Inadequate Functioning of Nebulizer System Compressors Used by Individuals With Cystic Fibrosis

Evanirso S Aquino, Alberto A Vergara, and Luiz Vicente R F Silva Filho

BACKGROUND: The treatment of cystic fibrosis involves the use of drugs delivered by nebulizer systems, and adequate functioning of the compressors and nebulizers is essential. We hypothesized that compressors of nebulizer systems used by individuals with cystic fibrosis would not work properly. Therefore, we aimed to assess the performance of the compressors from nebulizer systems used by individuals with cystic fibrosis. METHODS: This is a cross-sectional study to assess the performance of compressors from nebulizer systems used by subjects with cystic fibrosis registered at the Cystic Fibrosis Patient Association in Minas Gerais, Brazil. Compressors (Proneb Ultra II) brought by the individuals were tested with new nebulizer parts (Pari LC plus) to assess the variables of nebulization efficiency, including residual volume, solution output, and aerosol output rate. Compression performance was assessed by measuring the operating pressure using a PARI PG101 manometer. RESULTS: The performance of 146 compressors was analyzed. Fifty-seven (39%) of the compressors were ineffective, with operating pressure values well below the manufacturer's technical reference and the compressor time used for a median time of 36 (15 days to 156 months). The systems with low pressure values demonstrated significantly worse results for nebulization efficiency variables, and a significant correlation was found between residual volume (r = –0.5, *P* < .001), solution output (r = +0.5, *P* < .001), and aerosol output rate (r = +0.5, *P* < .001), and operating pressure values. CONCLUSIONS: A significant number of compressors generate low operating pressure values. These systems showed a compromised efficiency of nebulization, indicating that the pressure generated by the compressor is a critical aspect of treatment efficiency. *Key words: cystic fibrosis; jet nebulizer; compressor; nebulizer delivered volume; residual volume; aerosol therapy; nebulizer operating pressure.* [Respir Care 2021;66(5):829–836. © 2021 Daedalus Enterprises]

Introduction

Lung disease is the leading cause of morbidity and mortality in individuals with cystic fibrosis (CF).[1] The use of inhaled drugs, such as mucolytics and antibiotics, is essential for treating these individuals.[2,3] During aerosol formation, the particles remain suspended in the air due to low sedimentation velocity. The deposition occurs in different parts of the airway according to the density and particle size through different deposition mechanisms such as gravitational sedimentation and inertial impaction. This process is used in aerosol devices for clinical use, defined as heterodisperse particle size distribution, and the jet nebulizer is

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the most common system used for inhalation treatment for home use.[4]

Nebulizer-compressor systems play an important role in treating CF due to their clinical efficiency and low cost.[5,6] These systems include compressors, which generate air flow, and nebulizers, which promote the interaction between air (flow generated by the compressor) and liquid (drug solution), converting them into aerosol particles. The gas flow produced by the compressor is an important factor in generating pressure for the system to function; we therefore evaluate the pressures generated by the compressors directly related to the air flow produced by the compressors.[4,7] It is known that a flow increase from 4 L/min to 8 L/min results in a 50% decrease in the mass median aerodynamic diameter (MMAD) of the aerosol particles generated by the nebulizer. That is, the air flow produced by the compressor generates high pressure and forces this flow to pass through the narrow orifices of the nebulizers, generating an aerosol of small particles.[6] Compressors with low operating pressure may generate insufficient flow, lower nebulized flow volume, and higher MMAD.[4] Due to the large variety of inhalation devices marketed and the heterogeneity of their function, the U.S. Food and Drug Administration and consensus treatment recommendations require that inhalation drugs should be delivered only by aerosol systems approved in clinical studies.[8-11]

The inhaled mucolytic dornase alfa[12,13] was introduced in Brazil in 1995 for use by individuals with CF. Since then, those who are prescribed dornase alfa have received an inhalation system composed of a Proneb Ultra II compressor and a Pari LC PLUS nebulizer (Pari, Starnberg, Germany), according to dornase alfa package insert recommendations. Because many individuals with CF use different therapies by nebulization, other drugs are frequently used in the same equipment, despite the recommended use of different nebulizers for each inhaled medication. This attitude increases the average duration of daily use of these nebulizer compressor combination systems, which may contribute to their progressively decreased efficiency.

We hypothesized that compressors of jet nebulizer systems used by individuals with CF are dysfunctional, which could compromise aerosol formation and nebulizer efficiency by increasing the residual volume and reducing the aerosol output rate and solution output.

QUICK LOOK

Current knowledge

Drug inhalation via jet nebulizer is an essential component of cystic fibrosis (CF) treatment. The pressure generated by the compressors is a key aspect of the nebulization efficiency. Pressure reduction in the output of the compressors may affect aerosol delivery output and particle size and may increase residual nebulizer volume, compromising aerosol therapy efficiency.

What this paper contributes to our knowledge

In a real-life scenario, many compressors from jet nebulizers used by subjects with CF exhibited driving pressures well below the manufacturer's recommended reference values. Decreased driving pressures were associated with reduced aerosol delivery output and increased residual volume. Periodic assessment of driving pressure generated by compressors could identify malfunctioning devices, thereby minimizing inadequate aerosol delivery to individuals with CF.

Methods

This study is a cross-sectional descriptive study that assesses the compressors of inhalation systems used by individuals with CF who are registered at the Cystic Fibrosis Foundation of Minas Gerais. Individuals with CF and their family members were contacted and invited to bring their inhalation devices to be assessed at the outpatient clinic for inhalation therapy. Subjects who used the Proneb compressor along with the Pari LC Plus nebulizer (Pari) and made their devices available for the assessment were included in the study. Only 1 piece of equipment was included for each subject. The reference values for the pressure of the compressor were based on the manufacturer's instructions. The study was approved by the Research Ethics Committees of both institutions involved (CAAE: 15863413.3.0000.5125), and all participants signed an informed consent form.

Compressor Assessment

The pressure generated by the exit air flow from the compressor was measured using a digital manometer with atmospheric pressure compensation (Pari Test Device PG101, Pari), as shown in Figure 1. The manometer was previously calibrated with operating pressure units of 204 to 1,834 ± 12 cm H_2O.[14,15] Only the compressors were tested, connected to the socket marked "Compressor" on the PG101 test

Supplementary material related to this paper is available at http://www.rcjournal.com.

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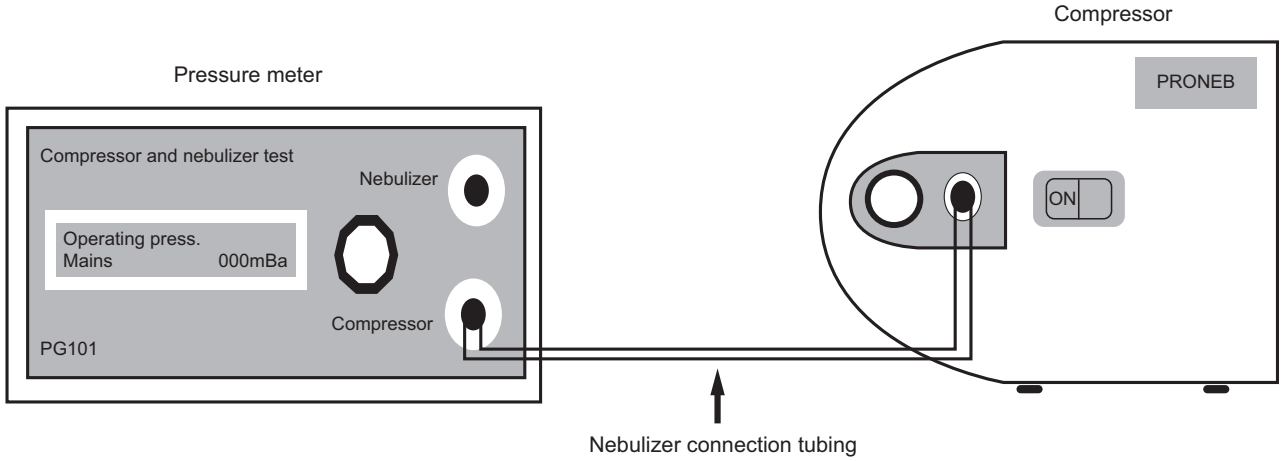

Fig. 1. Schematic setup for testing the Proneb compressor's generated pressures with the PG101 manometer.

device (Fig. 1). When the compressors were first switched on, the test device displayed the operating pressure; these operating pressures were taken via the internal reference nozzle after 10 s of stabilization.

According to the manufacturer's instructions, the compressor should be repaired when the driving pressure is < 897 cm H_2O, and the new compressors should generate a pressure range of 1,122–1,428 cm H_2O. The reproducibility of measurements was assessed by repeating measures 5 times, and the highest value was considered when the difference between measurements did not exceed 5%.

Assessment of Nebulization Efficiency

Nebulization efficiency was assessed according to the method reported by Coates.[16] Using a precision scale (BG440, Gehaka, São Paulo, Brazil), the nebulizers containing a standard volume of 2.5 mL saline solution were weighed. The nebulizers were then connected to a compressor and turned off 10 min after nebulization and were weighed again. The residual volume was determined by subtracting the weight of the device after nebulization from its dry weight. The solution output was determined by subtracting the post-nebulizing weight of the device from its pre-nebulizing weight.[16,17] After determining these parameters, the aerosol output rate was calculated based on the solution output after 10 min, using milliliters per minute (mL/min) as the unit of measure. The weight was measured in grams, and the volume was measured using a density unit of 1 g/mL. All compressors were assessed using a new air filter connected to a new nebulizer to prevent any use effects on the nebulization efficiency variables.

The predicted MMAD) of aerosol particles produced by the systems was calculated according to the equation proposed by Standaert et al[18]: Predicted MMAD $= \varphi$ (pressure)$^2 + \psi$ (pressure) $+ \omega$ (constant for calculation) correlation coefficient (r^2) 0.99. The use of this equation was only to demonstrate the impact of the compressor pressures on aerosol formation. The calculation was based on the pressures measured with the PG101 manometer in millibar and converted into pounds per square inch. The constants included were $\varphi = 0.0015$, $\psi = -0.1515$, and $\omega = 7.6557$, considering the system was composed of the Pari LC Plus nebulizer and the Proneb compressor.[18]

Assessment of Nebulizer Use and Maintenance

The study subjects and their parents or caregivers completed a standardized questionnaire addressing details of the device utilization, including the number of drugs inhaled through the same system, time used to inhale each drug, total amount of time of usage of the compressor, maintenance of the device, cleaning and disinfection methods, and whether the nebulizer and filter were changed according to the technical specifications (see the supplementary materials at http://www.rcjournal.com).

Statistical Analysis

The nebulizer systems were classified according to the manufacturer's technical reference values into 2 groups: adequate function (ie, pressure > 897 cm H_2O) and inadequate function (ie, pressure < 897 cm H_2O). In the descriptive analysis, the Shapiro-Wilk test of normality demonstrated an asymmetric distribution, so nonparametric tests were used to compare the groups. The results are expressed as median and interquartile range (IQR). The Mann-Whitney U test was used to compare groups, considering an alpha < 0.05 as significant. The Spearman coefficient was used to assess the correlations between pressure values and nebulization efficiency variables (ie, residual volume, solution output, and MMAD). To compare the effect of the pressures generated on the

Table 1. Pressure Values and Nebulization Efficiency Variables According to Nebulizer Functionality

Variables	Adequate Functioning	Inadequate Functioning	*P*
Pressure, cm H_2O	1,123 (1,031–1,184)	462 (121–716)	< .001
Solution output, mL	1.27 (1.09–1.39)	0.84 (0.16–1.14)	< .001
Residual volume, mL	0.73 (0.62–0.91)	1.16 (0.87–1.84)	< .001
Aerosol output rate, mL/min	0.12 (0.11–0.14)	0.08 (0.01–0.11)	< .001
Mass median diameter, microns	5.62 (5.53–5.75)	6.72 (6.27–7.38)	< .001

Data are presented as median (interquartile range). *P* values determined with the Mann-Whitney *U* test.

different times spent with inhalation, the Kruskal-Wallis test was used. To quantify the associations between the compressor pressures and nebulization efficiency variables, adjusted linear regression models were used. Associations were quantified using odds ratios and 95% CI.

Results

A total of 150 compressors were assessed. Four systems were excluded from the analyses due to methodological flaws of the measures. A total of 146 compressors were included (107 children and adolescents, 37 adults). The median duration of use of the compressor was 36 months, with an interquartile range of 15 d to 156 months. The subjects and their caregivers reported that the systems (ie, nebulizer cup and compressor) were being used twice a day, with a median duration of 20 min (IQR 15−25) for each nebulization, and a median interval of 12 months (IQR 5−12) for nebulizer system substitution. Only 58 of the subjects (40%) reported nebulizer replacement every 6 months according to the manufacturer's recommendations, despite being regularly instructed obtain new equipment. Thirty-five subjects (24%) reported previous filter substitution; however, they did not report the frequency or period. All subjects reported nebulizer cleaning with soap and tap water; disinfection methods included heat (boiling water) by 63 subjects (43%), alcohol by 17 (12%), hydrogen peroxide by 7 (4.9%), and bleach by 58 subjects (40%). Regarding cleaning and disinfection frequency, information was available for 142 subjects: 11 subjects (8%) once a week; 3 (2%) twice a week; 6 (4%) three times/week; 5 (4%) once a day; 19 (13%) twice a day; 3 (2%) three times a day, and 92 (65%) reported cleaning and disinfection after each inhalation. Since the subjects started their inhalation treatments, they used a median of 2 compressors (IQR 1–3).

Regarding the drugs used in the systems, 137 subjects (94%) reported using dornase alfa, 67 (46%) tobramycin, 29 (20%) colomycin, and 35 (24%) hypertonic saline solution. Seventy-two subjects (49%) reported the use of only 1 drug in the system, whereas 44 (30%), 28 (19%), and 3 (2%) reported the use of 2, 3, or 4 drugs, respectively.

Among the 146 systems assessed, 57 (39%) compressors had a pressure 51% lower (462 cm H_2O [IQR 121−716]) than the reference value; these compressors were classified as inadequate functioning. Systems with inadequate functioning had a significant decrease in nebulization efficiency, with a significant decrease in the solution output ($P < .001$) and higher residual volume ($P < .001$). The aerosol output rate had a 44% reduction in the systems with inadequate function ($P < .001$). Moreover, the predicted mass median diameter was significantly higher in the systems with inadequate function ($P < .001$) (Table 1).

The relationship between pressure measured with the PG101 manometer and nebulization efficiency was evaluated on 144 compressors (2 compressors were excluded from the analyses due to extremely low pressure values). This evaluation revealed a significant correlation with solution output, residual volume, and aerosol output rate (Fig. 2). The comparison between the pressure measured and duration of nebulization was performed by categorizing the duration into < 10 min, 11–20 min, 21–30 min, and < 31 min. The pressures observed were not significantly different among the categories of nebulization time ($P = .23$) (Fig. 3). There was a significant correlation ($r = 0.4$, $P < .001$) between the increase in nebulization time for each medication and the number of drugs used in the same system. There was no correlation between duration of use and nebulization efficiency variables (see the supplementary materials at http://www.rcjournal.com). In the multifactorial analysis, an increase of 607 cm H_2O (95% CI 515–699) in the driving pressure resulted in a 1-mL increase of the solution output ($P < .001$); a decrease of 631 cm H_2O (95% CI –722 to –539) resulted in a 1-mL increase of the residual volume ($P < .001$).

Discussion

This study demonstrated that several compressors from nebulizer systems used by subjects with CF did not function properly, which may have significantly compromised treatment efficacy. Moreover, our results indicate that the pressure generated by the compressor is a critical aspect of

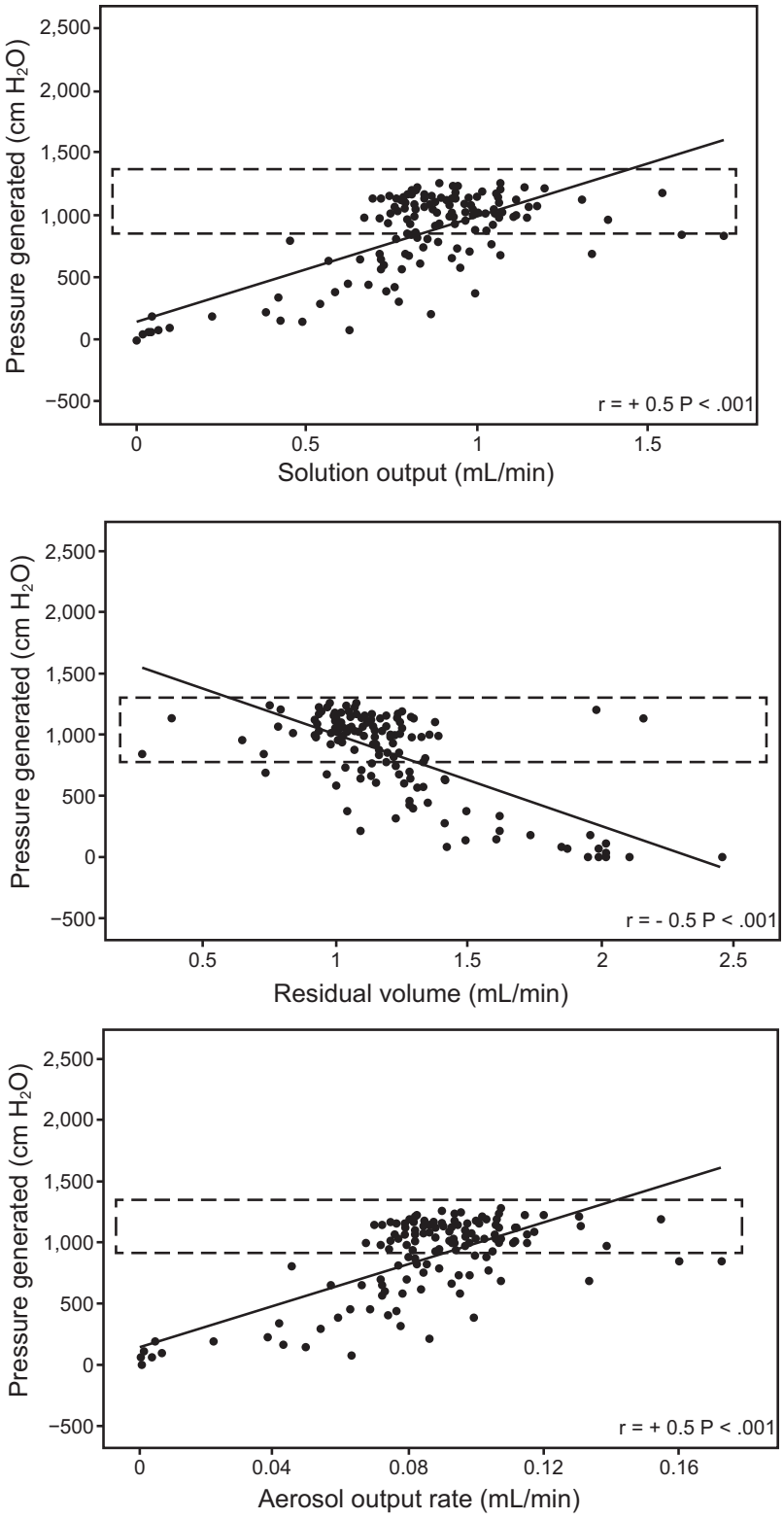

Fig. 2. Association between compressor pressures measured with the PG101 manometer, nebulizer efficiency variables, and reported duration of each nebulization (no. = 144 devices). Boxes indicate acceptable pressure range of operation.

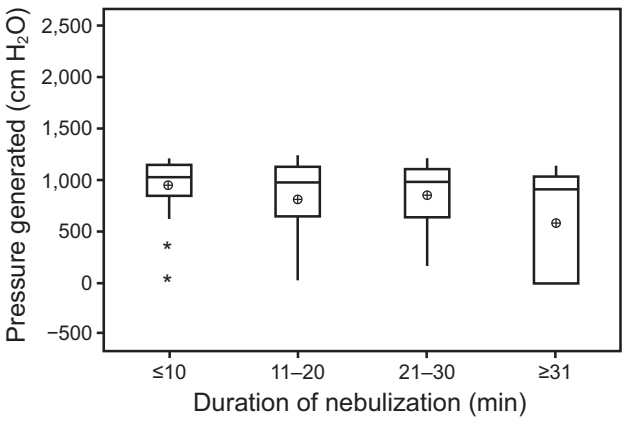

Fig. 3. Comparison between the reported duration of each nebulization and compressor pressures measured with the PG101 manometer (no. = 144 devices).

nebulization efficiency, representing an essential factor in the assessment of the nebulizer function.

Many of the compressors studied were used for a long time (median of 36 months) with > 1 drug daily, indicating intense use. While many of the systems did not work properly, there was no correlation between the duration of use and variables of nebulization efficiency. Nevertheless, a negative correlation was observed between the number of drugs used in the same system and the reported duration of each nebulization. A previous study reported reduced nebulizer performance during a 24-week follow-up, with a reduced flow at maximum pressure generated by the different systems over time.[19]

We noted a significant association between the reduced pressure generated by the compressor and the decrease in the rate of nebulization delivery. This finding is in accordance with previous studies that reported a significant increase in the efficiency of nebulization when the nominal pressure was approximately 50 psi (3.515 cm H_2O), with an impact on both nebulized delivered volume[20] and aerosol particle size.[18,21]

Nebulizer efficiency can be assessed by the ability to form respirable particles, aerosol output rate, and nebulized delivery volume.[15] In jet nebulizers, these variables depend on the pressure and flow generated by the compressor and affect the time spent on nebulization.[6] Smith et al[8] studied 23 nebulizers and compressors for home use and reported that, when both the nebulizer and compressor are functioning within acceptable ranges, treatment results in adequate particle size and desirable aerosol output rate. In our study, we found a significant association between compressor pressure and nebulization efficiency variables, suggesting that compressors that generate low pressure may compromise nebulization efficiency and possibly impact drug delivery.

Although particle size was indirectly calculated based on the measured pressures, it would be feasible to surmise that significant decreases in generated pressures could impact the quality of aerosol formation, resulting in a decrease in the number of respirable particles.[4,11] This could have negative implications for treatment success, particularly for individuals with CF. Treatment relies on the adequate drug deposition in the peripheral airways, the most compromised territory in the lungs of patients with CF.[22]

The correlation observed between the number of drugs used and the inhalation duration of each nebulization could be the result of the deterioration of nebulizer systems due to prolonged and recurrent use. However, there was no correlation between the number of drugs used and the pressure generated by the compressors. Because these data (ie, the number of drugs in use and the inhalation duration of each nebulization) stem from a questionnaire, it is possible that recall bias might have occurred; for instance, individuals using multiple drugs may have reported longer durations than those actually experienced. The manufacturer's instructions for the Proneb compressor include a 5-y warranty; however, the manufacturer does not specify how many times it could be used daily or how many drugs could be delivered through the same system. In Brazil, the leading system used for inhalation therapy by individuals with CF was the Proneb/Pari, due to its technical specifications and recommendation for dornase inhalation.[13] This situation might have caused excessive use of these devices, resulting in an increased frequency of malfunction. Because there are no established guidelines or recommendations for periodic revision and maintenance of these devices in Brazil, this may happen in other regions of the country as well.

The care of nebulizer systems, including cleaning and disinfection, should be a major component of treating individuals with CF.[23] The heat method used for disinfection, which was the most common method reported by the subjects in this study, may lead to deficient nebulizer performance, affecting the inhalation time, aerosol formation, and nebulized volume output.[24] While this aspect was not evaluated in this study (ie, all the tests were carried out with new nebulizers), it could represent a potential superimposed problem. We believe that, if we had evaluated subjects' nebulizer cups, our results likely would be even worse, adding to the risk of inadequate aerosol delivery. Many subjects reported the use of hypochlorite solution (bleach) for disinfection, which is no longer recommended for nebulizers by the North American Cystic Fibrosis Foundation.[23,25]

This study has several limitations. The temperature and relative humidity of the air were not assessed or controlled during the tests, which could affect gravimetric measurements[26] that were conducted to determine nebulization efficiency. A previous study has shown that an increase in the relative humidity of the air increases the MMAD of aerosol particles, decreasing the percentage of inhaled particles.[27] However, this same study also reported that air humidity did not affect the residual volume of the nebulizer,[27]

indicating that our main results of nebulization efficiency are probably reliable. Another limitation is that the use of the gravimetric method to determine the aerosol output rate does not adequately quantify drug delivery due to the reconcentration of the medication on the nebulizer cup. Despite the limitations of the gravimetric method, the observed reductions in pressure values at ranges $> 50\%$ support the hypothesis of compromised aerosol delivery. Another weakness was the absence of clinical data regarding the included subjects, since we did not use breathing simulation to test the solution output of a breath enhanced nebulizer and particle size evaluation. This research was conducted on an outpatient basis, there was no access to clinical follow-up data. Additionally, the use of a questionnaire could result in memory bias and a lack of accuracy of some variables, such as duration of use of the nebulizer systems. Furthermore, the use of new nebulizers to perform efficiency tests could result in overestimation of nebulization efficiency, given that several nebulizers brought by the subjects were in poor condition due to their prolonged use.

There are several nebulizer systems on the market, and the selection of a system should take into account the mechanism of aerosol generation, flow, breathing pattern, and drug formulation that will be used.[16,17] Because the treatment burden related to nebulization therapies is significant,[19] faster nebulizers such as vibrating mesh systems represent an excellent alternative. However, they are still not validated in clinical trials for many CF medications. Any inhalation device used regularly requires periodic maintenance, replacing some parts according to the recommendations of the manufacturer.[28] The standardized assessment of the compressors of nebulizer systems used by individuals with CF reported here showed a high proportion of inadequate functioning. Because many inhaled drugs routinely used in treating individuals with CF are costly, a strong recommendation is necessary to provide individuals with CF with high-quality, effective, and fully operational nebulizer systems. We therefore recommend routine measurement of compressor-generated pressures during scheduled visits to the CF clinic.

Conclusions

The majority of the compressors of nebulizer systems used for inhalation therapy by individuals with CF were not working properly. The pressure generated by the compressor seems to be a critical feature in system function and likely affects drug delivery to the patient, with significant clinical consequences.

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