Acoustic Pressure Pulsations Enhance Peripheral Aerosol Distribution and the Bronchodilating Effects of Albuterol in COPD

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INTRODUCTION

Drugs administered by inhalation are often required to reach the farthest parts of the bronchial tree, where they act or are absorbed. With many marketed aerosol delivery systems, less than 10% of the dose reaches the periphery of the lung, with the remaining drug depositing in the device, mouth, pharynx, large bronchi, or swallowed into the stomach.

Efforts to improve the lung deposition pattern of inhaled drugs focus primarily on controlling particles size and breathing pattern. Techniques for improving drug deposition pattern by modifying the characteristics of the airstream through which particles travel to reach their intended target have been relatively unexplored.

It is generally accepted that even optimally managed chronic obstructive pulmonary disease (COPD) patients do not reliably respond to inhaled short acting beta agonists bronchodilators (SABA). In fact, a defining feature of the disease is lack of "reversibility," meaning essentially little or no short-term spirometric improvement when a SABA is administered. In addition, it is widely believed that the fundamental pathophysiology of COPD is related to closure of small airways due to loss of alveolar septa tethering. To the best of our knowledge no interventions are available to directly elicit re-opening of alveolar airspaces.

Recently, Breuer *et al.* [1] reported a positive outcome when treating 22 moderate and severe COPD patients with a device that delivers sequences of pressure pulses into their airways via a mouthpiece. The effects of the pulsation treatment resulted in a significant improvement in their spirometric measurements, reduced air trapping, improved dyspnea score, and most importantly, a clinically meaningful improvement in their performance on the six minute walk (6MW) test.

The present study in COPD patients evaluated the acute effects of non-invasive treatment by acoustic wave pulsations applied before and during the administration of radiolabeled albuterol by nebulization, compared to albuterol nebulization alone. The primary outcome was distribution of radiolabeled aerosol in the lung quantified by gamma scintigraphy. Secondary outcomes were the functional pulmonary tests and subjective dyspnea patient evaluation.

METHODS

The study was approved by the Ethics Committee of Assaf Harofeh Medical Center and reported to ClincalTrials.org NCT01187589. 15 patients (11 men, 4 women) who were previously diagnosed with COPD based on symptoms, pulmonary function tests (PFTs), diffusing capacity of the lungs for carbon monoxide (DLCO) and computed tomography (CT) scans were enrolled. The patients maintained their regular medications throughout the study. Each patient visited the lab twice following their initial screening visit, and was subjected to technician supervised spirometry and patient-reported visual symptom score (0 to 5 Borg scale). In 7 out of 15 patients, 0.5 ml (2.5mg/ml) of albuterol in 2.5 ml of technetium 99M radioactively-tagged normal saline was placed in the nebulizer cup and administered during the first visit using a conventional air jet nebulizer (Family Silver; Medel, Italy) known to generate droplets in the range of 1.9 to 5.0 microns [2] ("nebulizer alone"). Time to nebulizer sputtering was 10 to 15 minutes, after which patients underwent single-photon emission computed tomography (SPECT) imaging.

Seven days after the first visit (the "washout" period), the sequence described above was repeated, except the albuterol nebulization treatment was preceded by 3.5 minutes of oral pulsations delivered by the PulseHaler™ (Respinova, Herzeliah, Israel) at various frequencies superimposed on a continuous positive airway pressure (CPAP) of 0 to 4 cm H_2O. The pulsations continued throughout the aerosol delivery period ("pulses + nebulizer").

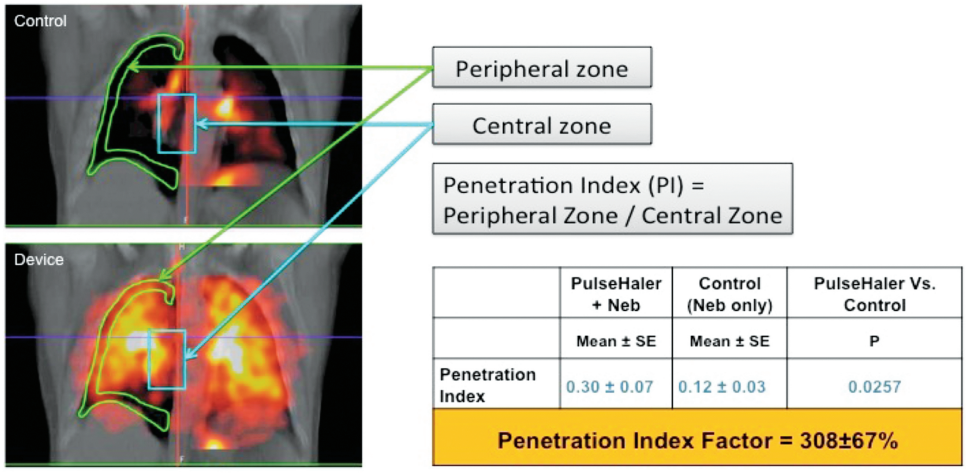
In the remaining 8 out of 15 patients, the order of treatment was reversed, but was otherwise identical. The data was evaluated statistically using paired students' t-test (two tail). Significance was determined by a p-value less than 0.05.

RESULTS

All patients completed both phases of the study without side effects or dropouts.

SPECT allows aerosol deposition in the periphery of the lung relative to the center to be quantified as the penetration index (PI). The PI increased by an average of 308% ($p < 0.05$) with pulses + nebulizer vs. nebulizer alone. The increased PI with pulses + nebulizer was observed in 12 of the 15 patients (Figures 1 and 2).

Compared to pre-treatment evaluation, substantial and statistically significant improvements were observed in FEV_1 and FVC (151 ml (11% increase) and 238 ml (8% increase)), respectively, when pulses + nebulizer was used, Smaller and non-statistically significant improvements were seen with nebulizer alone (66 ml (4% increase) and 145ml (5% increase)) in FEV_1 and FVC, respectively). Larger and highly significant improvement was seen in mid-flow measurements, with FEF25-75 increasing by 20% when pulses + nebulizer was used, but no discernable improvement was seen with nebulizer alone. These findings are compatible with sustained re-opening of collapsed small airways. Patients' dyspnea score also improved substantially: with pulses + nebulizer from 2.2/5.0 to 3.8/5.0 BORG scale units, compared to 2.1/5.0 to 2.9/5.0 BORG scale units with nebulizer alone.



	PulseHaler + Neb	Control (Neb only)	PulseHaler Vs. Control
	Mean ± SE	Mean ± SE	P
Penetration Index	0.30 ± 0.07	0.12 ± 0.03	0.0257
Penetration Index Factor = 308±67%			

Figure 1. Representative scintigraphic images and visual depiction of how penetration index is calculated. The table contains a summary of the results (table headings are described in the text).

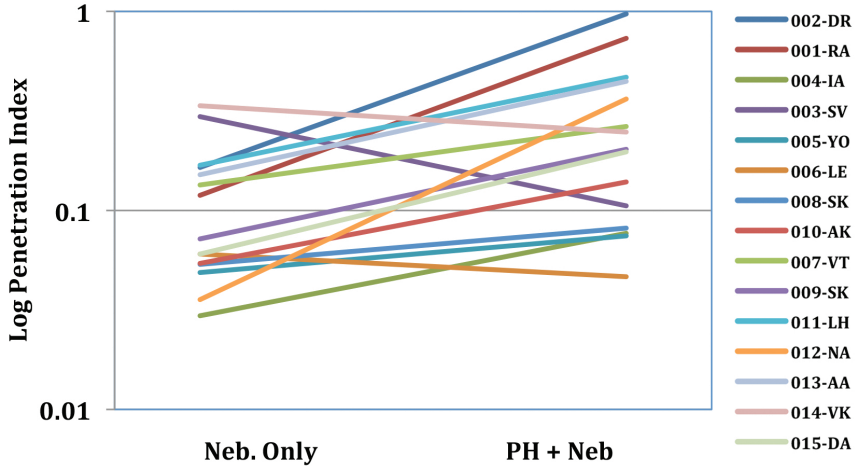


Figure 2. Penetration index with nebulizer alone and with PulseHaler (PH) + nebulizer in 15 COPD patients.

CONCLUSIONS

PulseHaler acoustic pulses technology can enhance terminal bronchiole and alveolar zone delivery of inhaled drugs in COPD patients. It significantly enhanced the efficacy of albuterol (a short acting beta agonist). It is likely that the suggested mechanism of improved drug deposition is independent of the particle size or delivery platform, and is related to the aerodynamics of the carrier stream, whereby acoustic pressure pulses act on the effected parts of the lung to open small airways.

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