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In-vitro nebulized albuterol delivery in a model of spontaneously breathing children with tracheostomy.

Ariel Berlinski, MD[1,2]

[1]University of Arkansas for Medical Sciences, Department of Pediatrics, Pulmonology Section

[2]Pediatric Aerosol Research Laboratory, Arkansas Children's Hospital Research Institute

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

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Corresponding Author

Ariel Berlinski, MD

Associate Professor

University of Arkansas for Medical Sciences

Department of Pediatrics, Pulmonary Medicine

1 Children's Way, Slot 512-17

Phone: 501-364-1006

Fax: 501-364-3930

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Little Rock, Arkansas 72202

E-mail: BerlinskiAriel@uams.edu

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Running head: Nebulized albuterol through pediatric tracheostomy

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Abstract

Background: Nebulized therapy is commonly used in spontaneously breathing tracheostomized patients despite lack of recommended devices and techniques. We compared albuterol dose delivered to a model of spontaneously breathing children with tracheostomy using different nebulizers, tracheostomy tube sizes, inhalation techniques, and breathing patterns.

Methods: A tracheostomy model was connected in series to a breathing simulator with a filter interposed. Breathing patterns of a 16 month old and 12-year old child and tracheostomy tubes with internal diameters (mm) of 3.5, and 5.5 were used. Albuterol nebulizer solution (2.5 mg/3 ml) was used. A breath enhanced (BEN), a breath actuated (BAN), and a continuously operated nebulizer (CON) were operated for 5 minutes and run at 6 L/min with wall air. The latter was tested with different interfaces (T-piece and mask), with an extension tube and operated with and without assisted technique (every breath and every other breath). The amount of albuterol delivered was analyzed via spectrophotometry (276 nm). Particle size distribution was analyzed with a cooled Next Generation Impactor.

Results: BEN was more efficient than others. Assisted technique for CON with extension increased albuterol delivery with every other breath (second best device/configuration) being superior to every breath technique. Adding an extension tube increased delivered albuterol. A T-piece was more efficient than a mask. Breathing patterns with larger Vt increased albuterol delivery. Tracheostomy size had less impact on drug delivery. Mass median aerodynamic diameter decreased between 48% and 74% when passing to the tracheostomies. 0.8% of the nominal dose was deposited in the tracheostomy tube.

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Conclusions: The amount of albuterol delivered to a model of spontaneously breathing children with tracheostomy is influence by type of device and its configuration, use of assisted delivery, breathing pattern and tracheostomy size. Aerosols significantly decrease in size after passing through the tracheostomy tube.

Key words: tracheostomy, nebulizer, delivery device, children

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Background

Nebulized aerosols are frequently prescribed to spontaneously breathing tracheostomized children. A recent survey demonstrated a wide variability in devices and techniques used.[1] Best practices guidelines are needed for the delivery of aerosols to spontaneously breathing tracheostomized children but little data are available.[2]

Pressurized metered dose inhalers (pMDI), nebulizers and dry powder inhalers have been adapted for aerosol delivery through tracheostomies.[3-12] Few in-vitro studies, mostly using adult models, have provided some information regarding the intricacies of delivering aerosols through artificial airways.[13-16] These studies, showed that aerosol delivery is significantly affected by tracheostomy size, interface, type of add-on device and its configuration, use of assisted technique and presence of bias flow. We previously reported that in a model of spontaneously breathing children with tracheostomy the use of assisted breathing reduced patient dose.[13] These data on pMDIs were not in agreement with data obtained using an adult model with nebulized therapy.[15] Data on nebulized therapy in spontaneously breathing tracheostomized pediatric patients are very limited. Extrapolation from adult data to pediatric scenarios could result in either under or overdosing.

In this in-vitro study we compared the amount of nebulized albuterol delivered to a model of spontaneously breathing children with tracheostomy using different nebulizers and techniques, tracheostomies of different sizes, and different breathing patterns.

We hypothesize: 1) that different devices will deliver different amount of albuterol; 2) that the use of assisted technique will decrease the amount of delivered albuterol; 3) that increasing tracheostomy size will increase the amount of delivered albuterol; 4) that breathing patterns with

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larger Vts will receive a larger the amount of albuterol that those with smaller Vts, 5) that the use of different interfaces will affect the amount of delivered albuterol, and 6) the passage of aerosols trough tracheostomy tube will alter their characteristics.

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Materials and Methods

Tracheostomy model

A previously published tracheal model of a 6 year child was used.[13] The model comprised of an 8 cm height and 1.2 cm internal diameter plastic tube (trachea) with an upper filter holder with a one way valve (PARI Respiratory Equipment Inc, Midlothian, VA) and a lower filter. The latter was connected in series to a breathing simulator (PARI Compass, Munich, Germany). The breathing simulator is a piston pump that can be programmed to deliver specified Vts, inspiratory times, and respiratory rates. The model was positioned in a horizontal fashion to prevent gravitational dripping of aerosol on the filters (Figure 1). [16] A circular incision was made 2 cm below the upper section of the plastic tube to allow placement of the tracheostomy tube. The model allows bidirectional airflow trough the tracheostomy tube and the trachea and unidirectional flow (exhalation) trough the upper filter.

Tracheostomy tubes

Uncuffed tracheostomies tubes (Tracoe, Boston Medical Products, Westborough, MA) with internal diameter (ID)/external diameters of 3.5 mm/5 mm, and 5.5 mm/7.6 mm were used.

Breathing patterns

Two different breathing patterns corresponding to a 16 month old (Vt = 80 ml, RR = 30 bpm, I:E = 1:3), and 12 years old (Vt = 310 ml, RR = 20 bpm, I:E = 1:2) were used. We chose

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these patterns to allow a better comparison with our previous work using pMDIs.[13] The chosen Vts represent 7 mls/kg for 16 month old and 12 year old male children with weights in the 50th percentile based on the growth charts of the Center for Disease Control and Prevention (Atlanta, GA). However, patients with neuromuscular diseases or with decreased respiratory drive can present similar patterns at older ages.

Devices, interfaces and delivery technique

Four units of nebulizers of 3 different operating principles were studied: a continuously operated nebulizer (HUDSON RCI UP-DRAFT II® Opti-neb Nebulizer, Teleflex Medical, Research Triangle Park, NC) (CON), a breath enhanced nebulizer (PARI LC Plus, PARI Respiratory Equipment Inc, Midlothian, VA) (BEN), and a breath actuated nebulizer (Aeroeclipse II, Monaghan, Plattsburgh, NY) (BAN). The BEN has a one-way valve that allows air entrainment into the nebulizer during inhalation therefore enhancing drug output. Drug is still released during exhalation in the BEN. The BAN only releases aerosol during inhalation (Breath actuated mode). However, the BAN we tested can also be used as a continuously operated nebulizer (continuous operation mode). Nebulizers were operated at 6 L/min with wall air. The BEN and BAN were only tested connected to the tracheostomy tube with an adapter (Ultra set®, Smiths Medical ASD Inc., Keene, NH). The CON was tested alone and with a 15 cm long/22 mm diameter tube (110 ml volume) placed after the nebulizer. The use of assisted breathing technique at the beginning of either every other breath or every breath was tested. The assisted technique uses a resuscitation bag to enhance the inhaled volume and flow (Figure 2). A self-inflating resuscitation bag (Pediatric Ambu Spur II, Ambu, Copenhagen, Denmark) with stroke

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volume of 450 ml was used. All CON configurations were tested with 2 different interfaces: a T-piece and a tracheostomy mask.

Procedure

Nebulizers were weight dry (W_D), and after loading albuterol sulfate nebulizer solution (2.5 mg/3ml) (W_L). New disposable filters (PARI Respiratory Equipment Inc, Midlothian, VA) were placed in both filter holders at the beginning of every procedure. A mass flowmeter (model 4043, TSI, Shoreview, MN) and its associated software were used to verify the accuracy of the tidal volume delivered by the breathing simulator and wall gas flow. Nebulizers were connected to the gas source and tracheostomy model and operated for 5 minutes. Upon completion, nebulizers were re-weighted (W_F) and 5 ml of ultrapure water were added and they were weighted again (W_{+5}). Nebulizers were swirled and the content was tested for albuterol concentration. The tracheal model was dissembled and filters, filter holders, tracheostomy, and trachea were washed with ultrapure water and analyzed for albuterol concentration with spectrophotometry at 276 nm (Biomate 3 UV-Vis Spectrophotometer, Thermo Electron Corporation, Waltham, MA).[13]

The amount of albuterol remaining in the nebulizer was calculated as follows: ($W_{+5} - W_D$)*spectrophotometry concentration. This was calculated for each run to verify that drug output in fact happened in the occurrence of an extremely low delivered dose, but it was not reported.

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Study Design

The 16 month old breathing pattern/3.5 mm tracheostomy (3.5/16M), the 16 month old breathing pattern/5.5 mm tracheostomy (5.5/16M), the 12 year old breathing pattern/3.5 mm tracheostomy (3.5/12Y), and the 12 year old breathing pattern/5.5 mm tracheostomy (5.5/12Y) were tested with BEN, BAN, and CON. The latter was tested in all combinations of configuration/interface/technique. Four units of each nebulizer type were studied and used in all scenarios.

Particle size determination

BEN, and BAN were tested with their adapter, and CON alone was tested with a T-piece and mask interfaces. The BAN was run in continuous operation mode. The 3 type of nebulizers were tested with both tube sizes (3.5 mm and 5.5 mm). A Next Generation Impactor (NGI, MSP Corporation, Shoreview, MN) with cooled technique was used to measure particle size of the aerosol leaving the tracheostomy tube.[17] The configuration of the NGI was changed to provide a more realistic measurement (Figure 3). The United States Pharmacopeia throat was replaced by the tube used as trachea with its upper end blocked by a cork and the lower end was connected via a custom made adaptor (MSP Corporation, Shoreview, MN) to the body of the NGI. The NGI was calibrated (15 L/min), cooled for 90 minutes, and used within 5 minutes of being removed from the refrigerator. All stages of the NGI and the nebulizer were washed with ultrapure water and tested for albuterol concentration with spectrophotometry at 276 nm. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), percentage of

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particles less than 5 µm were calculated using CITDAS 3.1 software (Copley Scientific, Nottingham, UK) with the drug recovered from stage 2 to the external filter.

Statistical analysis

Breathing simulation data were compared as delivery efficiency (µg of albuterol captured /2500 µg * 100). The following were used as outcome measures: lower airways dose (drug delivered to the lower filter and filter holder), tracheal dose [drug delivered to the trachea (8 cm x 1.2 cm plastic tube)], total patient dose (lower airways dose + tracheal dose), proximal/distal ratio (tracheal dose/lower airways dose) and dose deposited in the tracheostomy tube. The lower airways dose represents aerosol that escaped deposition in the trachea. Inter-device comparison for each scenario (breathing pattern/tracheostomy size) was done with analysis of variance (ANOVA). Intra-device comparison for tracheostomy size and breathing pattern was done with ANOVA for repeated measures. Tukey test was used when multiple comparison analysis was required. Two-way ANOVA was used to evaluate the effect of tracheostomy tube size and breathing pattern on albuterol delivery. Comparison of delivery techniques (assisted versus unassisted) was done with two tailed paired T test. A statistical software package was used for data analysis (Kaleidagraph 4.1, Reading, PA). A p value $< .05$ was considered statistically significant.

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Results

Lower airways Dose (Table 1)

Lower airways dose was higher for the BEN than for either the CON or the BAN for all combinations of breathing patterns and tracheostomy size ($p < 0.0001$) and CON was higher than BAN for all scenarios except 5.5/12Y ($p = 0.38$).

The addition of an extension tube to the CON/T-piece increased lower airways dose only for 3.5/16M ($p = 0.03$). No differences were noted for the CON/mask ($p > 0.18$).

The use of assisted technique (every other breath) with the CON-extension/T-piece increased lower airways dose for 3.5/16M and 5.5/16M scenarios ($p = 0.007$ and $p = 0.013$ respectively). The use of assisted technique (every other breath) with the CON-extension/mask increased lower airways dose for 3.5/12Y and 5.5/12Y scenarios ($p = 0.03$ and $p = 0.016$ respectively). The use of every breath technique reduced lower airways dose by 36% and 17% for the T-piece and mask interfaces respectively when compared to every other breath technique.

The use of mask interface with the CON led to an increase of lower airways dose only for 3.5/16M ($p = 0.002$). However, when the extension tube was added a decrease in lower airways dose was noted for 5.5/12Y ($p = 0.02$). When using assisted technique a decrease in lower airways dose was noted for 3.5/16M and 5.5/16M ($p = 0.001$ and $p = 0.011$ respectively).

Tracheostomy size and breathing pattern had a positive effect on lower airways dose for the BEN and the BAN devices ($p < 0.0001$ for both), while only breathing pattern positively affected the CON/T-piece device ($p = 0.0015$). The interaction of both variables was only

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significant for the BAN ($p = 0.0004$). The use of assisted technique with the CON removed the effect of the breathing pattern ($p = 0.4$).

Tracheal dose (Table 2)

Tracheal dose was higher for the BEN than for the CON and the BAN for all combinations of breathing pattern and tracheostomy size ($p < 0.0002$).

The addition of an extension tube to the CON/T-piece increased tracheal dose only for 5.5/12Y ($p = 0.013$). No differences were noted for CON/mask ($p > 0.2$).

The use of assisted technique (every other breath) with the CON-extension/T-piece increased the tracheal dose for all combinations of breathing patterns and tracheostomy size except for 5.5/12Y ($p = 0.06$). This modality was similar to BEN for all scenarios except for 5.5/12Y ($p = 0.01$). The use of assisted technique (every other breath) with the CON-extension/mask increased the tracheal dose for the 3.5/12Y and 5.5/16M scenarios ($p = 0.048$ and $p = 0.049$ respectively). The use of every breath technique reduced tracheal dose by 9% for the T-piece and mask interfaces when compared to every other breath technique.

The use of mask interface with the CON led to an increase of tracheal dose for 3.5/16M ($p = 0.005$) and a decrease in tracheal dose for 5.5/12Y ($p = 0.019$). When the extension tube was added to the CON, an increase in tracheal dose was noted for 3.5/16M ($p = 0.007$) as well as a decreased for 3.5/12Y and 5.5/12Y scenarios ($p = 0.002$ and $p = 0.0023$ respectively). When

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using assisted technique a decrease in tracheal dose was noted all combinations of breathing pattern and tracheostomy size ($p < 0.017$).

Tracheostomy size and breathing pattern had a positive effect the tracheal dose for the BAN ($p = 0.02$ for both) but not for the BEN devices ($p = 0.09$ and $p = 0.37$ respectively), while only breathing pattern positively affected the CON/T-piece device ($p < 0.0001$). The interaction of both variables was only significant for the BAN ($p = 0.017$).

Total patient dose (Figure 4)

Total patient dose was higher for the BEN than for CON and BAN for all combinations of breathing patterns and tracheostomy size ($p < 0.0001$).

The addition of an extension tube to the CON/T-piece increased total patient dose for the 3.5/16M and 5.5/12Y scenarios ($p = 0.02$, and $p = 0.03$ respectively). No differences were noted for the CON/mask ($p > 0.22$).

The use of assisted technique (every other breath) with the CON-extension/T-piece increased the total patient dose for all scenarios except 5.5/12Y ($p = 0.087$). This modality was the second highest and was similar to BEN for 3.5/16M ($p = 0.25$) but lower for other scenarios. The use of assisted technique (every other breath) with the CON-extension/mask increased total patient dose for 3.5/12Y and 5.5/12Y scenarios ($p = 0.022$ and $p = 0.042$ respectively). The use

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of every breath technique reduced total patient dose by 7% and 24% for the T-piece and mask respectively when compared to every other breath technique.

The use of mask interface with the CON led to an increase of total patient dose only for 3.5/16M ($p = 0.0006$). However, when the extension tube was added a decrease in total patient dose was noted for 3.5/12Y and 5.5/12Y ($p = 0.022$ and $p = 0.042$ respectively) while the increase was maintained for the 3.5/16M scenario ($p = 0.029$). When using assisted technique a decrease in total patient dose was noted for all scenarios when the mask interface was used ($p < 0.03$).

Breathing pattern had a positive effect on the total patient dose for the CON, BEN, and BAN ($p = <0.0001$, $p = 0.0016$, and $p = 0.003$ respectively). Tracheostomy size also positively affected the BAN devices ($p = 0.0002$). The use of assisted technique removed the effect of the breathing pattern on CON/T-piece ($p = 0.15$) but not for CON/mask ($p < 0.0001$).

Proximal/distal ratio (Figure 5)

BEN had a higher proximal/distal ratio than CON and BAN for all combinations of breathing patterns and tracheostomy size except for CON for the 3.5/12Y scenario ($p = 0.065$).

The addition of an extension tube to the CON increased the proximal/distal ratio only for 5.5/16M scenario with mask interface ($p = 0.03$).

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The use of assisted technique (every other breath) increased the proximal/distal ratio for 3.5/16M and 5.5/16M scenarios ($p = 0.0003$ and $p = 0.004$ respectively) with CON-extension/T-piece, but decreased the ratio for 5.5/16M scenario ($p = 0.007$) with CON-extension/mask. The former had a similar ratio than BEN except for 3.5/16M ($p = 0.001$).

The use of mask interface did not change the proximal/distal ratio when CON alone was used. The Addition of an extension tube lead to an increase in the ratio for the 35/16M scenario ($p = 0.01$) but a decrease in the ration for 3.5/12Y and 5.5/12Y scenarios ($p = 0.01$ and $p = 0.003$ respectively). The use of assisted technique resulted in a decrease in the proximal/distal ratio for all scenarios when the mask interface was used ($p < 0.006$)

Breathing pattern and tracheostomy size had a negative effect on the proximal/distal ratio for the CON ($p < 0.0001$ and $p = 0.02$ respectively) and the BEN ($p = 0.027$ and $p = 0.0002$ respectively) and no effect on the BAN ($p > 0.43$). When an extension tube was added to CON/T-piece the breathing pattern had a positive effect ($p < 0.0001$). When CON/mask was used instead, tracheostomy size exerted a negative effect ($p = 0.025$) while breathing pattern exerted a positive one ($p = 0.001$). When assisted technique was used with CON/T-piece breathing pattern and tracheostomy size exerted a negative effect ($p = 0.001$ and $p = 0.04$ respectively). When the mask interface was used instead, breathing pattern exerted a positive effect ($p < 0.0001$) while tracheostomy size had a negative one ($p = 0.0001$).

Drug deposited in the tracheostomy tube

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The amount of albuterol deposited in the tracheostomy tube was a median of 0.8 % with interquartile range from 0.5% to 1% of the nominal dose.

Particle Size (Table 3)

The MMAD with the 3.5 mm tracheostomy tube ranged from 1.20 µm ± 0.12 µm (CON/ T-piece) to 1.43 µm ± 0.12 µm (CON/mask) ($p = 0.13$). The GSD with the 3.5 mm tracheostomy tube ranged from 1.75 ± 0.15 (BAN) to 1.90 ± 0.17 (CON/T-piece) ($p = 0.38$). All nebulizers had 99.9% of their particles smaller than 5 µm ($p = 1$).

The MMAD with the 5.5 mm tracheostomy tube ranged from 1.38 µm ± 0.18 µm (CON/T-piece) to 1.77 µm ± 0.10 µm (BAN) ($p = 0.0006$). Post-hoc analysis showed that the difference was present only for CON/T-piece and BAN ($p = 0.035$). The GSD with the 5.5 mm tracheostomy tube ranged from 1.68 ± 0.07 (BAN) to 1.93 ± 0.07 (CON/mask) ($p = 0.0008$). Post-hoc analysis showed that CON/mask had a larger GSD than BAN and BEN ($p = 0.0009$ and $p = 0.026$ respectively). All nebulizers had 98.7% to 99.9% of their particles smaller than 5 µm ($p = 0.9$).

When aerosol characteristics were compared between the 3.5 mm and the 5.5 mm tracheostomy tube, the following was noted: 1) The MMAD with the 5.5 mm tube was larger for all nebulizers except for CON T-piece ($p = 0.26$), with an increase in size of 0.17 µm ($p = 0.011$), 0.32 µm ($p = 0.013$), and 0.55 µm ($p = 0.012$) for the CON mask, BEN, and BAN respectively; 2) No differences were noted in their GSD ($p = 0.25$) and 3) No differences were noted in their percentage of particles < 5 µm ($p = 1$).

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Discussion

Little data are available regarding efficiency of nebulized drug delivery using different devices and techniques in spontaneously breathing tracheostomized patients.[1-2] In this study we compared the amount albuterol delivered to a model of spontaneously breathing children with tracheostomy using different devices, inhalation techniques, tracheostomy tube sizes and breathing patterns. We found that aerosol deposition was low and that a breath enhanced nebulizer was the most efficient device followed by a continuously operated nebulizer used with every other breath assisted technique. Breathing pattern affected drug delivery more significantly that tracheostomy size and a T-piece was a more efficient interface than a mask. Smaller tracheostomy tubes, breathing patterns of younger children, and the use of assisted technique determined a more proximal deposition of nebulized aerosols. Finally, Aerosols decreased in size after traveling through the tracheostomy tube and little drug deposited in the tracheostomy tube.

Delivery device

The finding that the use of different type of nebulizers results in different outcomes is in agreement with Pitance et al.[16] They studied amikacin delivery in an adult tracheostomy (ID = 6.5 - 10 mm) model (Vt = 440 ml, RR = 20, I:E = 1:2) with a collecting filter placed at the tip of the tracheostomy tube creating a closed circuit. They tested a breath assisted nebulizer, and a continuously operated nebulizer alone and with an extension tube. The authors found that with the smallest ID tested (6.5 mm) the continuously operated nebulizer with an extension tube had a slightly higher respiratory dose than the breath assisted nebulizer. Their respiratory dose is

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equivalent to total patient dose. The other 2 reported studies tested only one type of nebulizer.[14-15] Our data are consistent with reports of spontaneously breathing models and supports the concept that data obtained with one operating type of nebulizer cannot be extrapolated to others.[18] We also found that the BEN delivered more drug proximally than distally. The CON-T-piece with extension using assisted breathing technique every other breath performed similarly to BEN. This feature could be used to target the trachea for the delivery of antibiotics for treatment of tracheitis. The lower airways dose delivered by BEN and CON-extension/T-piece bagged every other breath was equivalent to 2 to 3 puffs (pMDI 90 mcg/puff) delivered with a non-electrostatic valved holding chamber in a similar model for all scenarios except for 35/16M (range 3-5 puffs).[13] The poor performance of the BAN in this experimental setup could be due in part to the fact that the flows generated with the chosen breathing patterns were not large enough to activate and keep open the inhalation valve.

Assisted delivery

Weather to use or not assisted technique to deliver nebulized aerosols trough tracheostomies remains an important clinical question. Our positive findings for the younger breathing pattern and all small tracheostomy sizes are in agreement with Ari et al.[15] They used an adult type tracheostomy model (ID = 8 mm) (Vt = 450 ml, RR = 20, I:E = 1:2) and a continuously operated jet nebulizer. Their model had a collecting filter connected at the end of the tracheostomy tube connected in series to a passive test lung. Their results are equivalent to our total patient dose. Our model prevented the buildup of pressure by allowing aerosols to be expired if they were not deposited in the filters and also had a breathing simulator. These differences could explain the discrepancy in the magnitude of the improvement with 55%

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(55/12Y) and more than 300% in our and their study respectively. Our data are not in agreement with the one we obtained with pMDIs using the same model.[13] Similar results were replicated in a follow-up study.[19] We speculate that the difference noted in the behavior exhibited by nebulizers and pMDIs could be partially explained because the former produces a slower aerosol in a continuous fashion that fills the model/airway with aerosol during exhalation time. Conversely aerosol production by pMDI is intermittent and faster. We also found that every other breath assisted technique was superior to every breath technique. We speculate that difference might be due to the fact that the former allows for aerosol to collect in the reservoir in between breaths.

The use of assisted technique resulted in an increase of the proximal/distal ratio for the younger breathing pattern. This could be due to the turbulence created by the gas coming from the resuscitation bag. This phenomena could be use to target the proximal airways during treatment of tracheitis.

Extension tube

The enhancement in drug delivery found in some scenarios with the addition of an extension tube coupled to a T-piece is in agreement with Pitance et al. However, they reported a larger increase in delivered drug than us (12% to 22% vs, 53%-54% respectively). The difference in magnitude of improvement of drug delivery noted with the addition of an extension tube could be due in part to the difference in Vt used. The volume of the extension tube is larger than the Vt of the young child so no entrainment of air without aerosol occurs.

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Interface

The decrease in delivered dose found when the patient interface was switched from T-piece to trach mask is in agreement with findings of Ari et al. and Picuitto et al.[14-15] The former group reported a 50% decrease and the latter group reported a 15% decrease in an adult tracheostomy (ID = 8 mm) model (Vt = 400 ml, RR = 20, I:E= 1:2) when switching from T-piece to mask interface.[14-15] Their experimental setup also had a filter placed at the end of the tube making their data comparable to our total patient dose.[14-15]

Tracheostomy size

Our finding that tracheostomy size directly correlated with lower airways dose (BAN and BEN) and with tracheal and total patient dose (BAN) is consistent data reported for endotracheal tubes .[20] Pitance et al. using an adult tracheostomy model found a decrease in respiratory dose that ranged from 4% to 21% when changing from an ID of 10 mm to 8.5 mm and from 17% to 31% when changing from an ID of 8 mm to 6.5 mm using 3 devices.[16] We speculate that difference of impact of tracheostomy could be due to the fact that there might a specific ID that beyond its size the influence decreases. Once again the different setup could be responsible for the noted differences as well.

Breathing patterns

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Our finding that breathing patterns of older children led to higher lower airways dose, tracheal dose and total patient dose is in agreement with previously reported in-vivo studies and with in-vitro studies that used spontaneously breathing pediatric models.[21-22] We also found that the use of assisted technique removed the difference in patient dose among breathing patterns by significantly increasing lower airways dose (24% - 128%) and total patient dose (55% - 465%)). This finding is the opposite of what we reported for pMDIs using a similar model.[13] We speculate that the differences could be due to the fact that nebulization is a continuous process, that the nebulized aerosols are slower and that the nominal doses are significantly higher (2500 μg vs. 90 μg).

When tracheal dose was analyzed same findings were noted except for BEN that showed no differences across breathing patterns. Tracheal dose was 34-30-fold and 5-6-fold higher for BEN than for CON or BAN for the smallest tracheostomy with the youngest breathing pattern and for the largest tracheostomy and the oldest breathing pattern respectively.

Drug deposited in the tracheostomy tubes

The low amount of drug deposited in the tracheostomy tube (0.8% of nominal dose) contrasts with higher values reported with pMDIs using either similar (7.8%) or different (10%) setups. [13, 23] These differences could be due to the higher velocity of the aerosols generated by pMDIs therefore leading to more deposition on the tracheostomy walls by impaction. Our data shows significantly lower deposition than that of Pitance et al., using an adult model, who reported a range of 2% to 16% of the nominal dose.[16] This might be due to the differences in

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experimental setup. As noted above, aerosols did not have any escape and build of pressure could have occurred resulting in more deposition at the tracheostomy tube level.

Particle size

The finding that aerosols reduced their particle size when passing through tracheostomy tubes is in agreement with data obtained with radiolabelled aerosols passing through a 3.5 endotracheal tube size.[25] Arhens et al. also reported a decrease in MMAD from 3.4 µm at the mouth of a jet nebulizer to 1.2 µm, 1 µm, an 0.48 µm at the tip of endotracheal tubes with an ID of 3 mm, 6 mm, and 9 mm respectively.[20] The CON decreased its MMAD from 4.56 µm to 1.2 µm and 1.38 µm after passing a 3.5 mm and 5.5 mm respectively.[17] The BEN decreased its MMAD from 3.47 µm to 1.26 µm and 1.58 µm after passing a 3.5 mm and 5.5 mm respectively.[17] The BAN decreased its MMAD from 3.43 µm to 1.22 µm and 1.77 µm after passing a 3.5 mm and 5.5 mm respectively.[24] The reduction in particle size is most likely due to impaction of the larger droplets against the tracheostomy tube walls. Future studies should evaluate weather using aerosols with an MMAD of 1 µm can improve delivery.

Model

The use of a two-compartment model such as the one used in this study provides richer information and is an improvement from single compartment models that artificially increase the magnitude of certain phenomena. Arhens et al. also reported that the use of a two-compartment model prevented the overestimation created by condensation in the tubes and subsequent dripping.[20] In addition, a two-compartment model resembles more what happens in human

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subjects. However, our model is not perfect because it does not allow air entrainment through the mouth of around the stoma. Future studies should include anatomically correct models to overcome the limitation noted above.

The in-vitro nature of our study constitutes one of its main limitations. In particular, the fact that this setup leads to overestimation of the amount deposited in the lower airways because once the drug is trapped in the filter it cannot be exhaled. Another limitation is the fact that we used only one size trachea. Despite these limitations the current data advances the present knowledge on how to optimize delivery of nebulized to spontaneously breathing children with tracheostomy.

Clinical implications

Drug delivery was low in most scenarios/device-delivery technique studied. The use of assisted breathing when using a continuously operated nebulizer improves delivery efficiency and it should be considered especially when the trachea is the targeted area. This setup is as efficient as the breath enhanced device, making the former the device of choice. Breath actuated nebulizers should not be used unless opening of the valve by the patient is documented.

The best way of using these and other data and to be able to determine the applicability to a specific patient is by measuring the spontaneous Vt through the tracheostomy with a Wright manometer.[1,13]

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Conclusions

A breath enhanced nebulizer was the most effective device. The use of assisted technique increased aerosol delivery with every other breath (second best) being superior to every breath technique. Tracheostomy size and breathing pattern significantly affected drug delivery. T-piece was a more efficient interface. Aerosols changed their characteristics when traveling through tracheostomy tubes. Smaller tracheostomy tubes, breathing patterns of younger children, and the use of assisted technique determined a more proximal deposition of nebulized aerosols. These data underscores that extrapolation from different devices and different scenarios might lead to erroneous conclusions.

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References

1. Willis D and Berlinski A. Survey of Aerosol Delivery Techniques to Spontaneously Breathing Tracheostomized Children. Respir Care 2012;57(8)1234-1241.
2. Amirav I, Newhouse MT. Aerosol therapy in tracheotomized children: time for guidelines! Respir Care 2012;57(8):1350.
3. O'Callaghan C, Dryden S, Cert DN, Gibbin K. Asthma therapy and a tracheostomy. J Laryngol Otol 1989; 103(4):427-428.
4. Subhedar NV, Doyle C, Shaw NJ. Administration of inhaled medication via a tracheostomy in infants with chronic lung disease of prematurity. Pediatr Rehabil 1999;3(2):41-42.
5. Monksfield P. Modification of a spacer device for paediatric tracheostomy. Clin Otolaryngol. 2008;33(2):193-194.
6. Webber PA, Brown AR. The use of a conical spacer after laryngectomy. Br Med J (Clin Res Ed). 1984;288(6429):1537.
7. Nakhla V. A homemade modification of a spacer device for delivery of bronchodilator or steroid therapy in patients with tracheostomies. J Laryngol Otol 1997;111(4):363-365.
8. Mirza S, Hopkinson L, Malik TH, Willatt DJ. The use of inhalers in patients with tracheal stomas or tracheostomy tubes. J Laryngol Otol 1999;113(8):762-764.
9. Meeker DP, Stelmach K. Modification of the spacer device. Chest 1992;102(4):1243-1244.
10. García Pachón E, Casan P, Sanchís J. [Bronchodilators through tracheostomy]. Med Clin (Barc) 1992;99(10):396-397. [Article in Spanish]

RESPIRATORY CARE Paper in Press. Published on May 14, 2013 as DOI: 10.4187/respcare.02419

11. Newhouse MT. Hemoptysis due to MDI therapy in a patient with permanent tracheostomy: treatment with mask AeroChamber. Chest 1999;115(1):279-282.
12. Nandapalan V, Currey M, Jones TM. A modified spacer device for inhalational drug therapy for chronic bronchitis/asthma in laryngectomised patients. Clin Otolaryngol 2000;25(2):118-119.
13. Berlinski A and Chavez A. Albuterol delivery via Metered Dose Inhaler in a spontaneously breathing pediatric tracheostomy model. Pediatric Pulmonology 2012 Nov 5 [Epub ahead of print].
14. Piccuito CM, Hess DR. Albuterol delivery via tracheostomy tube. Respir Care 2005;50(8):1071-1076.
15. Ari A, Harwood R, Sheard M, and Fink JB. An in-vitro evaluation of aerosol delivery through tracheostomy and endotracheal tubes using different interfaces. Respir Care 2012;57(7):1066-1070.
16. Pitance l, Vecellio L, Delval G, Reychler G, Reychler H, and Liistro G. Aerosol delivery through tracheostomy tubes: an in-vitro study. J Aerosol Med Pulm Drug Deliv 2012 [Epub ahead of print].
17. Berlinski A and Hayden JB. Optimization of a Procedure Used to Measure Aerosol Characteristics of Nebulized Solutions Using a Cooled Next Generation Impactor. *J Aerosol Med Pulm Drug Deliv* 2010,23(6)397-404.
18. Barry PW, O'Callahan C. An in-vitro analysis of the output of salbutamol from different nebulizers. Eur Respir Care 1999;13(5)1164-1169.

RESPIRATORY CARE Paper in Press. Published on May 14, 2013 as DOI: 10.4187/respcare.02419

19. Chavez A, Holt S, Heulitt M, and Berlinski A. Albuterol Delivery Via MDI/Spacer In A Spontaneously Breathing Pediatric Tracheostomy Model: Does Bagging Improve Drug Delivery? *Am. J Respir Crit Care Med* 2011;183:A3383.

20. Ahrens RC, Ries RA, Popendorf W, Wiese JA. The delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol 1986;2(1):19-26.

21. Chavez A, McCraken A, Berlinski A. Effect of face mask static dead volume, respiratory rate and tidal volume on inhaled albuterol delivery. Pediatr Pulmonol 2010;45(3):224-229.

22. Chua HL, Collis GG, Newbury AM, Chan K, Bower GD, Sly PD, Le Souef PN. The influence of age on aerosol deposition in children with cystic fibrosis. Eur Respir J 1994;7(12):185-191.

23. O'Riordan TG, Palmer LB, and Smaldone GC. Aerosol deposition in mechanically ventilated patients. Optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214-219.

24. Berlinski A, Hayden J. Aerosol characteristics of 7% nebulized hypertonic saline delivered by 4 different nebulizers. *Ped Pulmonology* 2011;supplement 34:336.

25. Fok TF, Al-Essa M, Monkman S, Dolovich M, Girard L, Coates G, Kirpalani H. Pulmonary deposition of salbutamol aerosol delivered by metered dose inhaler, jet nebulizer, and ultrasonic nebulizer in mechanically ventilated rabbits. Pediatr Res 1997;42(5):721-7.

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Figures

Figure 1: Experimental setup used to measure nebulized albuterol delivery a model of spontaneously breathing children with tracheostomy. The hollow arrows represent the direction of the airflow.

Figure 2: Devices, interfaces, adaptors, and tracheostomies used for different configurations.

BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; and CON = continuously operated nebulizer.

Figure 3: Experimental setup used to measure particle size distribution.

Figure 4: Total patient dose expressed as percentage of nominal dose.

BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; CON = continuously operated nebulizer; -T = T-piece interface; -M = mask interface; EXT = with extension tube placed after the nebulizer; BAGGED = every other breath assisted breathing.

Figure 5: Proximal/distal ratio.

BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; CON = continuously operated nebulizer; -T = T-piece interface; -M = mask interface; EXT = with extension tube placed after the nebulizer; BAGGED = every other breath assisted breathing.

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Table 1: Lower filter dose expressed as percentage of nominal dose (%)

Device/Scenario	3.5/16M	3.5/12Y	5.5/16M	5.5/12Y
BEN	1.64 ± 0.08	2.63 ± 0.28	3.69 ± 0.26	5.19 ± 0.36
BAN	0.15 ± 0.08	0.55 ± 0.24	0.58 ± 0.23	2.08 ± 0.30
CON-T	0.99 ± 0.13	1.40 ± 0.13	1.09 ± 0.07	1.71 ± 0.46
CON-M	1.71 ± 0.11	1.33 ± 0.07	1.02 ± 0.43	1.74 ± 0.53
CON-T-EXT	1.57 ± 0.33	1.33 ± 0.20	1.32 ± 0.21	2.28 ± 0.37
CON-M-EXT	1.88 ± 0.28	1.16 ± 0.19	0.96 ± 0.24	1.50 ± 0.33
CON-T-EXT-BAGGED	2.46 ± 0.18	3.04 ± 0.21	2.77 ± 0.60	2.83 ± 0.91
CON-M-EXT-BAGGED	1.74 ± 0.17	1.74 ± 0.34	1.33 ± 30	2.18 ± 0.18

BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; CON = continuously operated nebulizer; -T = T-piece interface; -M = mask interface; EXT = with extension tube placed after the nebulizer; BAGGED = every other breath assisted breathing.

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Table 2: Tracheal dose expressed as percentage of nominal dose (%)

Device/Scenario	3.5/16M	3.5/12Y	5.5/16M	5.5/12Y
BEN	10.51 ± 0.97	10.17 ± 3.73	7.10 ± 1.72	9.49 ± 1.41
BAN	0.35 ± 0.70	0.32 ± 0.39	0.34 ± 0.13	1.57 ± 0.41
CON-T	0.31 ± 0.11	1.81 ± 0.27	0.05 ± 0.08	1.77 ± 0.28
CON-M	0.75 ± 0.17	1.40 ± 0.64	0.17 ± 0.16	1.13 ± 0.29
CON-T-EXT	0.38 ± 0.08	1.95 ± 0.00	0.44 ± 0.50	3.11 ± 0.71
CON-M-EXT	0.99 ± 0.29	1.13 ± 0.32	0.31 ± 0.11	1.09 ± 0.36
CON-T-EXT-BAGGED	8.53 ± 1.36	5.12 ± 1.44	5.77 ± 0.68	5.50 ± 1.74
CON-M-EXT-BAGGED	0.82 ± 0.13	1.60 ± 0.18	0.14 ± 0.07	1.43 ± 0.30

BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; CON = continuously operated nebulizer; -T = T-piece interface; -M = mask interface; EXT = with extension tube placed after the nebulizer; BAGGED = every other breath assisted breathing.

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Table 3: Particle size distribution of nebulized albuterol exiting tracheostomy tubes

	CON/T-piece		CON/mask		BEN		BAN	
Tracheostomy size (mm)	3.5	5.5	3.5	5.5	3.5	5.5	3.5	5.5
MMAD (μm)	1.20 ± 0.12	1.38 ± 0.18	1.43 ± 0.12	1.60 ± 0.10	1.26 ± 0.18	1.58 ± 0.10	1.22 ± 0.15	1.77 ± 0.10
GSD	1.90 ± 0.17	1.85 ± 0.06	1.79 ± 0.01	1.93 ± 0.07	1.78 ± 0.13	1.77 ± 0.04	1.75 ± 0.15	1.68 ± 0.07
% particles < 5 μm	100	99	100	99	99	99	100	99

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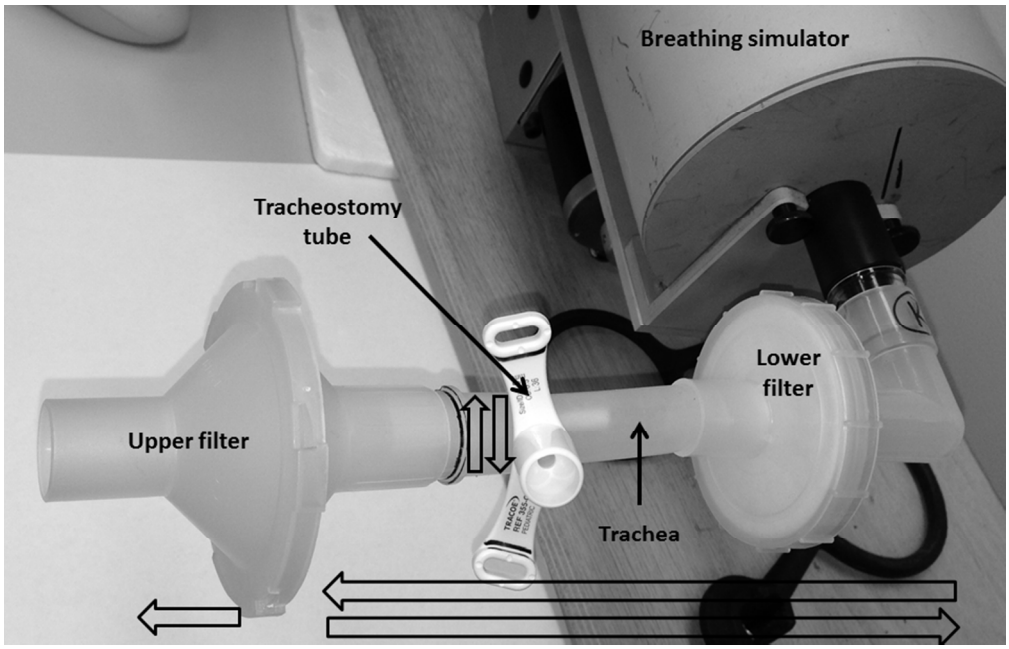

Figure 1: Experimental setup used to measure nebulized albuterol delivery a model of spontaneously breathing children with tracheostomy. The hollow arrows represent the direction of the airflow.
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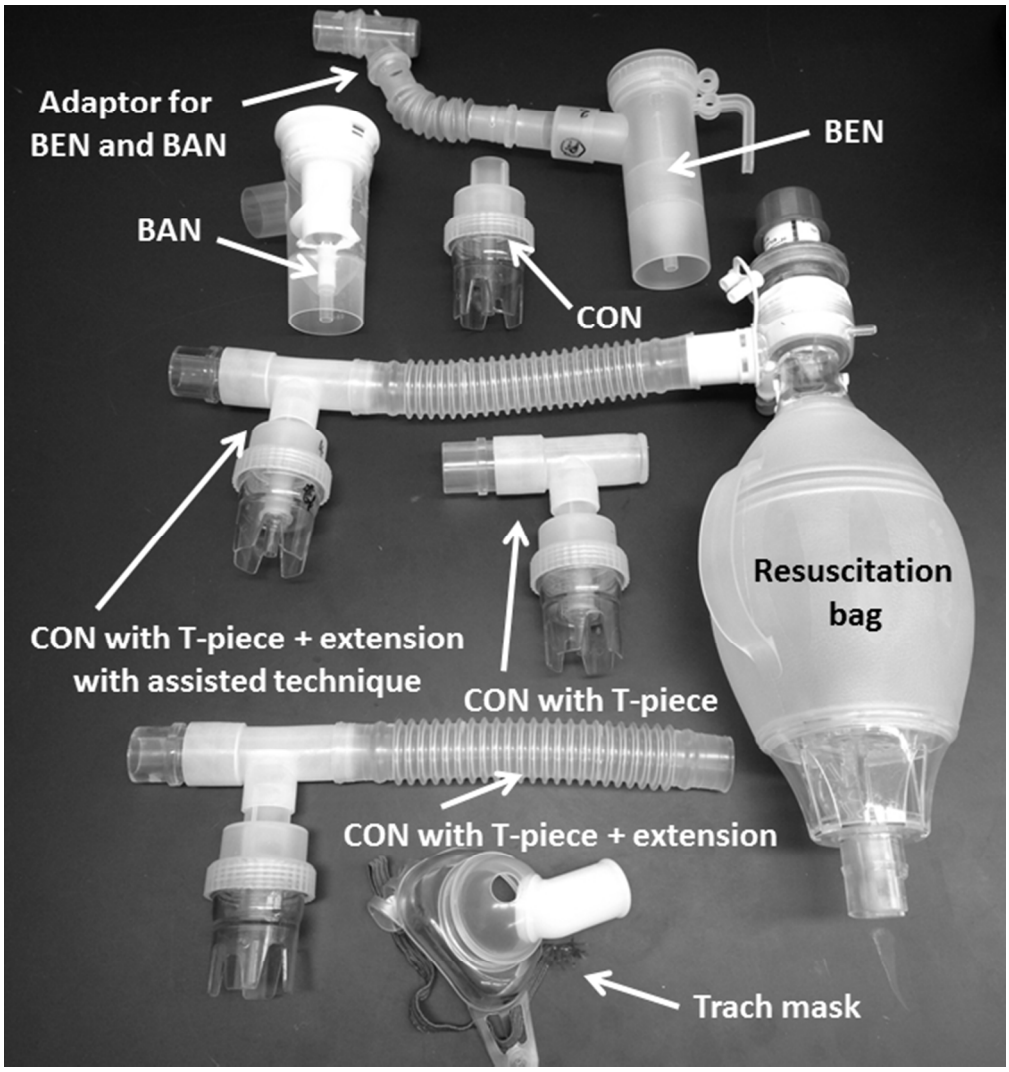

Figure 2: Devices, interfaces, adaptors, and tracheostomies used for different configurations. BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; and CON = continuously operated nebulizer.

178x189mm (96 x 96 DPI)

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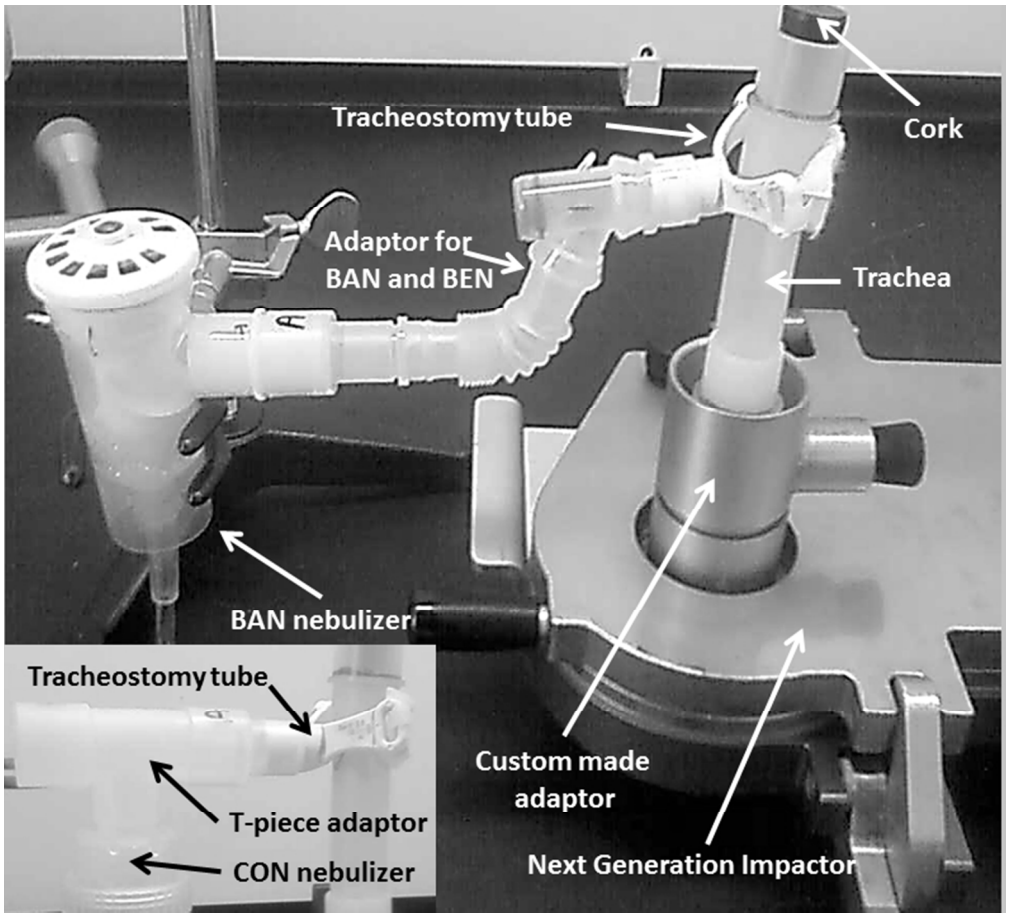

Figure 3: Experimental setup used to measure particle size distribution.
209x189mm (96 x 96 DPI)

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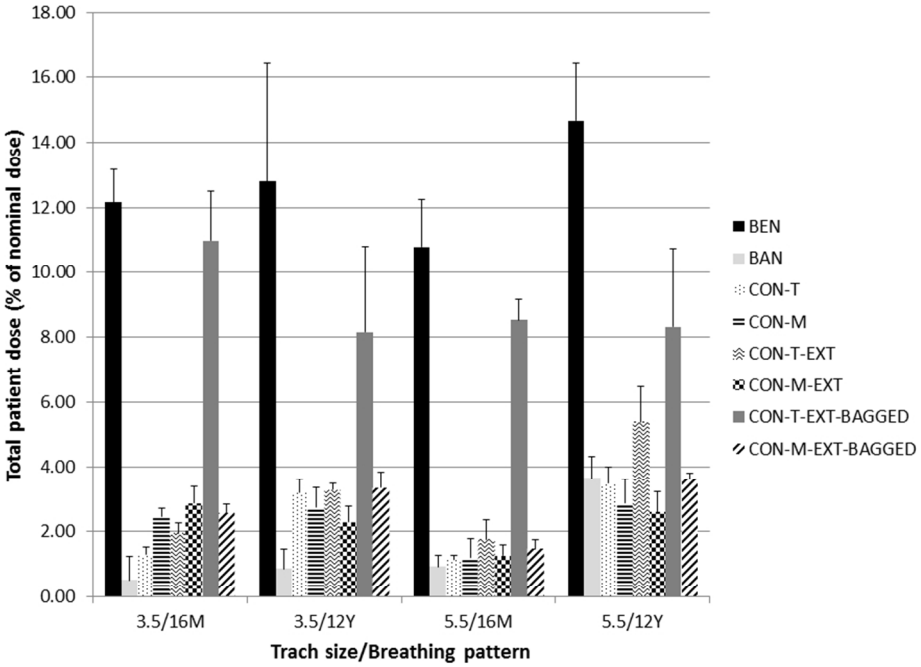

Figure 4: Total patient dose expressed as percentage of nominal dose.
BEN = breath enhanced nebulizer; BAN = breath actuated nebulizer; CON = continuously operated nebulizer; -T = T-piece interface; -M = mask interface; EXT = with extension tube placed after the nebulizer; BAGGED = every other breath assisted breathing.
254x190mm (96 x 96 DPI)

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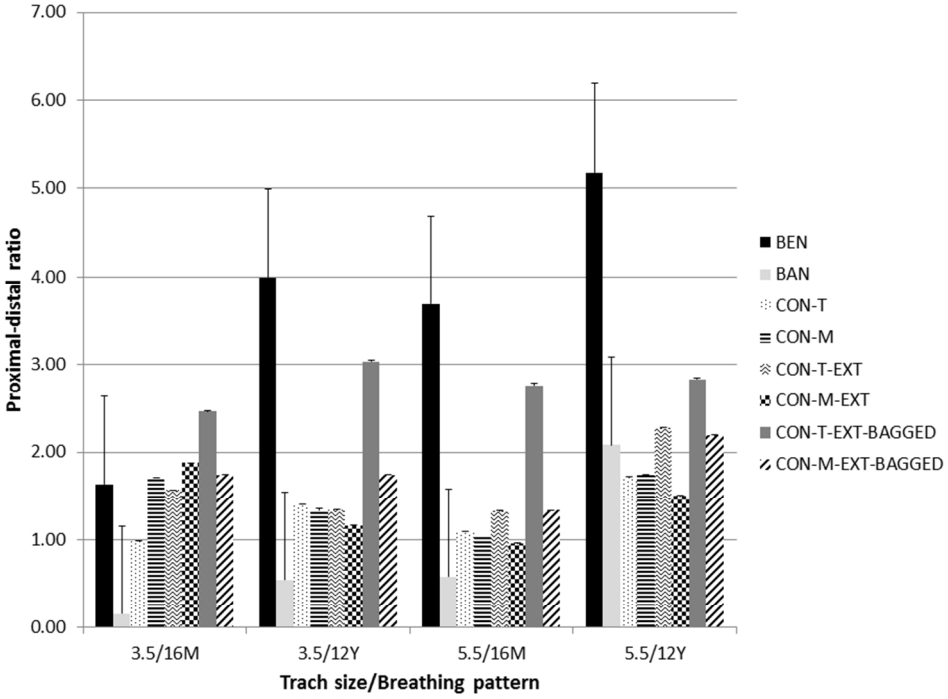

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254x190mm (96 x 96 DPI)