Comparison of Breath-Enhanced to Breath-Actuated Nebulizers for Rate, Consistency, and Efficiency*

Kitty Leung, BSc; Emily Louca, BSc, RRT; and Allan L. Coates, B Eng(Elect), MDCM

Objectives: To evaluate differences between three new-generation nebulizers—Pari LC Star (Pari Respiratory Equipment; Mississauga, ON, Canada), AeroEclipse (Trudell Medical International, London, ON, Canada), and Halolite (Medic-Aid Limited, West Sussex, UK)—in terms of rate and amount of expected deposition as well as the consistency of the doses delivered.

Methods: The in vitro performance characteristics were determined and then coupled to the respiratory pattern of seven patients with cystic fibrosis (age range, 4 to 18 years) in order to calculate expected deposition. The Pari LC Star and AeroEclipse were characterized while being driven by the Pari ProNeb Ultra compressor (Pari Respiratory Equipment) for home use, and by a 50-psi medical air hospital source. The Halolite has its own self-contained compressor. Algorithms for the rate of output for the inspiratory flow were developed for each device. Patient flow patterns were divided into 5-ms epochs, and the expected deposition for each epoch was calculated from the algorithms. Summed over a breath, this allowed the calculation of the estimated deposition for each patient’s particular pattern of breathing.

Results: The rate of deposition was highest for the Pari LC Star and lowest for the Halolite. Rate of deposition was independent of respiratory pattern for the Pari LC Star and AeroEclipse, but proportional to respiratory rate for the Halolite. The differences between the Pari LC Star and AeroEclipse were less when driven by the 50-psi source. The AeroEclipse had the least amount of drug wastage. As designed, the Halolite delivered a predetermined amount of drug very accurately, whereas expected deposition when run to dryness of the other two devices had significant variations.

Conclusions: To minimize treatment time, the Pari LC Star would be best. To minimize drug wastage, the AeroEclipse would be best. To accurately deliver a specific drug dose, the Halolite would be best.

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Key words: aerosols; asthma; breath-actuated nebulizers; breath-enhanced nebulizers; cystic fibrosis; pediatrics

Abbreviations: CF = cystic fibrosis; CI = confidence index; Ot = total drug output; RF = respirable fraction; UV = ultraviolet; Vr = residual volume

Jet nebulization is one of the mainstays of treatment for cystic fibrosis (CF), where it is used to deliver medications ranging from antibiotics\(^\text{1}\) to mucolytics\(^\text{2,3}\) and is also commonly used to deliver bronchodilators for the emergency department treatment of asthma.\(^\text{4}\) From previous studies,\(^\text{5–7}\)

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breath-enhanced nebulizers are more efficient than unvented nebulizers, but not all breath-enhanced nebulizers have the same efficiency, with differences in residual volume (Vr) and particle size resulting in significant differences in expected pulmonary deposition. There is a new generation of jet nebulizers that are breath actuated, producing medication only during inspiration, which makes them potentially even more efficient than the breath-enhanced devices. At present, there are little comparative data available to help the clinician choose between devices for specific applications.

All jet nebulizers have a nebulizing chamber containing liquid medication and a high-pressure, high-velocity jet of gas that creates a partial vacuum at the exit orifice of the jet, resulting in the medication being drawn up toward the high-velocity orifice, where shear forces fragment the liquid into a polydisperse aerosol. The aerosol passes around a series of baffles, where larger particles are removed by inertial impaction and fall back into the reservoir for nebulization. Particles that escape the baffles either leave the nebulizer, or “rain out” and fall back into the medication chamber under the influence of gravity. Simplistically, the major difference between unvented and breath-enhanced nebulizers is that the patient’s inspiratory flow is entrained into the device, and particles that would otherwise rain out are swept along into the patient during inspiration. Hence, the rate of output of breath-enhanced nebulizers increases with increasing inspiratory flow and falls back to baseline during expiration when no flow is entrained. Furthermore, since inertial impaction of droplets on the baffles is in part dependent on velocity of the particle, increases in entrained flow increases the likelihood that larger particles will impact on the baffles. This may give rise to a smaller particle size distribution during inspiration as the inspiratory flow increases. Particles between 1 μm and 5 μm in diameter are ideal for pulmonary drug delivery, in that they are small enough so as not to be removed by inertial impaction at the posterior pharynx, but large enough to carry a significant amount of drug. Given that particle volume is proportional to the third power of the radius, particles < 1 μm carry little drug. The fraction of the volume of the nebulizer output carried in particles with a diameter ≤ 5 μm is defined as the respirable fraction (RF).

In terms of the appropriate choice of device, a number of factors come into play. Clearly, the ability to produce a high-density aerosol with a large RF during the inspiratory phase is the basic principle, but other factors such as Vr at end nebulization are an issue, especially if the medication is very expensive. Since one of the challenges in the treatment of CF is patient adherence to recommended treatment regimens, devices that reduce treatment time would be expected to offer advantages to the already very time-consuming daily multifaceted treatment activities of these patients. The devices should therefore be evaluated on the expected pulmonary deposition of a specific dose, and the delivery time required. The breath-enhanced nebulizer, the Pari LC Star (Pari Respiratory Equipment; Mississauga, ON, Canada) [Fig 1], has been shown to be one of the more efficient breath-enhanced nebulizers. Breath-actuated nebulizers, such as the AeroEclipse (Trudell Medical International, London, ON, Canada) [Fig 2] and Halolite (Medic-Aid Limited, West Sussex, UK) [Fig 3] have recently been developed. The Halolite uses an adaptive aerosol delivery system that can adapt the drug delivery to each patient’s breathing pattern. Table 1 provides a functional comparison of all three devices.

The purpose of this study was to compare the three devices in terms of in vitro performance, expected in vivo rate of deposition, and in vitro efficiency using the respiratory pattern of patients with CF breathing through a nebulizer. Significant end points are considered to be the percentage of the initial dose that would be delivered to the lungs, the time required to deliver a “target” dose, and the ability to deliver a precise pulmonary dose. It is recognized that the importance of these variables depends on the expense of the drug being delivered, the value in terms of possible greater adherence to recommended therapy from rapid delivery, and the therapeutic safety profile of the drug in terms of accurately delivering a specific amount.

**Methods and Materials**

*Device Operation*

The nebulizers and compressors used in this study were the Pari LC Star nebulizer driven by the Pari Proneb Ultra compres-
sor (Pari Respiratory Equipment); the AeroEclipse nebulizer, which was also driven by the Pari compressor, as no specific compressor was recommended; and the Halolite nebulizer with a built-in compressor. The Halolite is a microprocessor-controlled device that activates the compressor on each inspiration. Three examples of both the Pari LC Star and the AeroEclipse were studied, but only a single Halolite device was available. The test drug was 2.5 mg (0.5 mL) of albuterol (Ventolin Respirator Solution; GlaxoSmithKline; Mississauga, ON, Canada) diluted with 3.5 mL of saline solution. This was chosen because it lends itself to ultraviolet (UV) spectrophotometry for quantification of output.8 The Pari LC Star and the AeroEclipse were also evaluated using compressed dry air (hospital air, 50-psi source) at 8 L/min, which is the same flow recommended by the manufacturer for the AeroEclipse. Flow from the compressor was measured by a flow calibration instrument (Timeter RT200; Allied Health Care Products, St. Louis, MO), and the flowmeters on the hospital air line were calibrated to adjust for “back pressure.”12 so as to deliver the expected driving nebulizing flow. When driving either the AeroEclipse or the Pari LC Star, the output of the ProNeb Ultra compressor was 4.9 L/min.

**Particle Size Distribution and Determining Nebulizer Output**

Both the Pari LC Star and the AeroEclipse were characterized in terms of particle size distribution and rate of output during steady-state conditions. Briefly, the device was mounted to allow aerosol to pass through the laser beam of a Malvern Mastersizer X (Malvern Instruments; Worcestershire, UK), and particle size was measured using the Mie theory for transparent droplets. Care was taken to avoid vignetting.13 This method has been described in detail elsewhere.19 Measurements were made after 2 min of nebulization, which allowed the nebulizer to attain a steady-state temperature,19 after which particle size distribution and RF were calculated. In order to mimic entrained flow, air at 40% relative humidity was added at the point of the inspiratory valve in flow increments of 5 L/min up to a maximum of 35
UV spectrophotometry and water vapor pressure osmolarity due to evaporative losses were assessed initially by changes in output, the devices were reweighed. Changes in drug concentration were measured in each situation. For the AeroEclipse, the first level of entrained flow was 8 L/min because the spring-loaded valve only opens when entrained flow reaches this level. The microprocessor control of the Halolite makes conventional particle sizing difficult since the device is not designed to run continuously. This intermittent operation results in differences in temperature of the aerosol when nebulized continuously vs pulsed. The increased accuracy of 2,000 sweeps during data gathering by the Malvern Masterizer X for particle size distribution calculations in “continuous” mode offsets the limited data achieved from a “pulse,” even with differences in temperature of the aerosol being particle sized. To create a continuous mode, the device was dismantled and the back pressure created by the compressor when driving the Halolite handset, which contains the nebulizing device and microprocessor, was measured as 28 to 30 psi. The compressor uses an elastic reservoir that allows pressure to increase during expiration, and contributes to the compressor output during the pulse of aerosol. This resulted in a driving pressure that is considerably higher than that which would have occur if the compressor were driving the nebulizer continuously. The microprocessor within the Halolite handset was dismantled, and the nebulizer was driven by a dry air gas source at a flow matching the back pressure previously measured from the Halolite compressor, which resulted in an output flow of 5.4 L/min. The mouthpiece of the handset was positioned to send a continuous stream of aerosol across the laser beam. Since there is no entrained flow, only one measurement condition was necessary.

Prior to the particle size measurements, devices were weighed empty (for the Halolite, this was only the medication chamber), filled, and reweighed using an electronic balance (BL150; Sartorius Corporation; Edgewood, NY). After 4 min of steady-state output, the devices were reweighed. Changes in drug concentration due to evaporative losses were assessed initially by changes in UV spectrophotometry and water vapor pressure osmolarity (Advanced Micro-Osmometer 3300; Advanced Instruments; Norwood, MA). Eventually, only osmolarity was used since the simpler technique gives identical results to the more complex UV spectrophotometry. The drug output over the nebulization period was calculated from the Vt and the changes in concentration, as seen in Appendix 1.

For each 4-min run under each condition of entrained flow, the total rate of output and that in the RF was calculated, and the mean taken for the three examples of both the Pari LC Star and the AeroEclipse. Polynomial curve-fitting techniques were used to create the algorithm for the rate of output—total and within the RF—over the range of entrained flow. Finally, both the Pari LC Star and the AeroEclipse were run to dryness, defined as the absence of mist for at least 10 s, to allow the calculation of the total output of the device. The details of these techniques have been described.8,10,20 Output data for the Halolite were collected by connecting it to a modified Harvard pump (Model 613; Harvard Apparatus; Holliston, MA) that delivered two half-sine waves, with an inspiratory time/total time of respiratory cycle (Ti/Tot) of 0.4, a tidal volume of 500 mL, and a respiratory rate of 20 breaths/min. These settings approximate the tidal volumes and timing of actual patient flow traces (see below). The Harvard pump was run until the Halolite sensed that the preset volume had been delivered. The output was calculated from the drug remaining in the nebulizer cup via gravimetric techniques and changes in osmolarity, which had complete agreement with UV spectrophotometry. When the output multiplied by the RF is divided by the number of breaths, the result is the expected deposition per breath.

### Table 1—A Functional Comparison of the Pari LC Star, AeroEclipse, and Halolite

<table>
<thead>
<tr>
<th>Pari LC Star</th>
<th>AeroEclipse</th>
<th>Halolite</th>
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<tr>
<td>Breath enhanced</td>
<td>Breath enhanced</td>
<td>Breath actuated</td>
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<tr>
<td>Inspiratory valve allows air to entrain into the chamber during inspiration when the flow of patient is greater than nebulizing flow</td>
<td>When entrained flow is &gt; 8 L/m, a unique spring-loaded mechanism allows the actuator piston to be pulled down onto the jet and nebulization commences Aerosol is only produced during the inspiratory phase, making it potentially very efficient</td>
<td>Aerosolization begins when the patient pushes the appropriate button (albuterol for this study) and begins breathing Halolite analyses the first three breaths of the patient to determine the breathing pattern A pulse of drug is delivered every subsequent breath only during the first 50% of inspiration No entrainment of flow on inspiration Output is constant for each pulse and independent of the inspiratory flow Valves divert ventilation around nebulizing chamber</td>
</tr>
<tr>
<td>Expiratory valve on mouthpiece prevents exhaled gases from entering the nebulizer</td>
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<td>Treatment is complete when the preset dose has been delivered</td>
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<td>Treatment complete when device sputters</td>
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L/min, and particle size distributions were measured in each situation. For the AeroEclipse, the first level of entrained flow was 8 L/min because the spring-loaded valve only opens when entrained flow reaches this level. The microprocessor control of the Halolite makes conventional particle sizing difficult since the device is not designed to run continuously. This intermittent operation results in differences in temperature of the aerosol when nebulized continuously vs pulsed. The increased accuracy of 2,000 sweeps during data gathering by the Malvern Masterizer X for particle size distribution calculations in “continuous” mode offsets the limited data achieved from a “pulse,” even with differences in temperature of the aerosol being particle sized. To create a continuous mode, the device was dismantled and the back pressure created by the compressor when driving the Halolite handset, which contains the nebulizing device and microprocessor, was measured as 28 to 30 psi. The compressor uses an elastic reservoir that allows pressure to increase during expiration, and contributes to the compressor output during the pulse of aerosol. This resulted in a driving pressure that is considerably higher than that which would have occur if the compressor were driving the nebulizer continuously. The microprocessor within the Halolite handset was dismantled, and the nebulizer was driven by a dry air gas source at a flow matching the back pressure previously measured from the Halolite compressor, which resulted in an output flow of 5.4 L/min. The mouthpiece of the handset was positioned to send a continuous stream of aerosol across the laser beam. Since there is no entrained flow, only one measurement condition was necessary.

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### Calculation of Estimated Pulmonary Deposition

From a previous study,21 digitized breath tracings of seven patients with CF (age range, 4 to 18 years) breathing through a nebulizer (Table 2) were used. Patients with FEV1 values > 60%
predicted had essentially normal patterns of breathing, although the younger ones tended to be a bit tachypneic when breathing on the nebulizer. The child with the worse lung function (FEV1 < 30% predicted) was tachypneic at rest. The respiratory waveforms were broken into 5-ms epochs and were used to calculate the expected deposition. Three breaths were chosen from a pattern that showed regular respiration, and the same three breaths were used to calculate expected deposition for each apparatus. Entrained flow was calculated by subtracting the nebulizer driving flow from the inspiratory flow. When this resulted in a negative number it was defined as zero, since the one-way inspiratory valve would be closed. The spring-loaded valve on the AeroEclipse does not open until the entrained flow reaches 8 L/min; output was considered zero until this occurred. From the algorithms of the total rate of output and that in the RF for the Pari LC Star and the AeroEclipse, the output in each 5 ms-epoch for the specific entrained flow of the epoch was calculated and summed over the entire breath. These calculations are illustrated in Appendix 2. The results are reported as the mean of three breaths for each patient. This allows the efficiency, defined as the output during inspiration in the RF divided by total output over the entire respiratory cycle, to be calculated. For the Halolite, in vivo efficiency was equal to the output in the RF during inspiration since there is no expiratory drug loss.

**Validation of Assumptions**

To test the assumption that the output of the Pari LC Star and the AeroEclipse that was determined under steady-state conditions were valid under dynamic conditions, they were connected to the Harvard pump with the settings described above and run for 3 min. Total drug output (OT) was calculated as described above. The two half waves from the Harvard pump were known mathematically and were entered as the “patient’s” breathing pattern. Using the algorithm for rate of drug output, the output over 3 min was calculated and compared to the measured output.

Device evaluation and comparison included the expected pulmonary drug deposition per breath and per minute, in vitro efficiency, overall efficiency in terms of expected deposition in relation to the initial charge in the nebulizer, and for the Halolite the accuracy of the device to deliver a preset amount of drug. The calculated output and expected pulmonary deposition of the Pari LC Star and AeroEclipse, as well as the length of time to run to dryness were compared to the Halolite. To have comparable data, the time to deliver a selected predetermined dose was calculated for each device. The predetermined dose was defined as the dose delivered by the Halolite after four button presses, which was found to be essentially equivalent to its point of dryness. The time difference between the devices for each of the seven patients was calculated. The results are expressed as means ± 95% confidence limits. Differences in patient size and device performance were explored by regression analysis.

**RESULTS**

The steady-state in vitro assessment of both the total rate of output and that in the RF for the Pari LC Star and AeroEclipse is shown in Figure 4. With increasing entrained flow, the Pari LC Star increases both the OT and that in the RF. The AeroEclipse begins producing aerosol when the entrained flow reaches 8 L/min (patient inspiratory flow is 13 L/min when the compressor driving flow is taken into consideration), and there is a slight fall off in OT with increasing entrained flow, but there is an initial small increase in the RF, indicating a smaller particle size distribution with increasing flows. Given the design, the Halolite provides a constant output of 0.0029 mg per breath when it is activated.

When the mathematically predicted output of the Pari LC Star and the AeroEclipse for the two half sinusoidal waveforms for the Harvard ventilator are compared to the actual output, there is no difference between the two (0.0089 ± 0.0001 mg per breath vs 0.0090 ± 0.0000 mg per breath, and 0.0046 ± 0.0001 mg per breath vs 0.0045 ± 0.0002 mg per breath for the Pari LC Star and the AeroEclipse, respectively [mean ± 95% confidence index (CI)].
This gives credibility to the use of the mathematical model derived from steady-state data for the prediction of drug deposition during dynamic conditions. In other words, the quadratic equations that characterize the device performance during steady-state conditions can be applied during dynamic in vivo conditions.

The rate of deposition as a function of respiratory rate (Fig 5) is greatest for the Pari LC Star; it is intermediate for the AeroEclipse, and not related to respiratory rate. In contrast, the Halolite has the lowest rate of deposition with most respiratory rates, but shows a linear increase with increasing rates until > 40 breaths/min, where the expected deposition is comparable to the other two devices. As expected, the opposite is true with tidal volume since those subjects with the greatest lung disease had the highest respiratory rates and the lowest tidal volumes. The mean rate of deposition ± 95% CI was highest for the Pari LC Star (0.093 ± 0.0084 mg/min with compressor vs 0.120 ± 0.0122 mg/min for dry air), lowest for the Halolite (0.055 ± 0.016 mg/min, compressor only), and the AeroEclipse is in between (0.075 ± 0.0064 mg/min with compressor, and 0.108 ± 0.014 mg/min for dry air). The difference between the Pari LC Star and the AeroEclipse was significant, but there was variability among the patients, resulting in overlap in the 95% CI between the AeroEclipse and the Halolite. The in vivo efficiencies of Pari LC Star and AeroEclipse range from 51 to 55% and 71 to 77%, respectively, for the older group of children. For the younger group, the in vivo efficiencies are found to be 52 to 54% and 68 to 73%. The Halolite has an RF of 80%, which is equivalent to the in vivo efficiency. For the breath-actuated devices, the in vivo efficiency was essentially the RF since no drug is lost during expiration. For the Halolite, this is constant and independent of the subject, which is not the case for the AeroEclipse since increasing entrained flow played a role by increasing the RF (Fig 4). If the devices are run to dryness or “four button presses” for the Halolite, total expected drug deposition is greatest for the AeroEclipse (1.3032 ± 0.0296 mg, compressor; 1.4719 ± 0.0204 mg, dry air), least for the Halolite (0.8400 ± 0.0000 mg), and intermediate for the Pari LC Star (0.9421 ± 0.0307 mg, compressor; 0.9719 ± 0.0395 mg, dry air) and all independent of size of the subject. There is virtually no variation (95% CIs < 0.00005 mg of the initial dose of 2.5 mg of albuterol) in the expected dose delivered by the Halolite, despite large differences in size and breathing patterns. There was no relationship between the rate of deposition and the size of the subject, either in height or in weight. The larger (taller) subjects would have received less drug on a milligram per kilogram basis than the smaller subjects. This was most pronounced for the AeroEclipse, in which the 115-cm-tall subject would have received almost three times the amount in milligrams per kilogram body weight than the subject 174 cm in height. Furthermore, dosing differences due to device performance are greatest for the smaller subjects with much less discrepancy for the larger ones. With increasing entrained flow, the output and deposition are also increased, but the rate of OT starts to level off at approximately 20 L/min for the AeroEclipse and approximately 30 L/min for the Pari LC Star.

When evaluating the devices in terms of time to deliver a dose of medication, the Halolite consistently results in an expected pulmonary deposition of 0.8400 mg with four button presses, which is therefore selected as the comparing dose. Using the compressor, the Pari LC Star is fastest with expected pulmonary delivery in 9.2 ± 0.8 min (mean ± 95% CI) with the AeroEclipse taking 2.2 ± 0.4 min longer, and the Halolite requiring 8.0 ± 4.2 min longer. The much larger CIs with the Halolite are explained by the relationship of rate of output and respiratory rate with this device, whereas the other two devices are much less dependent on the respiratory pattern of the child. When driving the devices with hospital dry compressed air, the Pari LC Star delivers the dose in 7.1 ± 0.7 min, with the Aero-Eclipse requiring 0.9 ± 0.6 min longer.

![Figure 5. Rate of deposition as a function of respiratory rate for the Pari LC Star, AeroEclipse, and Halolite.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22018/)
**Discussion**

This study demonstrates that three of the new generation of nebulizers each has particular strengths and weaknesses. In terms of rapid drug delivery, a factor that may shorten treatment time and improve adherence with recommended therapy in a disease like CF, the Pari LC Star appears to be the superior device when using a compressor. If the nebulizers are driven at 8 L/min from a compressed air source, as would be likely in a hospital setting, the rate of output for the Pari LC Star increases 29%, but 44% for the AeroEclipse, making the performance equivalent for the two devices. In terms of maximizing drug delivery, an important factor if the drug is very expensive, the AeroEclipse is the superior device. From the perspective of a drug with a narrow therapeutic safety margin, the Halolite is much more predictable for drug delivery. Regardless of device, if a specific dose based on milligrams of drug per kilogram of body weight is desired, the initial dose put into the nebulizer will have to be individualized for the size of the patient. If the drug being nebulized is an antibiotic and minimal environmental contamination is desired, neither the AeroEclipse nor the Halolite allows significant (or any) antibiotic to leave the device except that which is exhaled by the patient.

There are some potential limitations to this study. The most obvious is that in vitro data are combined with in vivo respiratory patterns to estimate, as opposed to measure, pulmonary deposition. While there is no doubt that nuclear medicine techniques would have to be considered the “gold standard,” comparison studies would mean multiple exposures to radioactive material that would not be allowed under the current regulations for ethical research in children. The comparisons are estimates, and the following issues are the potential sources of error in the calculations. The first is whether or not output data derived under steady-state conditions can be applied to the dynamic situation of regular breathing. In terms of total rate of output, the agreement between the data generated by the modified Harvard pump, which produces perfect half-sine waves, and the mathematical data using the model of the device output coupled to the mathematical expression of the sine waves suggests that steady-state data could be applied with no loss of accuracy. The second issue that is not addressed in this study is whether or not particle size distribution measured under steady-state conditions would apply to the dynamic situation. In a previous study using the Pari LC Jet nebulizer in normal adults, very close agreement was found between the RF measured by laser diffraction and the in vitro RF measured by scintigraphy. However, in children, the definition of an RF as the mass of aerosol carried in particles ≤ 5 μm could be questioned. Recalculating the data of Wildhaber et al., it would appear that in smaller children a definition of ≤ 5 μm for the RF is too large. Support for this comes from Geller and colleagues who did not find evidence that smaller children received more tobramycin per kilogram of body weight from a Pari LC Jet nebulizer. They suggested that the lower RF in the small children limited pulmonary deposition. Since no specific data exist to give a valid estimate of RF based on size, this is a potential limitation that can be acknowledged but not scientifically corrected. Finally, the breaths used in the mathematical model assume a stable breathing pattern, by both the choice of where on the ventilatory pattern that the representative breaths are chosen, and the expression of the results as a mean of the three representative breaths. Such a stable pattern is frequently not the case in children. The device that would be most affected by an irregular pattern would be the Halolite because the timing of the output pulse is based on the previous three breaths. In a situation when breathing is irregular, the intended delivery of the pulse during the first half of inspiration may be mistimed. However, as a comparative study, the performance of each nebulizer is calculated on the same three breaths from each patient, thereby minimizing physiologic variations in device performance. Another theoretical issue is that the manufacturer of the Halolite suggests that a better distribution of drug will occur if the pulse is delivered only during the first part of inspiration, as compared to throughout the inspiratory cycle for the Pari LC Star and whenever inspiratory flow is > 13 L/m in the case of the AeroEclipse. There is no specific comparative data to support or refute this claim, but a comparison between the Halolite and the Pari LC Jet, a less efficient precursor of the Pari LC Star, did not support more uniform distribution in patients with CF.

There are differences in the in vitro performance between the Pari LC Star and the AeroEclipse. As in all breath-enhanced nebulizers, the entrained flow does two things: one is the reduction of rainout, thereby increasing output during the inspiratory phase; and the other is increasing the flow around the baffles, thereby increasing inertial impaction of the large droplets and reducing the particle size distribution. For the Pari LC Star, the predominant factor is the reduction of rainout so both the OT and that in the RF increases with increasing entrained flow. In contrast, the OT of the AeroEclipse fell, although the amount in the RF increases initially and then falls (Fig 4). As a result, the Pari LC Star is more efficient at rapid drug delivery than the Aero-
Eclipse; and both, due to their breath-enhanced design, are much faster than the unvented Halolite.

In conclusion, each of the three devices tested has strengths and limitations. Both the choice of the device and the amount of drug placed in it should be made on the basis of the targeted pulmonary dose sought coupled with the desire for rapid delivery, the minimization of drug waste, and the need for precision of the pulmonary dose delivered. Hence, for prescribing medication to be given by aerosol, the initial dose, the device, and the patient must all be considered together if predictable results are to be achieved.

**APPENDIX 1**

\[ V_r = \text{Weight}_{\text{post}} - \text{Weight}_{\text{dry}} \]

\[ O_T = D_I - (V_r \times C_I) \left( \text{Osm}_{\text{post}} / \text{Osm}_{\text{PRE}} \right) \]

\[ \text{ORF} = O_T \times RF \]

\[ \text{Rate of output} = O_T / \text{time for nebulization} \]

*In vitro* efficiency =

\[ \text{ORF} \text{ inspiration} / (O_T \text{ inspiration} + O_T \text{ expiration}) \]

where \( O_T \) = total drug output (in milligrams), \( D_I \) = initial dose of drug put into nebulizer (in milligrams); \( C_I \) = initial concentration of drug solution (milligrams per milliliter); \( \text{Osm}_{\text{POST}} \) = osmolality of drug solution after nebulization (millimoles per kilogram); \( \text{Osm}_{\text{PRE}} \) = osmolality of drug solution before nebulization (millimoles per kilogram); and \( \text{ORF} \) = output of drug within the RF (in milligrams).

**APPENDIX 2**

The principles of calculating estimated deposition is matching the device output to each patient’s pattern of breathing. Device output for the Pari LC Star and the AeroEclipse was characterized by fitting a polynomial curve to the data (Fig 4) for both the rate of total output and for the RF in relation to entrained flow. Quadratic equations offer a very good fit within the range of flows observed. Figure 6 is a schematic of a patient’s respiratory flow cycle. The inspiratory flow cycle is divided into epochs of time. The entrained flow during each epoch is the difference between the patient’s inspiratory flow and the nebulizer output. The total output per epoch can be calculated using this entrained flow in the quadratic equation shown below. Since an entrained flow of 8 L/min is necessary to activate the AeroEclipse, for flows < 8 L/min, the output is defined as zero. The output in the RF for each epoch can be obtained by multiplying the rate of total output by the RF for that entrained flow. The output in the RF for each epoch summed over the inspiratory time is the estimate of lung deposition per breath (see in vivo performance below). The total output per breath is the output summed over the entire respiratory cycle. For the expiratory phase, this is a constant for the Pari LC Star and zero for the AeroEclipse. The *in vivo* efficiency is defined as the expected deposition per breath divided by the total output per breath.

\[ \text{Out(tot)}/\text{min} = a + b \cdot \text{ORF} + c \cdot \text{ORF}^2 \]

\[ \text{Out(RF)}/\text{min} = \text{Out(tot)} \times RF \]

*In vitro* Performance

Expected deposition per respiratory cycle

\[ \text{Ti} = \sum \left[ (a + b \cdot \text{ORF} + c \cdot \text{ORF}^2) \times \text{RF} \right] \times \Delta t \]

Total output per respiratory cycle

\[ \text{Ti} = \sum \left[ a + b \cdot \text{ORF} + c \cdot \text{ORF}^2 \right] \times \Delta t + a \times T_e \]

Therefore,

*in vivo* efficiency per cycle = \( \frac{\text{Expected Deposition}}{\text{Total Output}} \)

Where,

\( a, b, c \) are coefficients of the quadratic equation

\( V_N \) is the flow driving the nebulizer

\( \text{ORF} = \text{entrained flow} + \text{ORF} \)

\( \text{ORF}(t) \) is patient flow

\( T_i = \text{inspiratory time} \)

\( T_e = \text{expiratory time} \)

The total output per breath is the output summed over the entire respiratory cycle. For the expiratory phase, this is a constant for the Pari LC Star and zero for the AeroEclipse. The *in vivo* efficiency is defined as the expected deposition per breath divided by the total output per breath.

**REFERENCES**