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LONGITUDINAL EVALUATION OF COMPRESSOR/NEBULIZER PERFORMANCE

Samah Awad, MBBS[1,4], David K Williams , PhD, MPH[2] and Ariel Berlinski, MD[1,3]

[1]University of Arkansas for Medical Sciences, College of Medicine, Department of Pediatrics, Pulmonology Section. [2]University of Arkansas for Medical Sciences, College of Public Health, Department of Biostatistics. [3]Pediatric Aerosol Research Laboratory, Arkansas Children's Hospital Research Institute. [1-3] Little Rock, Arkansas, U.S.A. [4] Current affiliation: Jordan University of Science and Technology, College of Medicine, Department of Pediatrics. Irbid, Jordan.

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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

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Phone: 501-364-1006

Fax: 501-364-3930

Little Rock, Arkansas 72202

E-mail: BerlinskiAriel@uams.edu

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Abstract

Background:

Inhaled medications are the mainstay of treatment for maintenance of lung health in patients with cystic fibrosis (CF). Compressor/nebulizer units are used an average of 100-120 minutes/day by patients with CF. Each compressor/nebulizer has unique flow/pressure characteristics that affect particle size distribution and drug output rate. Little data are available regarding longitudinal performance of compressor/nebulizers. We hypothesized that their use over a 24-week period under conditions similar to those of patients with CF will affect their performance.

Methods:

Four new units of compressor/reusable nebulizers from 3 brands (Pari Vios/Pari LC Plus, Pulmoaide 5650D/Viox and Inspiration Elite/SideStream Plus) commonly used by CF patients were tested. Compressor/nebulizers were operated 1 hour twice-daily/five days/week for 24 weeks. Compressor flow/pressure characteristics were measured every 6 weeks. Maximal flow was recorded without and with the nebulizer (MF, and MF/NEB respectively). Pressure was recorded at cero flow (MP) and at MF/NEB (P/NEB). Particle size distribution, inhaled mass (IM) and IM in respirable range (IM-RR) were evaluated at baseline and every 12 weeks.

Results:

Vios had significant decline in MP and P/NEB at each measurement compared to baseline (MP: 45.8 and 32.6 PSI and P/NEB: 16.7 and 14.3 PSI at week 0 and 24 respectively, $P<.05$) but other compressors didn't. MF and MF/NEB were stable over time but significantly varied among brands. Vios had the greatest slope of flow/pressure relationship (Vios> Pulmoaide> Inspiration

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Elite). Two Vios units stopped working at weeks 11 and 24 respectively. All compressors maintained baseline IM, IM-RR and aerosol characteristics.

Conclusion:

Long term use of compressor/nebulizers in a regimen similar to that of patients with CF affected their performance. Pari Vios was the most affected brand with decline in MP and P/NEB and 2 units that stopped working. Measurement of MF and MF/NEB could help identify compressors that are likely to fail.

Key words

Compressor, nebulizer, flow, pressure, aerosol, particle size, breathing simulation, Cystic Fibrosis

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Background

Cystic fibrosis (CF) is a fatal autosomal recessive disease affecting multiple organs. [1] The majority of mortality and morbidity is related to lung disease. [2] The CF gene defect impairs cystic fibrosis transmembrane regulator protein function leading to airway-surface-liquid depletion, loss of mucociliary clearance and vicious circle of inflammation and chronic bacterial infections. [3] An aggressive approach to treat CF lung disease has improved pulmonary outcomes and extended median predicted age of survival in the last three decades from 18 years of age in 1980 to 38.3 in 2010. [2] Inhaled medications constitute the main treatment options recommended for chronic maintenance of lung health in patients with CF. Recent guidelines have provided recommendations for the use of the following inhaled medications: tobramycin, dornase alfa, hypertonic saline, and β_2 - adrenergic receptor agonists . [4, 5]

The United States Cystic Fibrosis Foundation (CFF) recommends the use of inhaled tobramycin in patients older than 6 years with mild, moderate and severe lung disease who are chronically colonized by *P. aeruginosa*. Tobramycin is administered at a dose of 300 mg twice daily on alternating months (28 day on/28 day off) and it has been shown to increase lung function and decrease pulmonary exacerbations. [4,5] Tobramycin solution for inhalation (TSI) is registered under the brand name TOBI (300mg/5ml) and is used in combination with a Pari LC Plus reusable jet nebulizer and a suitable compressor, which has a flow rate of 4-6 L/min. [6] It is also available outside the United States as Bramitob (300mg/4ml) and used in combination with either Pari LC Plus reusable jet nebulizer and the Pari Turbo Boy compressor or Pari LC Sprint and Pari Boy Sx compressor. [7] Twice daily inhalation of tobramycin can take 40 min a day.

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The CFF also recommends the use of recombinant human dornase alfa for patients older than 6 years with variable spectrum of CF lung disease. Dornase alfa (Pulmozyme) reduces viscoelasticity of CF sputum by hydrolyzing extracellular DNA released by neutrophils in the inflamed airways and therefore enhancing mucociliary clearance. [8] It is available in ampoules of 2.5 mg/2.5 ml, given once daily and used in jet nebulizers connected to a compressor. In clinical trials device combinations such as Durable Sidestream with MOBILAIRE, Durable Sidestream with Porta-Neb, Hudson T Up-draft II with Pulmo-Aide, Respirgard II Nebulizer with Pulmo-Aide, Pari LC Plus with Pari Proneb, Pari Baby with Pari Proneb have been used. The estimated nebulization time ranges between 6 and 8 min. [9, 10]

The CFF also recommends the chronic use of nebulized hypertonic saline in patients with CF, 6 years of age and older, to improve lung function. [4, 5] By acting as an osmolar agent, hypertonic saline helps by hydrating the periciliary layer of the respiratory epithelium and hence enhance airway clearance. [11] Administration of 4 ml 7% saline twice daily improved FEV1, respiratory symptoms and mucus clearance; inhalation time can take 15 min a day. For patients with CF, 6 years of age and older, the CFF also recommends the chronic use of inhaled β_2 - adrenergic receptor agonists to improve lung function. [4, 5] Nebulization time can reach 30 minutes.

Patients with CF use their nebulizers an average of 100-120 min a day. Such use may reduce the performance of the compressors used to run these nebulizers. Manufacturers typically provide a 5-year warranty on the compressors but they do not specify in their operations manuals the number of hours that they will run. Many third party payers only allow compressor renewal

every five years. Our clinical experience at the Arkansas Children's Hospital Cystic Fibrosis Care Center as well as frequent reports in CF related professional listserv indicate that the life span of compressors used by CF patients is shorter than claimed by manufactures and covered by third-party payers.

Although several types of nebulizers are available, jet nebulizers are the most popular due to their low cost and widespread availability. Compressed air is needed for jet nebulizers to aerosolize liquid solutions or suspension and convert them into mist. [12, 13] Compressors constitute the only available air flow source at home and could be also used in hospital settings. The compressor gas flow/pressure relationship in addition to patient related factors, affect the nebulizer performance in term of droplet size distribution and drug output rate. [14, 15] Lower gas flow rates determine longer nebulization time and larger particle size aerosols. [15] The former hinders adherence to therapies and the latter could alter the site of intrapulmonary deposition. Therefore, information about performance of compressor/nebulizer systems is important for patient care.

Although several authors have reported the characteristics of different compressors and nebulizer, little is known about the effect of long-term use on their performance.[16- 20] Standaert et al. determined particle size distribution and output rate of durable Pari LC nebulizer after 100 runs and reported that particle size remained stable.[21]

In this study we evaluated the performance of 3 pairs of compressor/nebulizer combinations over a 24-week period of use typical of a patient with CF. We hypothesized that such use of

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compressor/nebulizer units will affect their flow/pressure, drug output, and aerosol characteristics. These changes are expected due to progressive deterioration of the compressor/nebulizer units and could have relevant implications for lung deposition and medication efficacy of aerosol treatments. In addition we hypothesized the presence of difference in performance among different compressor/nebulizer systems.

Materials and Methods

Compressors and nebulizers

Four new units of compressors from 3 different brands were used in our study with the reusable nebulizer recommended by the manufacturers: Pari Vios with Pari LC Plus reusable nebulizer (Pari Respiratory Equipment Inc, Midlothian, VA), Pulmoaide compressor Model 5650D with Viox one reusable nebulizer (DeVilbiss Healthcare LLC, Sommerset, PA) and Inspiration Elite (model # HS456) with SideStream Plus durable nebulizer (model # HS870) (Philips Respironics, Parsippany, NJ). The Viox nebulizer is a constant output nebulizer while Pari LC Plus and Sidestream Plus are breath enhanced nebulizers. The Inspiration Elite compressor has a self-resetting pressure relief valve that opens at 33 PSI. The technical specifications provided by the manufacturers can be seen in Table 1. These devices were chosen because they are the most commonly used and their manufacturers advertise their use in cystic fibrosis.

Study Design

Each compressor/nebulizer was operated without a solution for 1 hour twice daily five days a week for 24 weeks. The corresponding nebulizer was connected to each compressor. The same

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combinations of compressor/nebulizer units were used through the study. Environmental temperature and humidity were recorded at time of operation (23° C ± 1.4° C and 42.6% ± 5.7% respectively). Measurements of flow rates and pressures were done at weeks 0, 6, 12, 18, 24. Breathing simulation testing and particle size distribution measurements were done at weeks 0, 12, 24. Compressor filters were periodically reviewed for presence of dirt.

Flow and Pressure Measurements:

Previously published methodologies were used to measure flow and pressure characteristics of compressor/nebulizer systems (Figure 1).[16,17,19] The outlet of each compressor was connected in line with tubing to a pressure meter with a transducer with a max of 72.5 PSI and resolution 0.1 PSI (SPER Scientific LTD model 840065 Scottsdale, AZ) and thence to a flow meter with a range of 2 to 20 L/min (Cole Palmer Instrument Co, Vernon Hills, IL). The flow meter had a needle valve that allowed flow adjustment. Maximal flow (MF) was recorded as the flow rate (L/min) each compressor developed when the needle valve was completely open. Flow decrements of 1 L/min were used between flows similar to MF and the maximal flow with the nebulizer connected to the compressor (MF/NEB). Flow decrements of 0.5 L/min were used from between flows similar to MF/NEB to 2 L/min and then flow was decreased from 2 L/min to 0 L/min. These resulted in 12, 17, and 17 data points for Vios, Pulmoaide and Inspiration Elite respectively. Flow rate was adjusted with the needle valve and pressure was measured at each flow rate. The pressure that the compressor developed at zero flow (needle valve completely closed) was recorded as the maximal pressure (MP). Measurements were done after 2 min of

operation. The nebulizer without a solution was then connected to the flowmeter, MF/NEB and the pressure measured at MF/NEB (P/NEB) were recorded.

Particle size analysis:

Particle size distribution was measured by cascade impaction. A Next Generation Impactor (NGI, MSP corporation, Shoreview, MN) calibrated at 15 L/min was cooled to 4□ C for 90 minutes and used within 5 min of removing it from the refrigerator. [22] Albuterol sulfate 2.5 mg/3 ml (Nephron Pharmaceuticals Corporation, Orlando, FL) was loaded in the nebulizer. The nebulizer was connected to the inlet of the induction port of the NGI and was operated for 4 min (Figure 2). Air entrainment was allowed through the T-piece in the Viox nebulizer and through their inspiratory valve in the Pari LC Plus and Sidestream Plus nebulizers. Upon completion, all the collection cups, internal and external filters and nebulizer cup were diluted with ultrapure water and tested for albuterol concentration via spectrophotometry at 276 nm (Biomate 3 UV-Vis Spectrophotometer, Thermo Electron Corporation, Waltham, MA). [22] The following parameters were calculated using CITDAS V3.1 software (Copley Scientific, Nottingham, UK) according to United States Pharmacopeia and European Pharmacopeia recommendations: mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), percentage of drug mass contained in particles less than 5 μm (P% <5). [22] Nebulizers were disassembled, cleaned with ultrapure water and air dried.

Breathing Simulation:

This is a methodology used to study aerosol output of nebulizers and allows an accurate evaluation of those that have an increase in their aerosol output during inspiration such as breath

enhanced nebulizers. [23] A breathing simulator is a computerized piston pump that allows programming of respiratory parameters to mimic different breathing conditions. Calibration of breathing simulator (PARI Compass, Munich, Germany) was verified at the beginning of each testing by a mass flow meter (TSI 4043, Shoreview, MN) and its associated software. [24] Nebulizer dry weight (W_D) was obtained while still empty using a precision scale. Albuterol sulfate 2.5 mg/3 ml (Nephron Pharmaceuticals Corporation, Orlando, FL) was loaded in the nebulizer and a new weight was obtained (W_L). The nebulizer was connected to the breathing simulator. A low dead space filter was interposed between them (inspiratory filter). A filter holder (PARI Respiratory Equipment Inc, Midlothian, VA) with a one-way valve was connected to the nebulizer to capture the exhaled aerosol (expiratory filter) to minimize operator exposure (Figure 3). [25] New filters (PARI Respiratory Equipment Inc, Midlothian, VA) were placed at the beginning of each experiment. The nebulizer was connected to the compressor and operated for 10 minutes and then reweighed to obtain the final weight (W_F). The following breathing pattern was used: Tidal volume 500 ml, breathing rate 12 bpm, iT: 1.7s, and I: E ratio 1:2. After completion of nebulization, 5 mls of pure water were added to the nebulizer cup. The nebulizer was reweighed (W_{F+5}) and then swirled and the solution was tested for albuterol concentration. Albuterol remaining in the nebulizer cup was calculated as follows: (W_{F+5} - W_D) x albuterol concentration. The inspiratory filter was placed in a 50 ml tube with10 mls of ultrapure water and after vigorous shaking the solution was tested for albuterol concentration with spectrophotometry. The expiratory filter was discarded. Nebulizers were disassembled, cleaned with ultrapure water and air dried. Inhaled mass (IM, µg) was defined as the amount of the albuterol captured by the inspiratory filter. Inhaled mass in the respirable range (IM-RR) was calculated as (IM*P% <5)/100.

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Statistical Analysis

There were 5 parameters of interest related to pressure and flow measurements: MF, MP, MF/NEB, P/NEB and slope of flow/pressure relationship without nebulizer (MF/MP slope). A nonlinear model of the form Pressure = a*Exp (b*Flow) was fit to the data, which provided the slope and maximal pressure estimates using the 5% level of significance. Dunnet's test was used to compare maximal pressure, flow and flow-pressure relationship slope at each time level to time 0. Analysis of variance (ANOVA) followed by Tukey test was used to compare performance among the brands at weeks 0, 6, 12, 18, and 24. ANOVA was used to compare particle size characteristics and breathing simulation results across devices. ANOVA for repeated measures was used to compare particle size characteristics and breathing simulation results at weeks 0, 12, and 24 for each specific device. Bonferroni method was used for pot hoc analysis when multiple comparisons were required. A p value < 0.05 was considered statistically significant. A statistical software package was used for data analysis (SAS version 9.3, Cary, NC).

Results

The 4 tested units of Inspiration Elite and Pulmoaide compressors completed all planned studies. Two units of the Vios completed all planned studies. One unit stopped running after the 5th day of week 11 with total run of 110 hours. Another unit completed all pressure/flow and simulation breathing studies but although the compressor was running, no aerosol was produced and no

drug was recovered in the NGI at week 24. This was verified in triplicate. Therefore, the n for the Vios brand were 4 and 3 before and after the 11th week respectively for all measurements except for NGI at week 24 when n was 2.

Flow and pressure (Tables 2 and Supplementary Table 1)

MF and MF/NEB

Pari Vios experienced decline in MF at each time level compared to week 0 without statistical significance. However, the unit that stopped running at the end of week 11 showed a decrease in MF from 9 L/min at baseline to 7 L/min at week 6. Also the unit that malfunctioned on week 24 showed a decrease in MF from 9 L/min at baseline to 5 L/min at week 18. Vios also had a decline in MF/NEB with time which became statistically significant at week 24 ($P = .045$). The unit that malfunctioned on week 24 had a decrease in MF/NEB from 4.5 L/min to 4 L/min and 3.5 L/min at weeks 12, 18 and 24 respectively.

Pulmoaide and Inspiration Elite maintained baseline MF and MF/NEB measurements throughout the 24 week period.

Pari Vios MF and MF/NEB were lower than Pulmoaide and Inspiration Elite at all times ($P < .05$). There was no difference in MF values between Pulmoaide and Inspiration Elite but MF/NEB was higher in Pulmoaide than Inspiration Elite at all times ($P < .05$).

MP and P/NEB

Pari Vios had significant decline ($P < .05$) in MP at each time level compared to baseline but the other brands didn't. Also, it was noticed that MP showed an erratic behavior demonstrated by worsening during week 18 with partial recovery during week 24.

Vios and Pulmoaide demonstrated higher MP than Inspiration Elite. When performing all pairwise comparison among the brands, Vios had greater MP than Inspiration Elite at all times except on week 18. Pulmoaide was consistently greater than Inspiration Elite with significant difference at all times except at week 6. Vios had greater MP than Pulmoaide at weeks 0 ($P < .001$), 6 and 12. The trend is reversed at week 18 ($P < .001$) and week 24 where Pulmoaide had greater MP compared to Vios.

P/NEB was different among different brands with Inspiron Elite greater than Vios and greater than Pulmoaide ($P < .05$). P/NEB remained stable for Pulmoaide and Inspiration Elite but declined for Vios. The latter has a significant decline starting on week 18.

MF/MP slope (Supplementary Table 1 and online Figure 1)

The brands behaved in a similar pattern at all times. Pari Vios tended to have a greater absolute value of the MF/MP slope compared to Pulmoaide and Inspiration Elite. Pulmoaide tended to have a greater absolute value than Inspiration Elite. The difference in the slope when performing all pairwise comparisons was statistically significant with few exceptions. For weeks 12, 18, and 24 statistical significance was not achieved, but the trend of Pari Vios having a greater slope than the other brands remained. Also, Pari Vios had a greater variation around its trend compared to Pulmoaide and Inspiration Elite. This was especially true at weeks 6 through week 24 in which the standard error of the slope for Pari Vios was always greater than for the other two brands.

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The Vios unit that stopped running at the end of week 11 showed at week 6 a significantly lower pressure while the flow was set at 2.5 L/min. The other unit that malfunctioned at week 24 had lower pressures but not different from the other units.

Particle Size Analysis (Tables 2 and Supplementary Table 2)

All brands maintained baseline MMAD by week 24. Pari Vios had larger MMAD than Pulmoaide and Inspiration Elite at all times but it was only statistically significant at week 0 for Vios-Pulmoaide ($P = .04$) and at week 24 for Vios-Inspiration Elite ($P = .004$). Inspiration Elite had smaller MMAD than Pulmoaide with significance only at week 12 ($P < .0001$).

Vios and Pulmoaide had a decrease in GSD at week 24 compared to baseline ($P < .001$). Inspiration Elite didn't have significant change in GSD by week 24. Vios had significantly higher GSD than Pulmoaide at all times and higher than Inspiration Elite at weeks 0 and 12. Inspiration Elite has a larger GSD than Pulmoaide at week 24.

P%<5 had no significant change with time for the all brands. Inspiration Elite trended to have higher P%<5 followed by Pulmoaide and then Vios. The difference was significant compared to Vios at week 24 ($P = .006$) and to Pulmoaide at week 12 ($P = .009$).

Breathing simulation (Tables 3 and Supplementary Table 2)

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Vios and Inspiration Elite maintained baseline IM by the end of the study compared to baseline. Pulmoaide experienced significant increase in IM at week 24 ($P < .0001$). There was difference among the brands. Inspiration Elite had the highest IM, significance achieved in comparison to Pulmoaide at weeks 0 and 12. Vios had higher IM than Pulmoaide at weeks 0 and 12 but at week 24 when Pulmoaide was higher than Vios.

Pulmoaide had significant increase in IM-RR at weeks 12 and 24 but the others didn't experience change. Inspiration Elite had the highest IM-RR among the brands with significance at week 0 and 12 when compared to Pulmoaide (2.9- and 2.4-fold difference respectively). Vios had higher IM-RR than Pulmoaide that was significant at week 0 and 12 (1.6-fold difference).

Discussion

This study provides flow/pressure and drug output characteristics of 3 compressor/nebulizer combinations commonly used by patients with CF and evaluates their performance over 24 week period of use typical of that population. It also shows differences in the performance among brands, which could provide data to practitioners to help them in device selection process. These data should also provide manufacturers with additional information to help them improve their products.

Baseline flow and pressure values matched manufactures' specifications except for Pari Vios which had higher MF and MP than specified. Comparison of baseline data with previously

published compressor/nebulizer characteristics was not possible because none had used combinations similar to those used in our study [16-20] In agreement with Smith et al., who studied other compressor/nebulizer combinations, we found that different compressor/nebulizer combinations have different flow/pressure relationships. [16]

Pari Vios was the only compressor/nebulizer system that had significant decline in MF/NEB, MP and P/NEB. Two units of Vios/Pari LC Plus stopped working by the end of the study. A decrease in MF and MF/NEB identified compressors that would soon fail. Practitioners need to be aware of this occurrence and have a contingency plan prepared so patients do not miss treatments due to not having a working compressor.

One could speculate that the 2 compressors that stopped working were faulty from the beginning. However, a careful review of the MP data shows that they all worked appropriately at week 0 as noted by a SD representing 1.4% of the mean. On week 6 the SD represented 24% of the mean mainly due to the contribution of the unit that will stop working before week 12. During weeks 12 and 18 the SD represented 7-8% of the mean showing that the second unit that malfunction on week 24 was performing at the same level as the other ones. In addition the progressive decline of the different units can be visualize in the online figure 1.

In contrast to Vios, flow and pressure characteristics remained stable for Pulmoaide and Inspiration Elite.

Maximal flows significantly varied across brands but nebulizer design seemed to be more important than MF to determine IM-RR. .

In agreement with Standaert et al., we found that all compressor/nebulizer combinations maintained baseline MMAD.[21] Their study was limited to 100 runs and ours was done after

operating them 1 hour twice daily, 5 days a week for 24 weeks thus providing more long term data. Inspiration Elite had the lowest MMAD compared to Pari Vios and Pulmoaide however these differences are not likely to affect intrapulmonary deposition. Aerosol remained polydisperse (GSD $\geq$ 1.22) among all the brands and the noted differences are not likely to be of clinical relevance.

Pari Vios and Inspiration Elite maintained IM-RR while Pulmoaide experienced an unexplained increase by the end of the study period. Breath enhanced nebulizers (Pari LC Plus and Sidestream Plus) had higher IM-RR than the constant output nebulizers (Viox). Our results are in agreement with those of Bauer et al. obtained using arformoterol inhalation solution. [14] We speculate that the stable IM-RR showed by the Pari Vios brand could be partially explained by the pressure fluctuations (MP) noted during the study. Another possible explanation is that the compressors will maintain a stable IM-RR while they remain operational. A third explanation for this finding could the large individual variance at each time point.

Clinicians need to be aware of the differences in IM-RR that exist among different compressor/nebulizer combinations. Although up to almost 3-fold difference could not be meaningful for albuterol, it could result in either under- or over-dosing of other drugs especially those with a narrow therapeutic index.

There are some limitations to the present study. Devices were operated total 2 hours daily without a solution which could potentially minimize the effect of such use on the compressor/nebulizer systems and their characteristics. In addition, albuterol was the only medication used for particle size and breathing simulation measurements. If other

solutions/suspensions would have been used, characteristics could have potentially differed. Another limitation is that we tested only one breathing pattern (adult). However, although we expect the IM to be lower with a pediatric breathing pattern, we do not think that the choice of breathing pattern affects the validity of the findings. Longer studies with a larger number of units are needed to either verify or refute our findings. In addition, real life studies using the devices patients use daily are necessary to complement our findings.

Implication of the findings

We found that not all compressor/nebulizer combinations can endure the use that occurs during CF care. In addition, significant differences among combinations in several outcome measures are present. Data would help health care providers to come up with recommendations of which compressor/nebulizer systems are better suited for the use that takes place in real life of CF patients. Further longitudinal studies would have more relevant clinical implications than studying the characteristics of compressor/nebulizer units at the beginning of their use.

Manufacturers need to consider implementing the ability of their compressors to withstand long term use such as it occurs in patients with CF.

Since a decrease in MF is expected to increase treatment times, patients with CF should be asked at their clinic visits whether their treatments are taking longer.

Periodic assessments of MF could also be easily implemented in clinical settings to screen for compressor units that are likely to fail.

Conclusion

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The long term use of compressor/nebulizer units under conditions similar to those of patients with CF affects their performance. Pari Vios was the most affected brand experiencing significant changes in their flow-pressure characteristics including 2 units that stopped working by the end of the study. Periodic assessment of MF could help identify compressor that will fail. IM and IM-RR remained stable throughout the study. Inspiration Elite was the brand most able to keep baseline flow-pressure characteristics and also had the smallest MMAD, highest P% <5 and IM-RR through the study.

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Figure legends

Figure 1: Experimental setup used to measure compressor flow/pressure characteristics

Figure 2: Experimental setup used to measure particle size of aerosols generated by compressor/nebulizer systems

Figure 3: Experimental setup used to measure drug output under simulated breathing conditions of different compressor/nebulizer systems

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Figure 4: Flow/pressure relationship of different compressors

Online Figure 1: Flow/pressure relationship of different compressors at each tested time point.

The black line represents the fit of the flow/pressure curve, the gray shadow around the line of fit represents the 95% confidence interval around the mean, and each color represents an individual unit.

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Table 1: Compressor Specifications provided by manufacturers

Compressor	Weight (lbs)	Dimensions L x W x H (in)	MF (L/min)	MF/NEB (L/min)	MP (PSI)
Pari Vios	3	6.5 x 6.5 x 3.75	8.5	4.5	34
Pulmoaide	7.1	10.1 x 10.5 x6.5	≥ 9	x	≥30
Inspiration Elite	3.3	7.5 x 7.5 x 4.2	8.2	x	33

x: Information not provided by the manufacturer in compressor manual.

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Table 2: Flow/Pressure measurements*

	Pari Vios Pari LC Plus					Pulmoaide 5650D Viox					Inspiration Elite SideStream Plus				
Week	**0**	**6**	**12**	**18**	**24**	**0**	**6**	**12**	**18**	**24**	**0**	**6**	**12**	**18**	**24**
n	4	4	3	3	3	4	4	4	4	4	4	4	4	4	4
MF (L/min)	9.0 ±0	8.5 ±1	8.3 ±1	7.7 ±2.3	7.7 ±2.3	11.1 ±0.3	11.5 ±0	11.3 ±0.3	11.4 ±0.3	11.4 ±0.3	11.5 ±0	11.5 ±0	11.0 ±0.7	11.5 ±0	11.5 ±0
MF/NEB (L/min)	4.5 ±0	4.5 ±0	4.5 ± 0	4.3 ±0.3	4.0 ± 0.5	6.4± 0.3	6.5 ±0	6.5 ±0	6.5 ±0	6.5 ±0	5.1 ±0.3	5.0 ±0	5.0 ±0	5.1 ±0.3	5.1 ±0.3
MP (PSI)	45.8 ±1	36.2 ±8.7	30.7 ±2.2	25.7 ±2.1	32.6 ±9.8	37.4 ±3.5	36.5 ±3.5	36.5 ±3.3	37.7 ±3.4	37.2 ±3.6	27.8 ±0.5	27.3 ±0.6	27.3 ±1.1	26.6 ±0.6	26.5 ±0.9
P/NEB (PSI)	16.7 ±1.3	±16.0 ±0.9	15.3 ±1.2	14.2 ±0.9	14.3 ±3.9	11.9 ±0.6	12.3 ±0.7	12.3 ±0.7	12.3 ±0.8	12.6 ±0.7	20.2 0.9±	19.2 ±0.8	18.8 ±0.7	19 ±0.7	18.9 ±0.6
MF/MP SLOPE	-0.23 ±0.012	-0.248 ±0.020	-0.210 ±0.182	-0.211 ±0.022	-0.259 ±0.028	-0.181 ±0.011	-0.181 ±0.013	-0.183 ±0.011	-0.191 ±0.010	-0.189 ±0.013	-0.150 ±0.011	-0.158 ±0.014	-0.162 ±0.012	-0.164 ±0.011	-0.163 ±0.014

*Results are expressed as mean ± SD

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Table 3: Particle size analysis and breathing simulation data.

	Pari Vios/ Pari LC Plus			**Pulmoaide 5650D/ Viox**			**Inspiration Elite/ SideStream Plus**		
Week	**0**	**12**	**24**	**0**	**12**	**24**	**0**	**12**	**24**
n	4	3	2	4	4	4	4	4	4
MMAD (µm)	4.7±0.2	5.5±1.1 P>.99	5.2±0.4 P>.99	4.3±0.1	5.0±0.2 **P<.0001**	4.6±0.3 P>.99	3.8±0.7	4.3±0.2 P>.99	3.1±0.3 P>.99
GSD	2.1±0.0	2.1±0.1 P>.99	1.7±0.1 **P<.0001**	1.9±0.0	1.5±0.2 **P=.0004**	1.4±0.1 **P<.0001**	1.9±0.1	1.7±0.0 **P=.0003**	2.2±0.1 P>.99
P% < 5 (%)	50.7±1.6	43.6±10.4 P>.99	48.1±5.8 P>.99	56.9±1.0	50.0±4.0 P>.99	58.4±6.2 P=.09	64.9±9.9	60.4±2.9 P>.99	70.6 ±5.2 P>.99
IM (µg)	360.9±56.3	466.1±88.3 P>.99	273.8±31.8 P=.25	200.6±43.2	253.1±30.2 P>.99	356.9±48 **P<.0001**	503.7± 89	503.7±92 P>.99	417.9±166 P>.99
IM-RR (µg)	183.3±31.5	202.2±60 P>.99	140.6±19.4 P>.99	113.8±23.6	125.8±9.3 P>.99	209.2±41.4 **P=.0001**	329±89.1	304.4±58.4 P>.99	297.5±13.3 P>.99

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P values represent adjusted significance levels of different outcome measures comparing weeks 12 and 24 to week 0, significant values are bold. MMAD = Mass median aerodynamic diameter, GSD = Geometric standard deviation, P% < 5 = Percentage of drug mass contained in particles less than 5 μm, IM = Inhaled mass, IM-RR = Inhaled mass in the respirable range.

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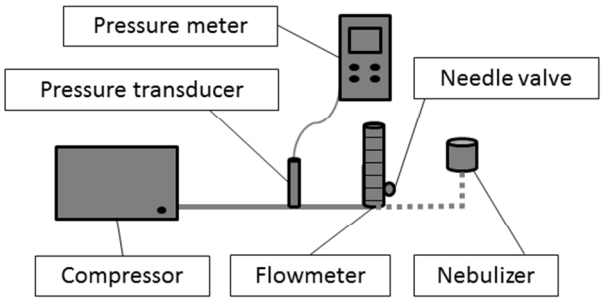

Figure 1: Experimental setup used to measure compressor flow/pressure characteristics
254x190mm (96 x 96 DPI)

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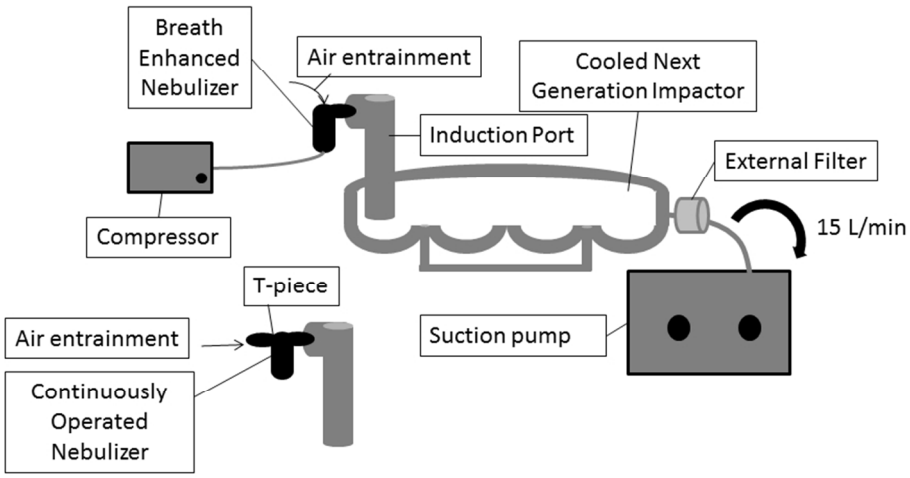

Figure 2: Experimental setup used to measure particle size of aerosols generated by compressor/nebulizer systems
254x190mm (96 x 96 DPI)

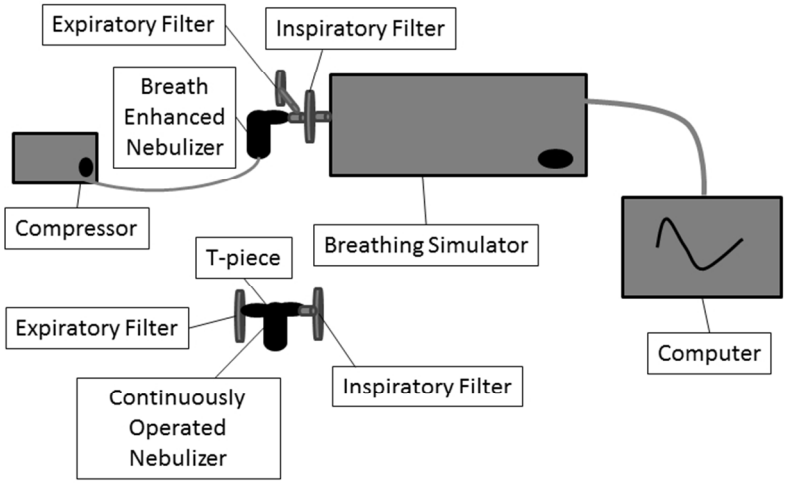

Figure 3: Experimental setup used to measure drug output under simulated breathing conditions of different compressor/nebulizer systems
254x190mm (96 x 96 DPI)

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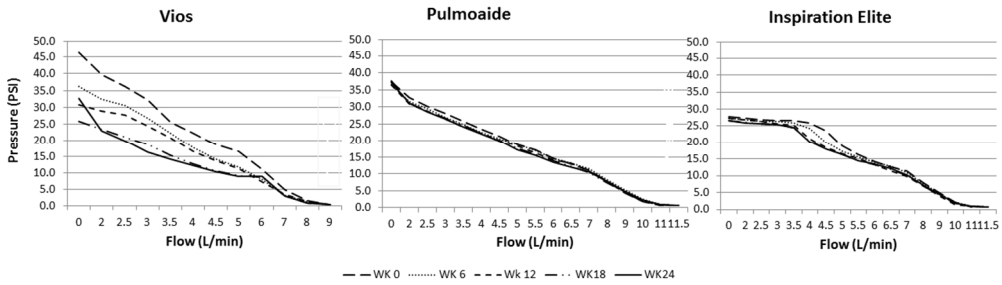

Figure 4: Flow/pressure relationship of different compressors
338x123mm (96 x 96 DPI)