deposition in normal subjects with nebulization in association to Acapella device. Placement of the jet nebulizer distal to the HFOPEP device decreased intrapulmonary deposition compared to either proximal placement or use of the nebulizer alone.

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LEGENDS TO FIGURES

Figure 1. Photos of the device and nebulizer configurations : A - nebulizer at the distal end of the HFOPEP device (distal); B - nebulizer attached with a "T" piece between the mouthpiece and device (proximal); and C - nebulizer alone with mouthpiece (control).

Figure 2. Delimitation of regions of interest (ROIs). A. Upper third (U), middle third (M) and lower third (L). B. Central region (C), intermediate region (I) and peripheral region (P).

Figure 3. Mean (± SD) deposition of radiation activity in right and left lungs with the three configurations of the study. *(P = .001). ANOVA and Tukey´s pos-hoc test.

Figure 4. Radioaerosol pulmonary deposition in the upper, middle and lower thirds of the right lung with configuration A (neb distal), B (neb proximal) and C (neb alone). *($p < .0001$), †($p = .001$), □($p = .002$), §($p = .003$). ANOVA test and Tukey´s pos-hoc test.

Figure 5. Pulmonary deposition of radioaerosol in the central, intermediate and peripheral regions of the right lung with configuration A (neb distal), B (neb proximal) and C (neb alone). * ($p < .0001$), □($p = .002$). ANOVA test and Tukey´s pos-hoc test.

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346 **Figure 6.** Difference in distribution of radioaerosol in the device with two configuration. A -
347 with configuration A (nebulizer distal). B - configuration B (neb proximal to subject). C
348 orientation of Acapella® used in figures A and B.
349

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Figure 1

A **B** **C**

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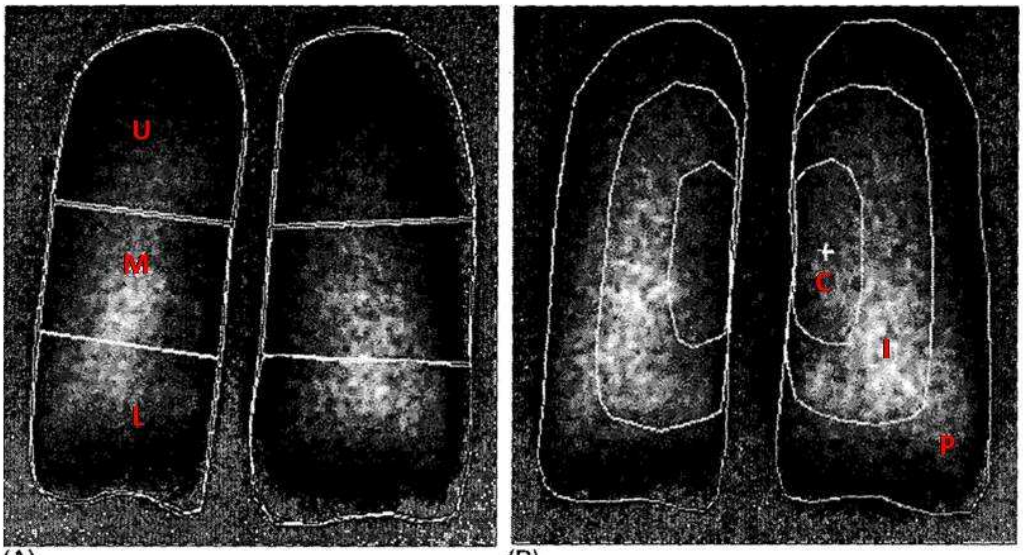
Figure 2



(A) (B)

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Figure 3

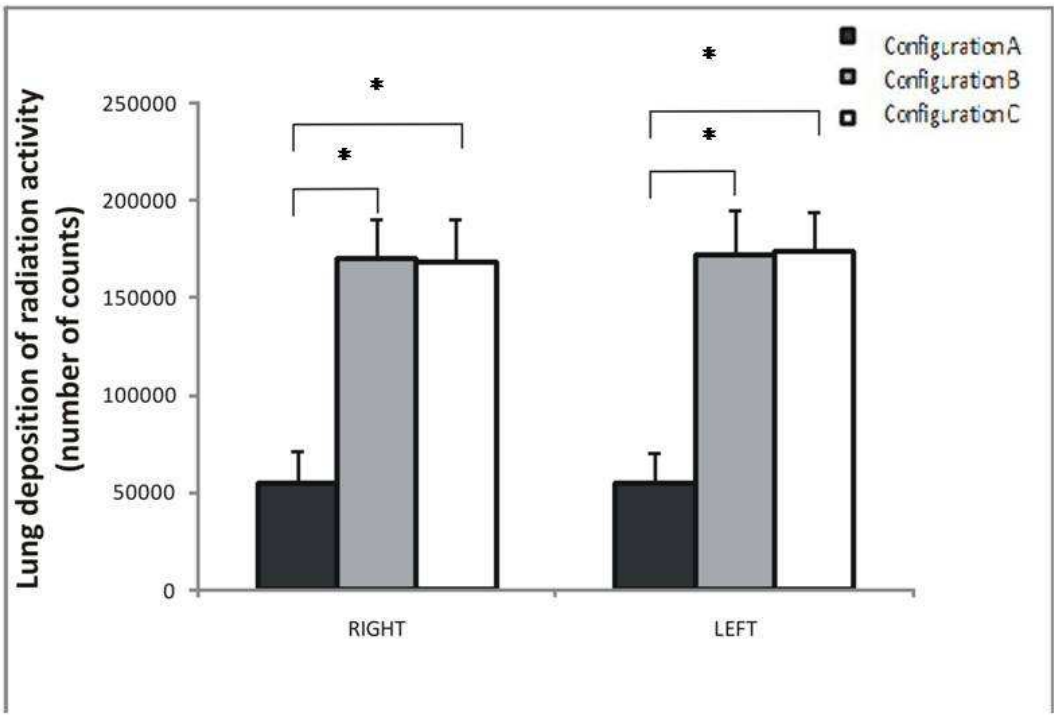

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Figure 4

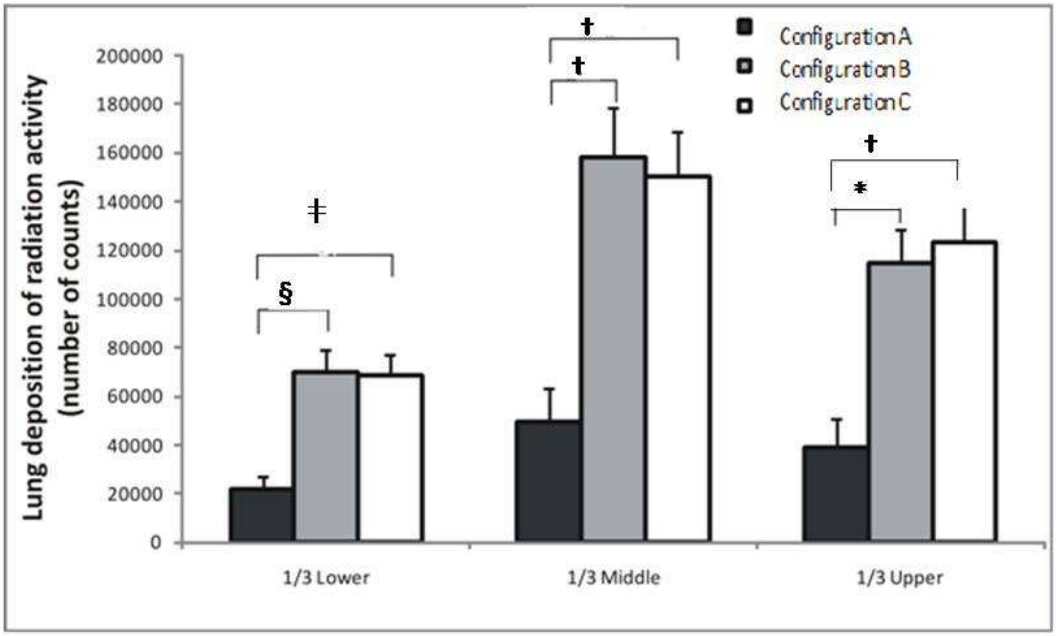

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Figure 5

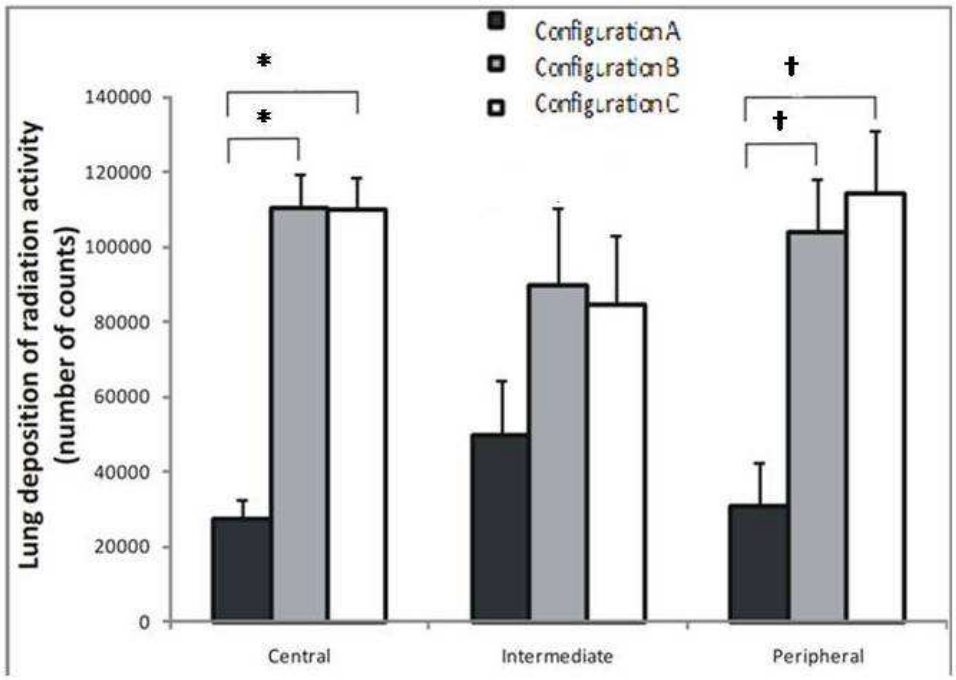

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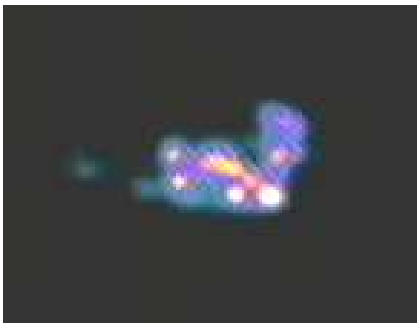
Figure 6

A



B

C