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Title: IN-VITRO EVALUATION OF POSITIVE EXPIRATORY PRESSURE DEVICES ATTACHED TO NEBULIZERS.

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The study was performed at the Pediatric Aerosol Research Laboratory (Arkansas Children's Hospital Research Institute).

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Running head: Nebulizers connected to positive expiratory pressure devices

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

Abstract

Introduction

Patients with Cystic fibrosis perform airway clearance techniques and receive nebulized medications on regular basis. Some positive expiratory pressure (PEP) devices allow concomitant administration of nebulized aerosols. We hypothesize that this practice may alter the aerosol characteristics and patient dose. We compared the aerosol characteristics and patient dose of nebulized albuterol generated by 2 different types of nebulizers alone and when connected to different PEP/vibratory PEP devices.

Materials and Methods

Three units of a continuously operated nebulizer (CON) and 3 units of a breath enhanced nebulizer (BEN) were tested alone and connected to PEP devices (acapella® choice, acapella® duet, and EzPAP® for CON and PARI PEP™ at 2 different settings and PARI PEP™ S system for BEN). Aerosol characteristics were evaluated by cooled cascade impaction technique. Nebulizers were loaded with 2.5mg/3mL albuterol solution and operated for 4 minutes (6L/min, central air). Patient dose was evaluated with simulated breathing technique using child, small adult, and large adult breathing patterns. Albuterol was assayed via spectrophotometer (276 nm).

Results

Connecting the BEN to PEP devices did not change either aerosol characteristics or patient dose.

Connecting the CON to PEP devices resulted in significant reduction of mass median aerodynamic diameter from 4.13 μm to 3.72 μm, 1.24 μm and 1.22 μm when connected to EzPAP® ($p = 0.021$), acapella® choice ($p < 0.0001$) and acapella® duet ($p < 0.0001$)

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respectively. Total amount of albuterol captured by the impactor decreased when connected to either acapella® choice (65%) or acapella® duet (69%) with 17%-25% retained in the PEP devices. Patient dose decreased by 76% to 84% when connected to acapella® choice and acapella® duet respectively.

Conclusions

Concomitant use of nebulizers and PEP/vibratory PEP devices that obstruct the aerosol pathway produce a significantly smaller particle size aerosol and a significant decrease of patient dose.

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Key words

PEP, vibratory PEP, nebulizer, particle size, aerosol characteristics, albuterol

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Introduction

Cystic fibrosis (CF) is the most common genetic lethal disease presenting in Caucasian population. A defect in the cystic fibrosis transmembrane regulator channel leads to a multiorgan disease mainly affecting the lungs and nutritional status.[1] Currently recommended therapies include several aerosol treatments (alfa dornase, 7% hypertonic saline, albuterol, antibiotics, and corticosteroids), airway clearance therapies (ACT), nutritional support, enzyme and vitamin replacement therapy.[2-3]

The addition of new therapies has increased the amount of time patients with CF devote to their treatments. Aerosol treatments and airway clearance therapies are combined to try to reduce the time burden. Aerosols are administered during high frequency chest compression (HFCC) without changing the configuration of the nebulizer. Positive expiratory pressure (PEP) and vibratory PEP devices can be adapted to concomitantly administer the aerosol and perform the ACT.[4]

Particle size is an important factor in determining intrapulmonary deposition of inhaled aerosols.[5] Laube et al. reported a decrease in intrapulmonary deposition with a slightly more peripheral aerosol distribution when a breath actuated nebulizer was coupled to a PEP device.[6] Dornelas de Andrade et al. reported a decrease in intrapulmonary deposition when a vibratory PEP device was coupled to a nebulizer.[7] The coupling of nebulizer and PEP/vibratory PEP could lead to an increase in aerosol impaction, thus affecting particle size and site of intrapulmonary deposition.

We hypothesize that the concomitant use of PEP/vibratory PEP devices connected to nebulizers will change the aerosol characteristics of nebulized albuterol. In this in-vitro study we compared

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

aerosol characteristics and patient dose of a continuously operated nebulizer and a breath enhanced nebulizer alone and when connected to PEP/vibratory PEP devices.

Material and Methods

This in-vitro study included 2 parts: determination of particle size by cascade impaction and determination of albuterol output by breathing simulation.

Nebulizers and PEP devices

Three units of a continuously operated jet nebulizer (UP-DRAFT II® Optineb Nebulizer, Teleflex Medical, Research Triangle Park, NC) (CON) and 3 units of a breath enhanced nebulizer (PARI LC® Plus, PARI Respiratory Equipment Inc., Midlothian, VA) (BEN) were tested. CON was tested with a t-piece and a 15 cm extension tube placed after the nebulizer; connected to acapella® choice with expiratory resistance setting of 1 (Smiths medical, Dublin, OH) with the nebulizer and a 15cm extension tube connected to the posterior part of the device; connected to acapella® duet with resistance setting of 1 (Smiths medical, Dublin, OH) with a 15 cm extension tube connected to the posterior part of the device and the nebulizer connected to the bottom of the device and connected to EzPAP® with pressure of 5 cm H_2O (Smiths medical, Dublin, OH) (figure 1). The acapella® duet is a transparent reusable vibratory PEP device that allows concomitant nebulization when placing the nebulizer at the port located at the bottom of the device. Corrugated tubing is placed at the end of the device to act as an aerosol reservoir. The device has a one-way inspiratory valve. The acapella® choice is a green reusable vibratory PEP device that allows concomitant nebulization when connecting the nebulizer at the distal fitting of the device via T-piece. The EzPAP® is a transparent PEP device that allows concomitant

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

nebulization by placing a T-piece with nebulizer between the PEP device and the mouthpiece. BEN was tested alone; with PARI PEP™ system with resistance settings of 1.5 and 4.5 (PARI Respiratory Equipment Inc., Midlothian, VA); and with PARI PEP™ S system with resistance setting of 1.5 (PARI Respiratory Equipment Inc., Midlothian, VA) (figure 2). All connections were made according to manufacturer recommendations. PARI PEP™ system replaces the nebulizer inspiratory valve of the PARI LC ® Plus and it is used with a mouthpiece without exhalation valve. PARI PEP™ S connects to PARI LC ® Plus replacing the mouthpiece and has different resistance settings providing a pressure range between 10 and 20 cm H_2O.

Particle size characterization procedure

Nebulizers were weighed on a precision scale when dry (W_D), and after loading a unit dose of albuterol sulfate 2.5 mg/3ml (DEY, Napa, CA) (W_0). Nebulizers were operated at 6 L/min with wall air and the accuracy of the flow was verified before each test with a mass flowmeter (TSI 4043, Shoreview, MN). The nebulizers were then connected to a Next Generation Impactor (NGI) (MSP Corporation, Shoreview, MN) assembled with internal and external filters (Advantec GC-50, Advantec MFS Inc, Dublin, CA) that had been previously cooled at 4C° for 90 minutes. The NGI was connected to a suction pump (HCP5, Copley Scientific, Nottingham, UK), calibrated to 15 L/min with a mass flowmeter (TSI 4043, Shoreview, MN) and used within 5 minutes of removing it from the refrigerator.[8] CON was adapted to the impactor's induction port with a T-piece and BEN was connected by its mouthpiece with its exhalation port sealed (figure 3). The nebulizers were operated for 4 minutes and upon completion the nebulizers were re-weighted (W_F) and the NGI was disassembled. They

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

were all washed with ultra pure water and the fluids were analyzed for albuterol content via spectrophotometry at 276 nm (Biomate 3 UV-Vis Spectrophotometer, Thermo Electron Corporation, Waltham, MA). Samples of known concentration of albuterol were used to verify the calibration curve. Acapella® choice and duet devices were washed with ultrapure water and the fluid was analyzed for albuterol concentration.

Nebulizers either alone or connected to PEP devices were tested in duplicate (n=6 for each configuration).

The following parameters were calculated according United States Pharmacopeia and European Pharmacopeia recommendations, using CITDAS V3.1 software (Copley Scientific, Nottingham, UK): mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), percentage of particles smaller than 5 µm (P%<5) and particles 1 to 3 µm (P%1-3).[8-10] In addition, the total albuterol mass captured by the NGI was calculated (NEB-NGI). Mass balance was calculated for each device.

Patient dose

Patient dose was evaluated with breathing simulation technique. Three units of CON and BEN were tested. The nebulizer was weighted dry (W_D), and after 2.5 mg/3 ml of albuterol sulfate were loaded in the nebulizer (W_0). Nebulizers were operated for 5 minutes at 6 L/min with wall air and. the accuracy of the flow was verified before each test with a mass flowmeter (TSI 4043, Shoreview, MN). The nebulizers were then connected to a low dead space filter holder containing an inhalation filter (PARI Respiratory Equipment Inc, Midlothian, VA) and connected in series to a breathing simulator (PARI Compass, Munich, Germany) (Figure 4).

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

Three different breathing patterns were used: older child (Tidal Volume (Vt) = 200ml; respiratory rate (RR) = 20/min; inspiratory to expiratory ratio (I:E) = 1:2); small adult (Vt = 500ml; RR = 15/min; I:E = 1:2); and large adult (Vt = 770ml; RR = 12/min; I:E = 1:2). The accuracy of the delivered Vt was verified with a mass flowmeter (TSI 4043, Shoreview, MN). Nebulizers were reweighted upon completion of testing. Filters were washed with ultrapure water. The filters and the nebulizer cups were analyzed for albuterol concentration via spectrophotometry.

Nebulizers were tested alone and connected to the different pep devices using each of the breathing patterns (n = 3 for each configuration).

Statistical analysis

Aerosol characteristics (MMAD, GSD, P%<5, P%1-3, NEB-GI, mass balance), drug remaining in the nebulizer cup and patient dose were compared with analysis of variance (ANOVA) followed by post-hoc analysis with Dunnet's test. Differences in patient dose among different breathing patterns were compared with ANOVA followed by Tukey test for multiple comparison analysis. Statistical significance level was set at 0.05. A statistical software package was used for data analysis (Kaleidagraph 4.1, Reading, PA).

Results

Particle size analysis (Table 1)

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

The MMAD for BEN alone was 3.42 µm ± 0.15 µm and ranged from 3.42 µm to 3.45 µm when connected to pep devices (p = .92) (figure 5). The GSD for BEN alone was 2.25 ± 0.04 and ranged from 2.26 to 2.29 when connected to pep devices (p = 0.31). The percentage of particles less than 5 µm was 66.9% ± 2.1% for BEN alone and ranged from 66.6% to 66.8% when connected to pep devices (p = .97). The percentage of particles between 1 µm and 3 µm for BEN alone was 35.9% ± 1.8% and ranged from 34.5% to 38.4% when connected to PEP devices (p = .11). The NEB-NGI was 1031 µg ± 57 µg for BEN alone and ranged from 1105 µg to 1122 µg (p = 0.013). The amount of albuterol that remained in the nebulizer cup was 1375 µg ± 30 µg for BEN alone and ranged from 1311 µg to 1372 µg when connected to pep devices (p = .11). The mass balance was similar among all devices (p = .06).

The MMAD for CON alone was 4.13 µm ± 0.4 µm and decreased to 3.72 µm ± 0.18, 1.24 ± 0.1 and 1.22 ± 0.09 when connected to EzPAP®(p = .02), acapella® choice (p < .001) and acapella® duet (p < .001) respectively (figure 5). The GSD for CON alone was 2.15 ± 0.12 and ranged from 1.89 to 3.12 when connected to pep devices (p = .06). The percentage of particles less than 5 µm for CON alone was 59.1% ± 5.3% and remained unchanged when connected to EzPAP® (63%, p = .56). However, it increased to 86.5% and 89.1% when connected to acapella® choice (p < .001) and acapella® duet (p < .001) respectively. The percentage of particles between 1 µm and 3 µm for CON alone was 25.1% ± 2.9% and remained unchanged when connected to EzPAP® (27.4%, p = .88). However, it increased to 46% and 44.3% when connected to acapella® choice (p < .001) and acapella® duet (p < .001) respectively (Table 1). The NEB-NGI was 570 µg ± 126 µg for CON alone, remaining unchanged with EzPAP® (p = .98) and decreasing by 65% - 69% when connected to acapella® choice (p < .001) and duet (p < .001) respectively. Both the acapella® choice and duet retained a significant

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

amount of albuterol (640 µg ± 108 µg and 419 µg ± 230 µg respectively). The amount of albuterol that remained in the nebulizer cup was 1953 µg ± 132 µg for CON alone and ranged from 1930 µg to 1957 µg when connected to pep devices ($p = .98$). The mass balance was equal among all devices ($p = .25$).

Patient dose (Table 2)

No differences in patient dose were noted among BEN and BEN/pep devices with older child, small and large adult breathing patterns ($p = .05$, $p = .37$, $p = .07$ respectively). Patient dose increased with patterns of larger Vt (older child < small adult < large adult, $p < .001$).

CON had a similar patient dose than CON/EzPAP® older child, small and large adult breathing patterns ($p = .99$, $p = .07$, $p = .06$ respectively). However, connecting CON to either acapella® choice or acapella® duet decreased patient dose by 76% to 84% for all breathing patterns. ($p = .003$ and $p = .003$ for older child, $p < .001$ and $p < .001$ for small adult, and $p < .001$ and $p < .001$ for large adult for acapella® choice and duet respectively). No differences in patient dose were found among the different breathing patterns for each configuration.

Discussion

This in-vitro study compared the aerosol characteristics and patient dose of nebulizers of 2 different operating principles (CON and BEN) used alone or connected to different PEP/vibratory PEP devices. We found that PEP/vibratory PEP devices that alter the aerosol pathway produced a smaller particle size aerosol and had a lower patient dose when connected

to a continuously operated nebulizer. We also found that breathing patterns with larger tidal volumes had larger patient dose when using BEN but not with CON.

The impaction analysis data for BEN alone were similar to previously published work using the same methodology.[8] Laube et al. compared the same BEN with and without the PEP device and found a reduction in MMAD from 4.07 μm to 3.26 μm (based on DTPA measurement) when PEP was used.[6] The authors also reported that the MMAD changed from 3.50 μm to 2.82 μm when the same experiments where done with albuterol sulfate. The different findings could be explained in part by several methodological differences between both studies. While Laube et al. operated a Marple Miller impactor at 12 L/min at room temperature, we operated a different impactor (NGI at 15 L/min) cooled to 4C° therefore minimizing evaporation loses. We used a different gas source (wall air vs. compressor). In addition, Laube et al. did not provide an explanation of the PEP device and its configuration. Therefore, it is possible that that model could obstruct the pathway of the aerosol generating impaction loses. In the in-vivo part of the study using Technesium^{99}-DTPA aerosols, Laube et al. reported a decrease of pulmonary deposition and a preferential peripheral deposition (larger inner/outer ratio) when using the PEP device. However when expressed as percentage of loading dose the addition of the PEP preferentially decreased deposition in the inner area as noted by inner and outer deposition of 2.7% and 2.4% (no PEP) and 1.3% and 1.5% (PEP). Unfortunately the authors did report other parameters such as P%<5 and P%1-3. These data could have help to better understand whether the change in aerosol characteristics especially on the smaller size fraction was responsible for these findings. Other studies have shown significant difference in distribution of deposition when aerosols of an MMAD of 1.01 μm and 3.68 μm were compared.[11]

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

When BEN was tested under breathing simulation conditions we found that larger Vts produced larger patient dose. These data are in agreement with Barry et al. who, using similar technology, found that pediatric type breathing patterns (Vt = 150 ml) had lower patient dose that adult type breathing patterns (Vt = 600 ml).[12]

The type of PEP/vibratory PEP device used determined the changes that the aerosols experienced when the device was added to a continuously operated nebulizer. The changes in MMAD that the aerosol experienced when the acapella® choice and duet were used (4.32 μm to ≈ 1.23 μm) are likely to alter the site of intrapulmonary deposition.[5,11] In addition, there is a significant reduction in the dose captured by the NGI (65% to 69%). Impaction loses is the most likely mechanism responsible for these changes since the aerosol travels through the housing of the device to reach the patients mouth. This was confirmed by the analysis of the washings of both devices. The amount of aerosol that remained in the nebulizer was similar to nebulizer alone reflecting the fact that a decrease in aerosol generation was not responsible for the decrease in drug captured by the NGI. The size selection resulting from the use of the acapella®-CON is also noted by the increase in the P%<5 and P%1-3 aerosol fractions. Our findings are in agreement with Dornelas de Andrade who found that the position of the nebulizer affects intrapulmonary deposition of a radiolabeled aerosol.[7] They compared a nebulizer alone and placed before and after the acapella® device and reported that placing the nebulizer after the acapella® significantly reduces lung deposition. More recently, Mitchell et al. reported a decrease in albuterol mass (70%) and MMAD when coupling a breath actuated nebulizer to the back of the acapella® device.[13] They also reported that a proprietary PEP device that is coupled to the nebulizer without interrupting the aerosol pathway did not decrease either albuterol mass or MMAD. The EzPAP®, that has the nebulizer placed between the PEP device and the

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

mouthpiece, only experienced a minor decrease in MMAD that is unlikely to be clinically significant. Moreover, the P%<5 and P%1-3 aerosol fractions remain unchanged after adding the EzPAP®.

Our findings of a decrease in patient dose by 76% and 84% when the nebulizer is connected to the acapella® device are in agreement with Mitchell et al.[13] As noted above, they also showed that similarly to EzPAP®, PEP devices that do not obstruct the aerosol pathway do not alter patient dose. The lack of increase in patient dose with larger Vts seen with acapella® could be due to the inefficiency of aerosol delivery resulting from increased impaction. However, we have no clear explanation why no changes were noted with the nebulizer alone and when connected to the EzPAP®.

The ideal size of aerosols for CF indications has been suggested by some authors to be between 2 and 3 μm.[14] However, clinical trials have not been able to provide conclusive evidence.[14] The ideal size depends on where the aerosols are targeted as well as on the inhalation technique. Drugs that target receptor located in the large airways would benefit from larger particles.[15] Laube et al. reported a significant increase in intrapulmonary deposition in small and medium size aerosols when a slow inhalation maneuver was used.[11]

The limitations of this study are related to its in-vitro nature and the methodology used. The breathing simulation technique overestimates patient dose due to the fact that it does not allow exhalation of particles that in human subjects would have not been deposited. Although it is widely accepted, the use of idealized breathing patterns could render different patient dose when compared to real life evaluation.

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

The clinical implications of our findings are significant. The concomitant use of nebulizers and PEP/vibratory PEP that interfere with the aerosol pathway should be discouraged. If this combination is used the patient is likely to be under-dosed and a significant waste of drug will occur. This might not be important for albuterol but it is crucial for alfa dornase. In addition, the change of particle size could lead to a redistribution of deposition with an increase of systemic absorption and a decrease in functional response.[15]

In conclusion, concomitant use of nebulizers and PEP/vibratory PEP devices that obstruct the aerosol pathway produce a significantly smaller particle size aerosol and a significant decrease of patient dose.

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Figures

Figure 1: Continuously operated nebulizer alone and connected to different PEP and vibratory PEP devices

Figure 2: Breath enhanced nebulizer alone and connected to different PEP devices

Figure 3: Experimental set-up used to measure aerosol characteristics with Next Generation Impactor

Figure 4: Experimental set-up used to measure patient dose with breathing simulation

Figure 5: Mass median aerodynamic diameter for nebulizers alone and connected to different PEP and vibratory PEP devices.

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

Bars (black for continuously operated nebulizer and grey for breath enhanced nebulizer) represent mean of 6 experiments and error bars represent standard deviation. * $p = 0.02$ when compared to nebulizer alone. † $p < .001$ when compared to nebulizer alone.

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

Table 1: Characterization of aerosols generated by nebulizers alone and connected to different PEP/vibratory PEP devices.

	Continuously Operated Nebulizer				Breath Enhanced Nebulizer			
	Alone	EzPAP®	Acapella® duet 1	Acapella® choice 1	Alone	PARI PEP™ 1.5	PARI PEP™ 4.5	PARI PEP™ S 1.5
MMAD (µm)	4.13 ±0.40	3.72 ±0.18*	1.24 ±0.10†	1.22 ±0.09†	3.42 ±0.15	3.42 ±0.20	3.45 ±0.19	3.44 ±0.17
GSD	2.15 ±0.12	2.34 ±0.20	1.89 ±0.05	3.12 ±1.54	2.25 ±0.04	2.27 ±0.04	2.29 ±0.11	2.26 ±0.04
P%<5 (%)	59.1 ±5.3	63.0 ±2.3	86.5 ±6.2†	89.1 ±8.2†	66.9 ±2.1	66.6 ±2.5	66.8 ±2.8	66.8 ±2.6
P%1-3 (%)	25.1 ±2.9	27.4 ±2.6	46.0 ±8.6†	44.3 9.4†	35.9 ±1.8	38.4 ±2.9	37.4 ±2.5	34.5 2.8
NEB-NGI (µm)	570 ±126	584 ±94	176 ±26†	200 ±68†	1031 ±57	1105 ±66	1116 ±62	1122 ±44
Reservoir (µm)	1953 ±131	1930 ±189	1957 ±162	1936 ±165	1375 ±30	1372 ±85	1311 ±46	1357 ±64
Device (µm)	--	--	419 ±230	640 ±108	--	--	--	--
Mass balance	2523 ±42	2514 ±117	2555 ±402	2773 ±254	2406 ±48	2478 ±102	2427 ±38	2479 ±37

* $p = 0.02$ when compared to nebulizer alone. † $p < .001$ when compared to nebulizer alone.

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

Table 2: Patient dose (μg of albuterol) generated by nebulizer alone and connected to different PEP/vibratory PEP devices

Delivery Device		Breathing Pattern		
Nebulizer	PEP/vibratory PEP	CHILD	ADULT 1	ADULT 2
Continuously Operated Nebulizer	None	244 ± 27	272 ± 25	296 ± 54
	EzPAP®	240 ± 71	227 ± 20	198 ± 43
	Acapella® duet	58 ± 9*	51 ± 11*	49 ± 7*
	Acapella® choice	49 ± 8*	38 ± 5*	34 ± 8*
Breath Enhanced Nebulizer	None	338 ± 6†	455 ± 24†	530 ± 18†
	PARI PEP™ 1.5	302 ±13†	478 ± 9†	558 ± 14†
	PARI PEP™ 4.5	349 ± 18†	493 ± 21†	537 ± 19†
	PARI PEP™ S 1.5	318 ± 17†	474 ± 24†	587 ± 25†

*$p < .001$ when compared to nebulizer alone. †$p < 0.001$ when compared to other breathing patterns.

RESPIRATORY CARE Paper in Press. Published on August 06, 2013 as DOI: 10.4187/respcare.02698

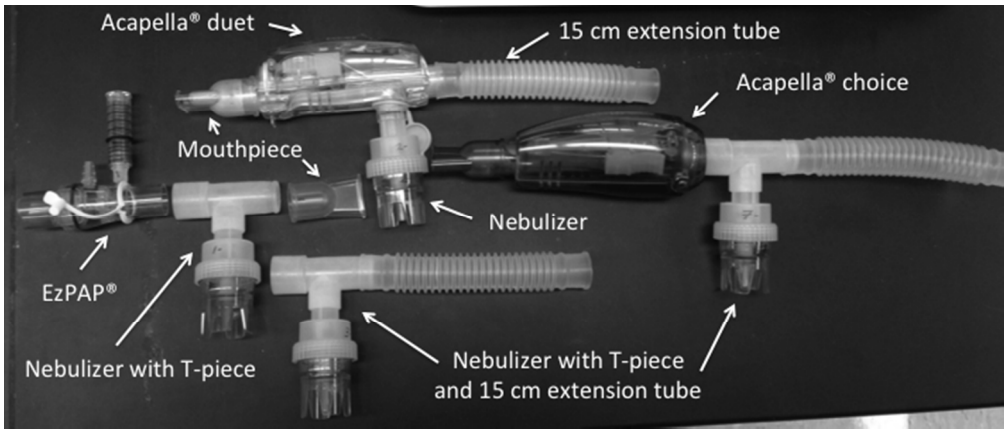

Figure 1: Continuously operated nebulizer alone and connected to different PEP and vibratory PEP devices
249x105mm (72 x 72 DPI)

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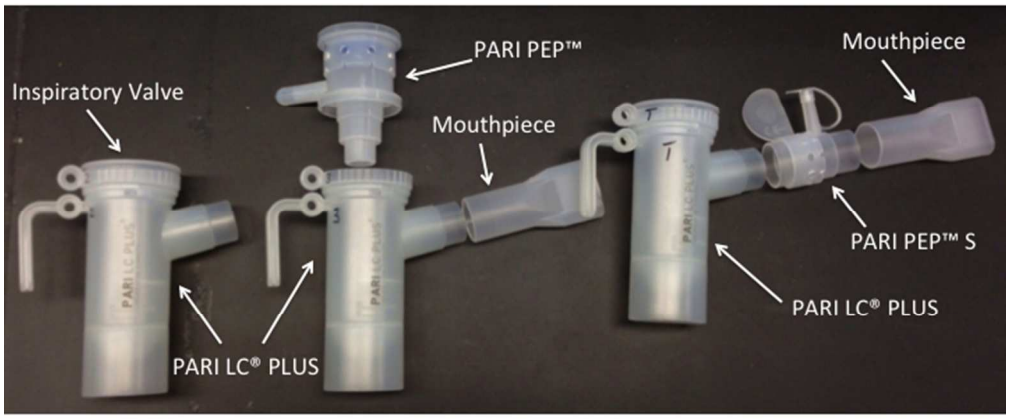

Figure 2: Breath enhanced nebulizer alone and connected to different PEP devices
253x105mm (72 x 72 DPI)

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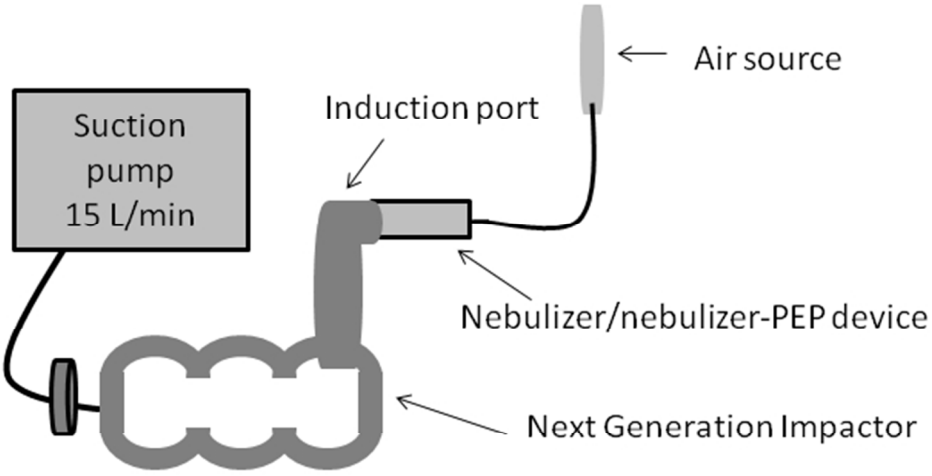

Figure 3: Experimental set-up used to measure aerosol characteristics with Next Generation Impactor
172x107mm (96 x 96 DPI)

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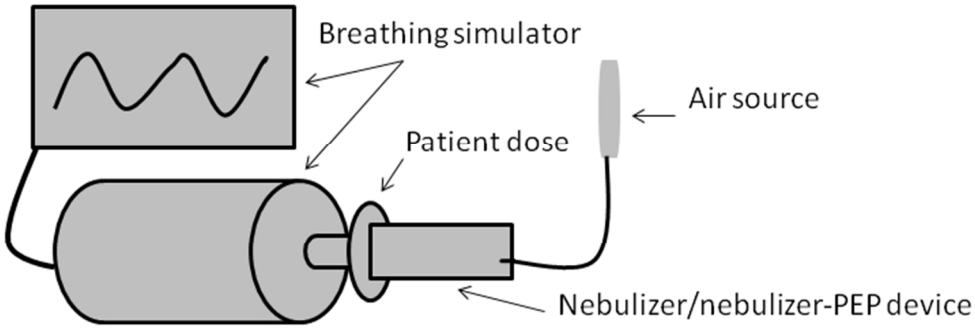

Figure 4: Experimental set-up used to measure patient dose with breathing simulation
194x76mm (96 x 96 DPI)

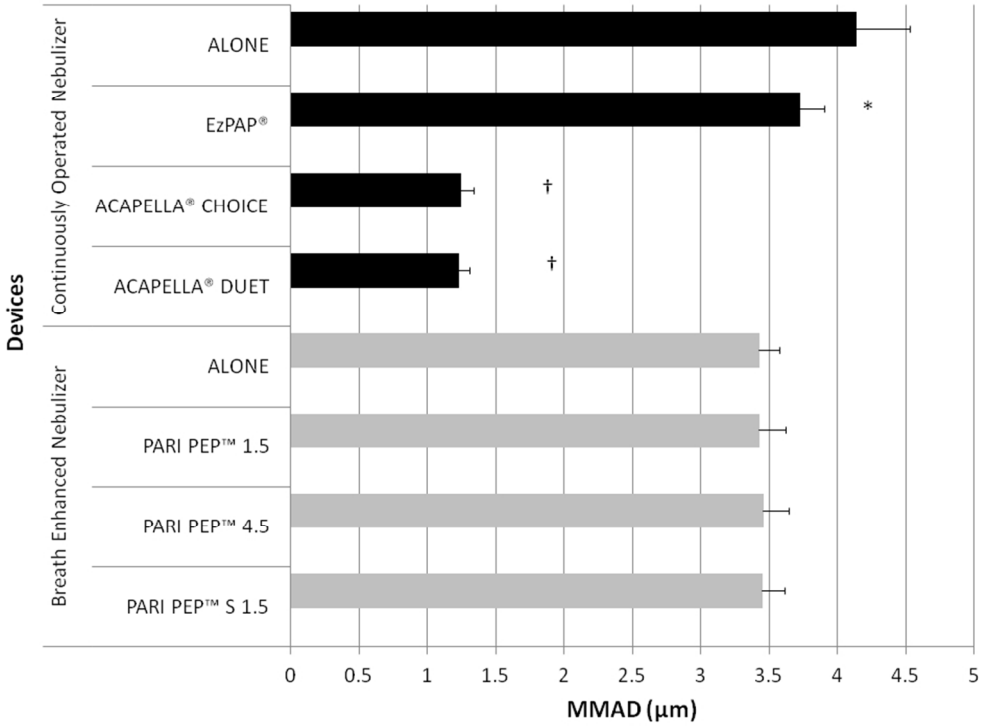

Figure 5: Mass median aerodynamic diameter for nebulizers alone and connected to different PEP and vibratory PEP devices.
Bars (black for continuously operated nebulizer and grey for breath enhanced nebulizer) represent mean of 6 experiments and error bars represent standard deviation. * p = 0.02 when compared to nebulizer alone. †p < .001 when compared to nebulizer alone.

254x190mm (96 x 96 DPI)