

A New System for Understanding Nebulizer Performance

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We have developed a conceptual and mathematical model for nebulizer performance that attempts to provide a unifying theoretical framework for subsequent in vitro studies. Specifically, we have created a lexicon and a way to describe the effects of a standardized breathing pattern for evaluating small-volume jet nebulizers. This model should help researchers communicate more clearly and study planners to design experiments whose data may be more comparable and thus amenable to meta-analysis. *Key words: small-volume nebulizer, compressor, aerosol output, nebulizer efficiency, inhaled aerosol, performance index.* [Respir Care 2007;52(8):1037–1050. © 2007 Daedalus Enterprises]

Introduction

Aerosol bronchodilator therapy is one of the most common respiratory treatments in the United States, ranking among the top 2 or 3 generators of respiratory care work

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load. For example, the respiratory care department at University Hospitals of Cleveland performed about 60,000 aerosol treatments in 2005. This represented about 30% of the billable procedure volume and 15% of the work load, second only to mechanical ventilation. Many departments have similar statistics. For this reason, there has been great interest in substituting metered-dose inhalers (MDIs) for the more common pneumatically powered jet nebulizer (or small-volume nebulizer [SVN]) because of the MDI's shorter treatment time and, hence, labor savings.

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The American Association for Respiratory Care Uniform Reporting Manual suggests an average adult treatment time (including equipment setup and patient evaluation) of about 9 min for MDI versus about 15 min for SVN. Yet, despite sufficient scientific evidence of equivalent outcomes, conversion from SVN to MDI has been slow. At least some of this resistance to change may be due to the difficulty in changing physician ordering practice. Another reason may be

the training required to deliver an effective MDI treatment.^{1,2} Further, when multiple-MDI-actuation “dose to effect” protocols are implemented, MDIs may not save any time.

An alternative approach to decreasing work load while avoiding the resistance to MDIs would be to simply decrease the time required for SVN treatment. The time required to nebulize a nominal dose (ie, the dose ordered) of a common bronchodilator (such as albuterol) depends on the design of the specific brand of nebulizer used and the flow from the pneumatic gas supply. A good nebulizer can deliver a treatment in about 6 min.³ But why not make a better nebulizer and/or delivery system that could deliver an adequate dose in, say, 1 min? What factors would affect drug delivery? What are the design constraints?

The purpose of this paper is to define the factors that affect SVN performance and to develop a model that will allow characterization of performance in terms of efficiency. The model and associated terminology also provide a standardized theoretical framework for comparing performance among different SVN designs and for comparing or combining data from different studies. And finally, for new students of aerosol science and the techniques of clinical aerosol delivery for therapeutic purposes, we also believe this model will demonstrate that a host of factors other than particle size are also at play with respect to determining aerosol delivery efficiency. This model applies not only for purposes of identifying cost-saving performance, but also important clinical performance factors related to fugitive emissions (ie, wasted aerosol, conserver properties, breathing pattern effects) and lung deposition.

The Problem

Unlike intravenous or oral drug delivery, inhalation of an aerosolized drug from an SVN results in a dose entering the patient that bears little resemblance to the dose ordered by the clinician. Indeed, as little as 1% of the prescribed drug placed in the nebulizer may be deposited in the patient’s respiratory tract,⁴ although deposition in the range of 10–20% may be more common. The basic problem is that when using an SVN powered by a continuous flow of gas, the aerosolized medication may not take a direct route to the patient. Figure 1 is a schematic of an SVN delivery system, composed of the nebulizer plus other components. One of the underlying reasons for the failure of these devices to deliver the entire dose is that the gas source that generates the aerosol is unidirectional and constant, whereas the flow generated by the patient is bidirectional and variable. Thus, a reservoir is necessary to reconcile the moment-to-moment difference between output aerosol flow and patient inspiratory and expiratory flow. The other major reason for failure to deliver the entire drug is the residual drug left in the device after nebulization has ceased. This may account for more than 60% of the drug loss.

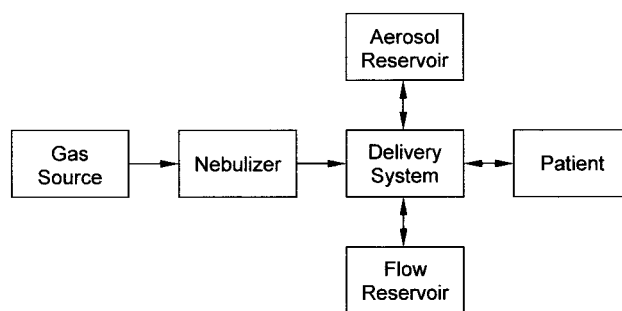


Fig. 1. Schematic of a typical nebulizer system. The gas source powers the nebulizer. The nebulizer is attached to some type of delivery system, if only a mouthpiece. The nebulizer and delivery system act as the reservoir for the generated aerosol, and there may be additional volume devoted especially to aerosol storage (eg, a reservoir bag or piece of reservoir tubing). The delivery system is also in communication with a reservoir for flow to accommodate the patient’s inspiratory flow when it exceeds the source gas flow. The flow reservoir may be a part of the delivery system (eg, a reservoir bag) or may simply be a communication to the atmosphere, which functions as a virtually infinite flow reservoir.

In this paper we will refer to the physical reservoir as a “conserving device” or “conserver.” The reservoir may be simply the atmosphere, as in the case of a nebulizer connected to a mouthpiece only. Though this satisfies the need to accommodate the patient’s flow demand, it wastes aerosol both during inspiration (if inspiratory flow is less than output aerosol flow) and during expiration (output aerosol is simply exhausted to the atmosphere along with the exhaled breath). A variety of strategies can be used to improve the drug delivery performance of the reservoir. The most common approach is to simply affix a small piece of flexible tubing to the nebulizer T piece, thereby lengthening and enlarging the reservoir, so as to retain a greater amount of the exhaled aerosol and make it available for the following inspiration (Fig. 2). The limitation of this approach is that the reservoir tubing contributes to the ventilatory dead space, so the volume and efficiency of reservoir tubing as a conserving device are limited by the patient’s ability to exhale carbon dioxide.

A slightly more sophisticated approach is to use valves to separate inspiratory from expiratory flow. This arrangement effectively separates the reservoir into 2 compartments, the flow reservoir and the aerosol reservoir (see Fig. 1). One example of this “vented” or “breath enhanced” design is the Pari LC Plus nebulizer, which has valves but no reservoir other than the nebulizer itself. With this type of device, the atmosphere is the flow reservoir and the enlarged volume of the nebulizer is the aerosol reservoir. Another example is the Healthline Medicator, which has a valve and an elastic reservoir bag. With this device the physical reservoir (bag) is both the aerosol and flow reservoir. Finally, it is possible to eliminate the need for a

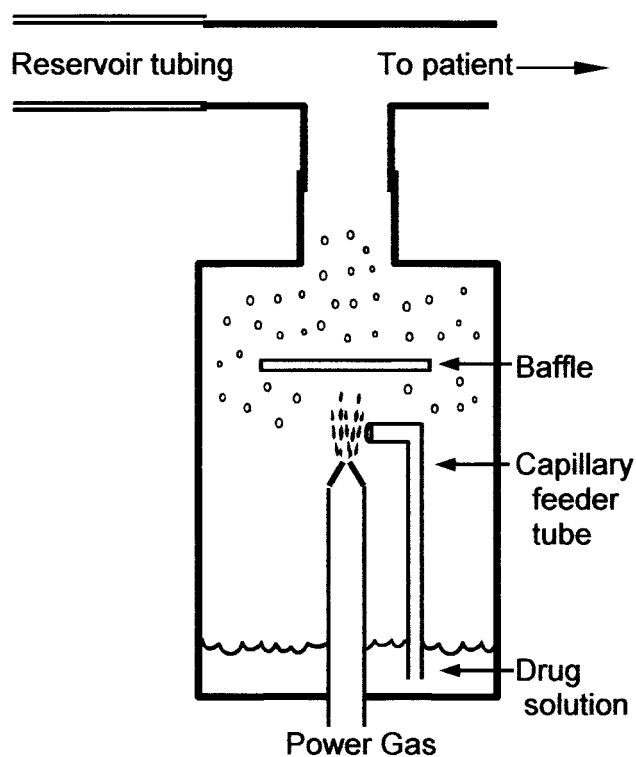


Fig. 2. Schematic of a small-volume jet nebulizer, with T-piece and reservoir tubing.

separate aerosol reservoir with a breath-actuated, or “dosimetric” nebulizer that generates aerosol only during the patient’s inspiration (eg, the Monaghan AeroEclipse). In this case the nebulization chamber itself acts as the aerosol reservoir, storing a small amount of aerosol during exhalation. These design principles have been extensively described by Rau.⁵ It is important to remember that, no matter what design approach is used, drug delivery can still be affected by the patient’s breathing pattern. Even a perfect conserving device will deliver only as much aerosol as the patient can inhale with a given breathing pattern. And even if the patient inhales all the available aerosol, the deposition and distribution within the lungs is still subject to various factors (which are beyond the scope of this article).

A Conceptual Model of Nebulizer Performance

With the common SVN, failure of drug delivery can occur at several stages. These stages of drug delivery form the basis of the conceptual and mathematical models of nebulizer performance presented here. They also provide a convenient rationale for defining various terms used to describe nebulizer performance (Fig. 3). Thus, an added benefit of the model developed in this paper is a practical, defined, and systematic lexicon that can be the basis of further discussion, refinement, and, hopefully, consensus.

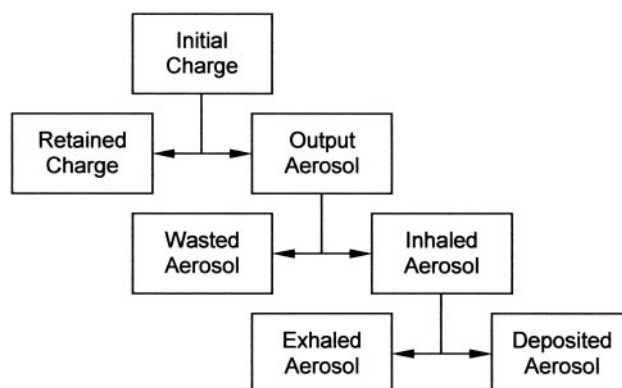


Fig. 3. Basic terms that describe nebulizer performance based on the various stages of drug delivery.

Note that in the following definitions, the units of measurement may be static quantities (eg, volume or mass), rates (eg, mass or volume per unit of time), or percentages, as appropriate. Generally, the mass of drug nebulized is of more interest when talking about delivered dose, whereas the gaseous volume and flow of aerosol is of more interest when examining the effects of breathing pattern on dose delivery and nebulization time. The liquid volume of drug solution nebulized is of interest in assessing the retained volume. It is important to maintain consistent units when using these quantities in equations.

Primary Variables

Input Flow (IF). The input flow is the flow of gas (usually air or oxygen) used to power the jet nebulizer (ie, to create the aerosol). The input flow may or may not equal the *output flow* (see below), depending on whether there is deliberate air entrainment (such as with a breath-enhanced device). The input flow is basically an operational setting and does not enter into the mathematical model as a variable. However, it does influence other aspects of jet nebulizer performance. Aerosol droplet size and nebulization time are inversely proportional to gas flow through the jet. The higher the flow, the smaller the particle size and the shorter the nebulization time.⁴ Also, the density of the input gas affects aerosol generation and lung deposition. For example, for a given jet nebulizer, use of helium-oxygen mixture (heliox) requires a 300% increase in input flow to produce a mass of aerosol per minute comparable to that produced if air or oxygen is used to create the aerosol, although heliox increases the amount of aerosol deposited in the lungs.⁶

Output Flow (OF). The output flow is the flow of gas leaving the jet nebulizer. The output flow is also the carrier gas for transporting the aerosol out of the device. For a given nebulizer design, the output flow is the primary determinant of aerosol output by the nebulizer.⁷ If the

output flow is more than the patient's inspiratory flow, excess aerosol will be vented to the atmosphere and/or sent to the reservoir apparatus. If the output flow is less than the patient's inspiratory flow, additional flow will be entrained from the atmosphere and/or the reservoir apparatus. Thus, output flow is a major factor in the determination of the breathing pattern efficiency (ie, the inhaled aerosol as a percentage of output aerosol).

Initial Charge (IC). The amount of drug initially placed in the nebulizer is called the initial charge. It may be expressed as either a drug mass, a total volume (ie, drug plus diluent), or a drug concentration, depending on the purpose. The initial drug mass has also been referred to as the "nominal dose," which is the amount of drug that defines one of the necessary components of a legal drug prescription by an ordering physician (ie, drug, *drug amount (mass)*, frequency, and route).

Retained Charge (RC). After operating for a period of time, the typical nebulizer ceases to produce aerosol, even though some solution remains on the nebulizer's inner walls, baffles, and at the bottom of the solution cup. The total amount of liquid remaining in the nebulizer has been called the "dead volume"⁵ or "residual volume."⁸ However, nebulizer performance is affected by the breathing pattern (which we will discuss below), so, to avoid confusion with the terms "dead space volume" and "residual volume" associated with the respiratory system, the liquid left in the nebulizer after nebulization has ceased will be referred to as the *retained charge*, expressed as either volume or mass, depending on the context. Retained *volume* is difficult to measure directly, because it cannot all be collected in a measuring device. Retained *mass* can, however, be closely estimated with drug assay techniques³ or radioactive tracers.^{9,10} The retained volume of SVN's is reported to be 0.5–2.2 mL (41–66%).¹¹ The greater the retained charge, the less efficient the nebulizer. It also follows that the greater the initial charge volume, the more efficient the nebulizer, other factors being equal, because the retained volume, as a fraction of the initial charge volume, decreases proportionally.

The point at which nebulization ceases is debatable. "Sputtering" is when aerosolization becomes visually and audibly erratic.⁵ Complete cessation of aerosol generation typically follows sputtering within a few seconds to a few minutes, depending on the nebulizer brand. Hess has suggested that, based on the literature, aerosolization past the point of initial sputtering is ineffective and should indicate the end of treatment.⁴

Output Aerosol (OA). The output aerosol is the difference between the initial charge and the retained charge. Output can be measured directly with the "standing cloud" technique,¹² or by calculating the difference between starting and ending mass. Note that the latter method may overestimate nebulized drug mass if there is substantial

reconcentration of drug with the nebulizer during the nebulization time.^{13–17} Reconcentration may occur if nebulization time is long enough and the carrier gas is dry enough for a substantial amount of the liquid solvent to evaporate from the SVN chamber. Thus, some of the total mass loss during nebulization is water in the vapor phase, rather than drug, and does not contribute to inhaled drug mass.

Nebulization Time (NT). The period from the start of nebulization to the time nebulization terminates (eg, after sputtering causes a > 1-s break in aerosol output).

Output Rate (OR). The output aerosol divided by the nebulization time.

Inhaled Aerosol Rate (IAR). The inhaled aerosol divided by the nebulization time.

Wasted Aerosol (WA). The portion of the initial charge that is aerosolized but lost to the atmosphere or deposited on the device walls is called wasted aerosol. It is unlikely that any commercially available nebulizer can conserve perfectly, so there will probably always be some wasted portion. Wasted aerosol is difficult to measure directly because the measurement apparatus affects the measured value. For example, output aerosol is usually measured by collecting it on a filter. However, placing a filter in the path from the nebulizer to the atmosphere introduces a resistance that may decrease the (passive) flow in that direction and hence lead to underestimation of wasted aerosol during normal use (ie, with no filter present). Conversely, imposing expiratory resistance by placing a filter in the expiratory path of a T piece nebulizer system may increase the output aerosol measurement, as measured by filter collection. Wasted aerosol has been reported to depend on the brand of nebulizer. In a study with 9 different brands of SVN, wasted aerosol ranged from 21.7% to 36.0% (mean \pm SD 27.3 \pm 4.9%) with a T piece setup with the same simulated breathing pattern.¹⁸ In addition, wasted aerosol is also affected by the breathing pattern (see Appendix).

Inhaled Aerosol (IA). Inhaled aerosol is defined as any aerosol that enters (or would enter) the patient's airway opening. It is usually determined in vivo by measuring the drug or radioactive tracer deposited on an absolute filter placed at the airway opening. It can also be determined by having the patient inhale aerosol that contains a radioactive tracer, then the deposition is quantified via nuclear lung scanning and compared to the nebulizer charge. It may also be determined in an in vitro lung model or simulated patient, using filter capture techniques. Smaldone coined the term "inhaled mass" to represent that portion of the nebulizer charge that enters the airway or is inhaled.¹⁹ Inhaled mass and inhaled aerosol are essentially synonymous, with the latter being a more general term that does not imply any particular unit of measurement. Inhaled aerosol can be expressed as either a percent of initial charge or as actual mass (eg, mg or μ g of drug).

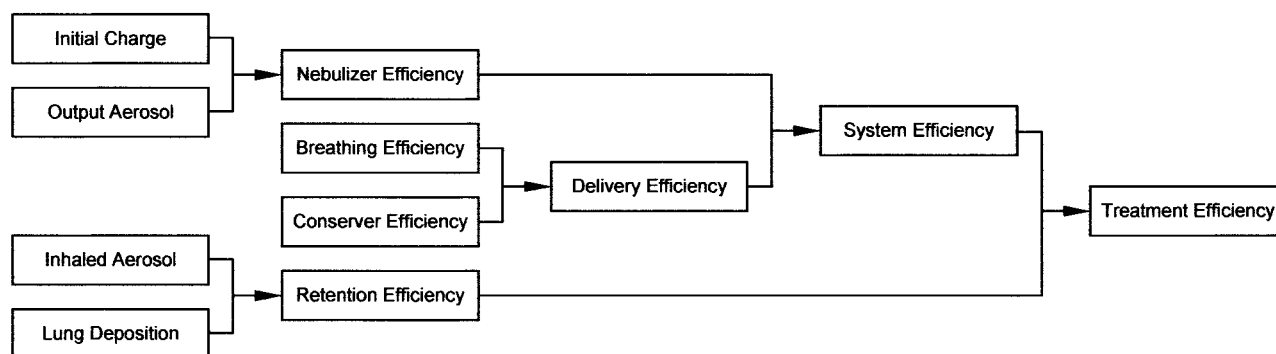


Fig. 4. Schematic of nebulizer performance efficiencies. See Table 1 for the mathematical relationships among the variables. Treatment efficiency depends on system efficiency and retention efficiency ($TE = RE \times SE$). System efficiency depends on delivery efficiency and nebulizer efficiency ($SE = DE \times NE$). Delivery efficiency depends on conserver efficiency and breathing efficiency ($DE = CE + BE$). Nebulizer efficiency is the ratio of output aerosol to initial charge ($NE = OA/IC$). Retention efficiency is the ratio of lung deposition to inhaled aerosol ($RE = LD/IA$).

Lung Deposition (LD). Lung deposition, also called deposition fraction, is the amount of aerosol that is retained in the lungs due to breathing. It can be measured *in vivo* via lung scanning with a gamma camera after the subject inhales a radiolabeled aerosol. A cascade impactor can measure the aerodynamic size distribution of the incoming aerosol, from which the “respirable mass fraction” less than a stated size is obtained. This is typically, but not always, $< 5\text{--}6 \mu\text{m}$.²⁰ The respirable mass is normally calculated from the product of the total mass (usually determined with the nebulizer attached to some form of breathing simulator) and respirable mass fraction. This is the practice recommended in the Comité Européen de Normalisation (CEN) standard for nebulizers: EN 13544: 2001.²¹ The clinical relevance of its use in mathematical and *in vitro* models has been extensively detailed by Laube.²² However, as Smaldone et al²⁰ pointed out, the concept of respirable mass is not useful for certain groups of patients, in whom the effects of age and other factors (such as disease state) that change airway geometry can have a major influence on deposition.

Exhaled Aerosol (EA). Aerosol particles between $0.1 \mu\text{m}$ and $1.0 \mu\text{m}$ are so small that a substantial portion of them that enter the lungs *in vivo* are exhaled.⁴ Exhaled aerosol is calculated as the difference between lung deposition and inhaled aerosol. Exhaled aerosol can be measured *in vivo* by placing a filter in the exhalation path,²³ but these measurements may be confounded by the presence of wasted aerosol. Accurate *in vitro* measurements are generally impossible, because a lung model on the test bench captures all the inhaled aerosol on a filter, and thus does not exhale any aerosol.

Performance Efficiency

Having specified the various quantities associated with nebulizer operation, we can now calculate the efficiency of

aerosol delivery at various stages (Fig. 4 and Table 1). The general definition of efficiency is output divided by input. The efficiency of any particular device design may be defined by what portion of the drug solution is delivered.^{7,24} Thus, efficiency at each stage of aerosol delivery, or at each part of the delivery system (eg, nebulizer or reservoir) can be expressed (in percent) as a ratio of 2 quantities.

Simple Efficiencies

In the following definitions, efficiency is mathematically defined as a fraction, but may also be expressed as a percent.

Nebulizer Efficiency (NE). Nebulizer efficiency is relatively easy to calculate, because the initial charge is known and the output aerosol is readily calculated once retained charge is measured:

$$(1) \quad NE = \frac{OA}{IC}$$

where NE is nebulizer efficiency, OA is output aerosol, and IC is initial charge in the nebulizer.

Conserver Efficiency (CE). In theory, conserver efficiency is the ratio of the incremental change in inhaled aerosol due to the conserving properties of the nebulizer to the inhaled aerosol without the conserver, using a standardized breathing pattern:

$$(2) \quad CE = \left(\frac{IA_{\text{with conserver}}}{OA} - \frac{IA_{\text{without conserver}}}{OA} \right) = \frac{\Delta IA}{OA}$$

where CE is conserver efficiency, OA is output aerosol, and IA is inhaled aerosol. In practice, CE may be evalu-

A NEW SYSTEM FOR UNDERSTANDING NEBULIZER PERFORMANCE

Table 1. Variables and Calculated Parameters for Characterizing Nebulizer Performance

Variable	Symbol	Primary Measured Variable or Equation
Output Flow	OF	Primary measured variable
Initial Charge	IC	Primary measured variable
Retained Charge	RC	Primary measured variable
Nebulization Time	NT	Primary measured variable
Inhaled Aerosol	IA	Primary measured variable
Lung Deposition	LD	Primary measured variable
Output Aerosol	OA	$OA = IC - RC$
Output Rate	OR	$OR = \frac{OA}{NT}$
Inhaled Aerosol Rate	IAR	$IAR = \frac{IA}{NT}$
Wasted Aerosol	WA	$WA = OA - IA = IC - RC - IA$
Exhaled Aerosol	EA	$EA = IA - LD$
Nebulizer Efficiency	NE	$NE = \frac{OA}{IC}$
Conserver Efficiency	CE	$CE = \frac{SE}{NE} - BE = \frac{IA}{OA} - BE = DE - BE$
Breathing Efficiency (assuming sinusoidal flow and $CE = 0$, see Appendix)	BE	$BE = \frac{IA}{OA} = \frac{f \times \left(-V_T \cos \left(\sin^{-1} \left(\frac{OF}{\pi f V_T} \right) \right) + V_T + OF \times \left(\frac{1}{2f} - \left(\frac{\sin^{-1} \left(\frac{OF}{\pi f V_T} \right)}{\pi f} \right) \right) \right)}{OF}$
Retention Efficiency	RE	$RE = \frac{LD}{IA}$
System Efficiency	SE	$SE = (CE + BE) \times NE = DE \times NE = \frac{IA}{IC}$
Delivery Efficiency	DE	$DE = \frac{SE}{NE} = \frac{IA}{IC} \times \frac{IC}{OA} = \frac{IA}{OA} = CE + BE$
Treatment Efficiency	TE	$TE = \frac{LD}{IC} = \frac{LD}{IA} \times \frac{IA}{IC} = RE \times SE$

ated by first calculating breathing efficiency and delivery efficiency and then calculating CE as the difference between the two (see Fig. 4, Table 1, and Appendix). For a breath-actuated device that can be operated in continuous-flow mode, CE can be calculated as the increase in inhaled aerosol using the triggered mode (ie, with conserver), compared to the inhaled aerosol in continuous-flow mode without conserver, as a fraction of output aerosol. A breath-actuated nebulizer is just a demand valve designed to conserve aerosol, analogous to the demand valve in an oxygen-conserving device.²⁵ The CE of an ideal breath-actuated nebulizer evaluated with a sinusoidal-flow breathing waveform would approach 50% (see Appendix). However, the efficiency of an actual device is degraded by the

aerosol lost in the dead space between the mouth and the exhalation valve. If the breath-actuated nebulizer cannot be operated in the continuous-flow mode, then conserver efficiency and breathing efficiency are undefined, and we must be content with an evaluation of delivery efficiency (ie, inhaled aerosol divided by output aerosol [see below]).

Published studies have indicated the percent increase in inhaled aerosol with various conserving devices, but no standardized breathing pattern was used, so the actual efficiency ratings of the conserving devices have not been described.^{10,26-28} A standardized procedure for determining conserver efficiency is described in the Appendix.

Breathing Efficiency (BE). Breathing pattern efficiency is a key concept in describing nebulizer performance. The

breathing pattern affects the wasted aerosol and thus the calculation of conserver efficiency (see Appendix). Conceptually, breathing efficiency may be defined with a standardized breathing pattern for a nebulizer with no aerosol conserving properties, to eliminate effects on wasted aerosol due to the interaction between breathing pattern and conserver (see Appendix). Breathing efficiency can be calculated as:

$$(3) \quad BE = \frac{IA_{\text{without conserver}}}{OA}$$

where BE is breathing efficiency, OA is output aerosol, and IA is inhaled aerosol.

Retention Efficiency (RE). Lung retention efficiency can be calculated if the amount of drug deposited in the lungs can be measured from lung scans:

$$(4) \quad RE = \frac{LD}{IA}$$

where RE is lung retention efficiency, LD is lung deposition, and IA is inhaled aerosol.

Compound Efficiencies

System Efficiency (SE).

The efficiency of the nebulizer-patient system can be expressed as:

$$(5) \quad SE = \frac{IA}{IC}$$

where SE is system efficiency, IA is inhaled aerosol, and IC is initial charge in the nebulizer. Conceptually, inhaled aerosol must be affected by both breathing pattern efficiency and conserver efficiency (see Fig. 4). Thus, the equation for SE may be expressed in a form that can be used to derive conserver efficiency (see Appendix):

$$(6) \quad SE = (CE + BE) \times NE = \left(\frac{\Delta IA_{\text{with conserver}}}{OA} + \frac{IA_{\text{without conserver}}}{OA} \right) \times \frac{OA}{IC} = \frac{IA}{IC}$$

where SE is system efficiency, CE is conserver efficiency, BE is breathing efficiency, ΔIA is the increase in inhaled aerosol due to conserver efficiency, OA is output aerosol, IC is initial charge in the nebulizer, and IA is total inhaled aerosol with conserver. That is:

$$IA = \Delta IA_{\text{with conserver}} + IA_{\text{without conserver}} = [IA_{\text{with conserver}} - IA_{\text{without conserver}}] + IA_{\text{without conserver}}$$

Delivery Efficiency (DE). If conserver efficiency cannot be evaluated independently of the breathing efficiency (because of the design of the system or when the minute ventilation is less than the nebulizer output flow), then CE and BE can be combined into a generalized transfer efficiency derived from Equation 6:

$$(7) \quad DE = \frac{SE}{NE} = \frac{IA}{IC} \times \frac{IC}{OA} = \frac{IA}{OA}$$

where DE is delivery efficiency, SE is system efficiency, NE is nebulizer efficiency, IA is inhaled aerosol, IC is initial charge, and OA is output aerosol.

Treatment Efficiency (TE).

The efficiency of the nebulizer treatment can be calculated as:

$$(8) \quad TE = \frac{LD}{IC} = \frac{LD}{IA} \times \frac{IA}{IC} = RE \times SE$$

where TE is treatment efficiency, LD is lung deposition, IC is initial charge, IA is inhaled aerosol, RE is retention efficiency and SE is system efficiency.

All of the primary measured variables and the calculated efficiencies are summarized in Table 1.

Indices of Optimum Performance

The performance variables and calculated efficiencies defined in this paper allow nebulizers to be characterized in great detail. However, when applied to real-world systems, it becomes obvious that none of them allow a clear identification of optimum performance.

Rate Efficiency Index (REI). Suppose our purpose was to identify which among the systems would be best for a large-volume purchase. We would need to have an index of performance that optimized some combination of performance factors. Intuitively, an optimum system would have the highest output and give it in the shortest time. We can therefore define a rate efficiency index as:

$$(9) \quad REI = OR \times NE$$

where REI is rate efficiency index, OR is output rate, and NE is nebulizer efficiency expressed as a decimal. High REI values are more favorable than low values.

Nebulizers differ dramatically in nebulizer efficiency and delivery efficiency. In fact, it is possible to have a nebulizer with a relatively high NE but at the same time a

Table 2. Indices for Identifying Optimum Nebulizer Performance

Variable	Symbol	Equation
Rate efficiency index	REI	REI = OR × NE or REI = OR × DE
Sound noise index	SNI	SNI = volume of compressor case × sound level
Total performance index	TPI	TPI = K × (REI/SNI)

OR = output rate (see Table 1)
 NE = nebulizer efficiency
 DE = delivery efficiency
 K is an arbitrary scaling factor used to make TPI values a convenient size

relatively low DE. Of course, it is the DE that is most important in terms of treatment effect. Therefore, whenever possible, REI should be calculated with DE instead of NE:

$$(9A) \quad REI = OR \times DE$$

Size Noise Index (SNI). The rate efficiency index may not be enough to define an optimum system, because in the home-care environment, size and noise are factors that need to be considered. A second index is thus created:

$$(10) \quad SNI = \text{volume of compressor case} \times \text{sound level}$$

where SNI is the size noise index, volume is any convenient unit (eg, cubic inches), and sound level is in decibels. Low SNI values are more favorable than high values.

Total Performance Index (TPI). Of course, we still have not identified the best system, because there is no guarantee that a high REI will correlate with a low SNI. We would like a system that provides the most aerosol in the least time, with the smallest and quietest compressor. Thus, we may create a combined index that finally will serve to identify optimum performance as follows:

$$(11) \quad TPI = K \times \frac{REI}{SNI}$$

where TPI is the total performance index, REI is the rate efficiency index (preferably calculated with DE instead of NE), SNI is the sound noise index, and K is an arbitrary scaling factor used to make TPI values a convenient size (eg, 1.5 vs 0.000015). In practice, we might value the therapeutic benefits of a system with a high REI over the benefits of a small quiet system.

These indices are listed in Table 2.

Discussion

Pneumatic jet nebulizers are inherently inefficient devices inasmuch as drug delivery is concerned. Their “performance” is subject to many variables and conditions, which have been the subject of various investigations for many years. Further confounding the issue is the fact that different nebulizers perform differently under similar conditions. The disparity in function among the many different brands and types of nebulizer, coupled with a large variety of drugs and a multitude of patient breathing patterns, provides an almost unlimited number of combinations that require us to grapple with 2 even more fundamental issues: (1) how should nebulizer performance be measured, and (2) how should nebulizer operation be described or compared?

With respect to the former, many techniques have been devised for measuring nebulizer performance, including gravimetric analysis (weigh the nebulizer before and after a specific period of nebulization), volumetric analysis (derive the amount emitted from the amount remaining after a period of nebulization), measure particle size distribution by mass (eg, cascade impaction), capture emitted drug on an absolute filter, and analyze inhaled drug via in vivo radionuclide lung scanning or infrared photospectrometry. All of these methods and their different permutations are outside the scope of this paper to critique, but they have their supporters and detractors, as well as merits and shortfalls. Consequently, little uniform agreement on a suitable performance test method has arisen. However, the Comité Européen de Normalisation has attempted to comprehensively standardize performance and in vitro testing methods for nebulizers and nebulizer systems, based on guidelines that were proposed in the United Kingdom as early as 1994.²⁹ Through the publication in 2001 by the European Respiratory Society (an organization roughly equivalent, in terms of objectives, to the American Thoracic Society) of what has come to be informally known as the European Nebulizer Standard (EN 13544:2001),²¹ a comprehensive set of guidelines now exists for measuring nebulizer output and droplet size. Though we have only briefly touched on the existence of the European Nebulizer Standard in the present paper, we refer interested readers to 2 review papers for historical details and specifics.^{30,31}

Though the guidelines embodied in EN 13544:2001 are arguably a step in the right direction, it should be noted that they do not cover all permutations of aerosol delivery device testing that can reasonably be expected to be encountered clinically, and they are not universally accepted by experts in the field, so they are still the subject of considerable controversy. To which we add that the European Nebulizer Standard does nothing to help us answer the second question posed above: how should nebulizer operation be described or compared? To the latter question

we wish to propose the model that has been defined in this paper.

Our purpose in writing this paper was to further the effort to standardize in vitro evaluation of nebulizer systems. As Dennis and Pieron pointed out:

Delivery of nebulized drug aerosols is to date still uncontrolled and poorly understood by the clinical community . . . This leaves open the choice of which nebulizer device to use . . . The decision is often left to . . . a hospital clerk who may choose a device that will become the hospital's standard nebulizer . . . usually decided on price or effective marketing material . . . Standardization of in vitro methodology should greatly help clinicians when they need to decide on the most appropriate nebulizer . . . If standardization of the in vitro assessment of aerosol output were to occur, then a commonly derived data set between all nebulizers could be more easily interpreted and the best choice made. . . . Standardization of in vitro performance measures can only serve to improve patient safety and drug efficacy. Moreover, in the long-term, standardization of in vitro performance can help provide a more solid foundation for development of better nebulizer technologies, as manufacturers can be assured that the marketplace is better prepared to recognize and appreciate the real benefits of any new technology. At the present time, if a manufacturer produced a better nebulizer, how would the clinician know? It would just get absorbed into the marketplace with yet another "best performance" nebulizer claim, with perhaps a few supporting papers written by individuals with personal bias and affiliation. It is for these reasons that standardization is required.³²

Many studies in the literature mention "nebulizer efficiency" and the effects of breathing pattern during in vitro evaluation of nebulizer performance. Unfortunately, many of the definitions and results in those studies bear little resemblance to each other because of the variety of methods used. To our knowledge, the present paper is the first to systematically define and quantify both concepts. Quantification of the breathing pattern effects and conserver efficiency is of particular importance when evaluating constant-output and breath-enhanced (vented) nebulizer systems. It may be possible to distinguish breathing pattern effects from conserver effects for some breath-actuated nebulizers if, for example, they can be operated in the continuous-flow mode.

Use of a true sinusoidal breathing pattern for in vitro nebulizer testing has several advantages. First, a sinusoidal inspiratory phase is highly similar to the customary human inspiratory flow waveform. Second, it allows quantification of predicted inhaled aerosol, based on conventional mathematical derivations. Third, it is easily reproduced in

the laboratory, with sophisticated commercially available computerized lung simulators (eg, the IngMar Medical ASL5000), or even custom-built equipment. Fourth, most published reports of actual patient breathing duty cycles are in the range of 10–50%.^{19,33,34} A sine wave (duty cycle 50%) represents a best-case scenario for predicting inhaled aerosol, because the larger the duty cycle, the more aerosol is inhaled whenever conserver efficiency is less than 100%. That is, for patient safety, it may be better to overestimate the drug delivered than to underestimate it, particularly with drugs that can be toxic at a high dose. However, we emphasize that the use of a sine wave to simulate patient breathing is primarily intended to standardize nebulizer performance comparisons, not to predict drug delivery to actual patients.

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Appendix

Conservor Efficiency

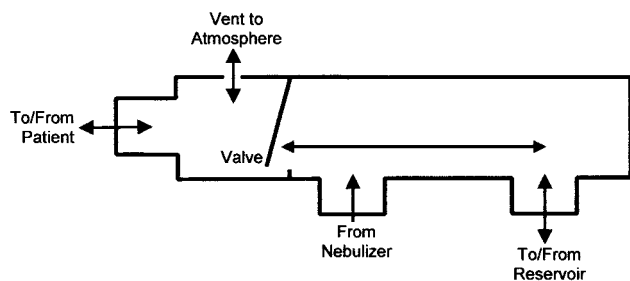
Wasted aerosol is an important concept in determining nebulizer performance. If the goal is a 1-minute nebulization time, designers would be unreasonable to simply boost output aerosol without regard to conserving expensive drug and protecting health care workers from potentially harmful exposure. Thus, conservor efficiency is a crucial performance characteristic of a nebulizer system. The following discussion applies to constant-output and breath-enhanced (vented) nebulizer systems wherein aerosol is generated continuously throughout the breathing cycle. With these systems, aerosol is vented to the atmosphere (wasted) and/or stored in a reservoir during exhalation.

Wasted aerosol is affected by the efficiency of the nebulizer’s aerosol-conserving features (if present) and the breathing pattern. If the conserving device is open (eg, a reservoir tube open to the atmosphere) the duty cycle (ie, the ratio of inspiratory time to the sum of inspiratory time plus expiratory time, usually expressed as a percent) may influence inhaled aerosol by 7-fold.¹ This makes sense because most of the aerosol wastage occurs when the patient exhales. Therefore, as the duty cycle decreases, wastage increases and conservor efficiency decreases. If the conserving device is closed to the atmosphere (eg, reservoir closed to the atmosphere, with a valve separating inspiratory from expiratory flow) then the wasted volume per breath is only the small volume of delivery tubing

filled with aerosol between the valve and the airway opening (Appendix Fig. 1).

The total wasted aerosol will depend on this volume and the number of breaths taken (assuming that breathing lasts as long as the nebulization time). Aerosol may also be wasted during inspiration. When the inspiratory flow is less than the nebulizer output flow, the excess aerosol goes into the conserving device (if present). If peak inspiratory flow never goes above the output flow (eg, with infants), the patient may never inspire aerosol from the conservor. Even if inspiratory flow rises above output flow, it must be sustained long enough to inspire the volume of aerosol stored in the conserving device, or waste may occur. Thus, to avoid any wasted aerosol, the tidal volume (V_T) must be equal to or greater than the aerosol inhaled plus the aerosol potentially stored in the conservor during both inspiration and expiration. By extension, if the breathing pattern produces a minute ventilation (\dot{V}_E) equal to or greater than the nebulizer output flow, we can be assured that all the aerosol potentially stored in the conservor will be inhaled.

Equation 6 and Figure 4 (in the main text) show that system efficiency depends on both conservor efficiency and breathing efficiency. The practical problem is finding a way to evaluate these 2 components separately. The definition of conservor efficiency suggests that one could simply measure inhaled aerosol with and without the conservor (eg, a reservoir tube or bag) and plug the difference into Equation 2 (in the main text). However, from the



Appendix Fig. 1. Schematic of the Healthline Medicator, which is an example of a conserving device that uses a valve and a reservoir to separate inspiration from expiration. Note the small dead space (rebreathed volume) between the mouthpiece and the vent to atmosphere.

discussion in the previous paragraph it is clear that the *only way to assure that the breathing pattern does not affect conserver function is to guarantee that \dot{V}_E is at least as large as the nebulizer output flow*. Thus, if we set the minute ventilation of the simulated breathing pattern equal to or greater than the nebulizer output flow, and we know the breathing efficiency, then conserver efficiency can be easily found by rearranging Equation 6 (from the main text):

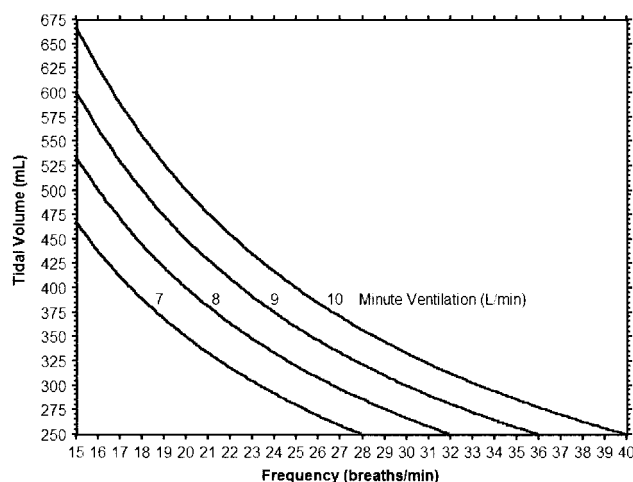
$$(1) \quad CE = \frac{SE}{NE} - BE = \frac{IA}{OA} - BE = DE - BE$$

where SE (system efficiency) and NE (nebulizer efficiency) are relatively easy to determine from the measurements of inhaled aerosol (IA), initial charge (IC), and output aerosol (OA). *Therefore, a key step in characterizing nebulizer performance is determining a way to describe a standardized breathing pattern and determine its efficiency relative to a particular nebulizer system.*

Breathing Pattern Efficiency

To date, studies of nebulizer performance with simulated breathing have often maintained a consistent breathing pattern for all nebulizers within the study, but there has been little consistency of experimental breathing patterns between studies, despite published standards. Nikander et al² pointed out that the 500-mL V_T sine-wave breathing pattern proposed by the European Standard EN13544-1³ may not be sufficient to distinguish output aerosol differences between nebulizers. Lack of a standard makes comparison of nebulizer performance between studies difficult or impossible, because we cannot tell how much of the inhaled aerosol was due to the breathing pattern versus the conserver.

The breathing pattern model can be greatly simplified by constraining it to a sinusoidal waveform, because sinusoidal waveforms are relatively easy to describe mathematically and are easily reproduced physically in the laboratory (eg, using



Appendix Fig. 2. Isopleths showing combinations of tidal volume and frequency for the same minute ventilation.

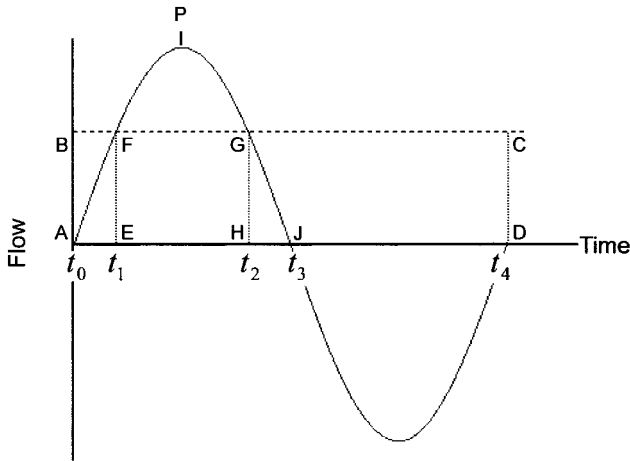
the Ingmar Medical ASL 5000 lung simulator). Modeling human breathing with sinusoidal waveforms has been a standard practice in pulmonary physiology for over 50 years.⁴ Given the variability of human breathing patterns, it would be prudent to conduct in vitro nebulizer evaluation with a simple sinusoidal-flow breathing pattern and a representative \dot{V}_E .⁵ The validity of this approach was demonstrated by Roth et al, who concluded that a sine wave breathing pattern is preferable to a square wave or an actual human waveform for simulating breathing when bench testing drug delivery from vented jet nebulizers.⁶ Another advantage of sine waves for nebulizer testing is that the inspiratory-expiratory ratio is always 1:1 (duty cycle of 50%), by definition of a sine wave, which removes a major variable in the creation of wasted aerosol. Note that we are specifying the entire respiratory cycle (ie, inspiration and expiration) as sinusoidal. This is not to be confused with other authors (eg, Nikander et al²) who describe a “sinusoidal” pattern with various duty cycles; that is, they specified just the inspiratory phase to be sinusoidal (using a Harvard pump) and presumably the passive expiratory phase was a decaying exponential flow waveform.

The derivation of breathing pattern efficiency (assuming conserver efficiency is zero) is as follows:

A. *Set the breath parameters.* Select an appropriate breathing frequency (f) and V_T such that the \dot{V}_E is equal to or greater than the nebulizer output flow. Suitable values can be obtained from Appendix Figure 2.

B. *Determine the times when inspiratory flow equals nebulizer output flow.* Determining the breathing efficiency requires calculating the inhaled aerosol, which in turn requires calculating certain areas under the inspiratory flow/time curve (Appendix Fig. 3).

In Appendix Figure 3 the inspired aerosol volume is equal to area AFGJ. This area is equal to twice the area AFE plus the area EFGH. Both of these areas can be easily calculated if we know times t_1 , t_2 , and t_3 relative to time t_0 .



Appendix Fig. 3. Comparison of theoretical sine wave breathing pattern with the constant-flow output of a small-volume nebulizer.

Because the duty cycle with a sine wave is 50%, t_3 (the inspiratory time) is simply half of t_4 (the period of the sine wave). The period of a sine wave is the reciprocal of f . Therefore,

$$(2) \quad t_3 = \frac{1}{2f} = \text{inspiratory time}$$

where f is in cycles/s, and inspiratory time is in seconds.

Time t_1 is when inspired flow (\dot{V}_1) equals nebulizer output flow (OF). We know the general expression for a sine wave (ie, $A \sin \omega t$, in which A is the amplitude of the sine wave, ω is the angular frequency in radians per second and t is time in seconds) and we know the nebulizer output. Thus,

$$(3) \quad \dot{V}_1(t_1) = \dot{V}_{\text{Imax}} \sin 2\pi f t_1 = \text{OF}$$

where \dot{V}_1 is inspiratory flow (in mL/s) as a function of time (t , in seconds), \dot{V}_{Imax} is the peak inspiratory flow (in mL/s), \sin represents the sine function (evaluated in radians rather than degrees), π is approximately 3.14, f is in cycles/s, and OF is nebulizer output flow (in mL/s).

It can be shown, using calculus, that for the first half of a sine wave, the peak value (P in Appendix Fig. 3) is $(\pi/2)$ times the average value. The average value of the first half of the sine wave in Appendix Figure 3 (ie, inspiration) is the average inspiratory flow. The average inspiratory flow is equal to the V_T divided by the inspiratory time. Thus,

$$(4) \quad \dot{V}_{\text{Imax}} = \frac{\pi}{2} \times \frac{V_T}{t_3} = \frac{\pi}{2} \times V_T \times 2f = \pi f V_T$$

where \dot{V}_{Imax} is the peak inspiratory flow (in mL/s), π is approximately 3.14, V_T is in mL, and f is in cycles/s. Note that, because of the initial constraint that $\dot{V}_E = (f \times V_T)$ be equal to or greater than OF, Appendix Equation 4 shows that peak inspiratory flow will always be greater than OF by a factor of at least π .

Substituting Appendix Equation 4 into Appendix Equation 3 yields

$$(5) \quad \dot{V}_1(t_1) = \pi f V_T \sin 2\pi f t_1 = \text{OF}$$

Solving Appendix Equation 5 for t_1 yields

$$(6) \quad t_1 = \frac{\sin^{-1}\left(\frac{\text{OF}}{\pi f V_T}\right)}{2\pi f}$$

where \sin^{-1} is the arcsine of a number, in radians, of a number in the range of $-\pi/2$ to $\pi/2$, t_1 is the time (in seconds) when inspiratory flow equals nebulizer output flow, OF is nebulizer output flow (in mL/s), π is approximately 3.14, V_T is in mL, and f is in cycles/s.

Because the sine wave is symmetrical, t_2 can easily be found by subtracting t_1 from t_3 :

$$(7) \quad t_2 = t_3 - t_1$$

Substituting Equation 3 (from the main text) and Appendix Equation 6 we get

$$(8) \quad t_2 = \frac{1}{2f} - \left[\frac{\sin^{-1}\left(\frac{\text{OF}}{\pi f V_T}\right)}{2\pi f} \right]$$

C. Calculate the inhaled aerosol. When inhaled flow is less than nebulizer output flow, inhaled aerosol volume is represented by areas AFE and HGJ in Appendix Figure 3:

$$(9) \quad \text{area AFE} = \text{area HGJ} = \int_{t_0}^{t_1} \pi f V_T \sin 2\pi f t$$

Appendix Equation 9 has the general form

$$(10) \quad \int A \sin B t dt = A \int \sin B t$$

which, by U substitution (a calculus procedure), has the general solution

$$(11) \quad -\frac{A}{B} \cos Bt + \frac{A}{B}$$

so that the solution of Appendix Equation 9 is

$$(12) \quad \text{area AFE} = \text{area HGJ} = \left(-\frac{V_T}{2} \cos 2\pi ft_1 \right) + \frac{V_T}{2}$$

Substituting Appendix Equation 6 for t_1 yields:

$$(13) \quad \text{area AFE} + \text{area HGJ} = \left(-V_T \cos \left(\sin^{-1} \left(\frac{OF}{\pi f V_T} \right) \right) \right) + V_T$$

When inhaled flow is greater than the nebulizer output flow, inhaled aerosol volume is represented by area EFGH in Appendix Figure 3:

$$(14) \quad \text{area EFGH} = OF \times (t_2 - t_1)$$

Substituting Appendix Equations 6 and 8 for t_1 and t_2 yields:

$$(15) \quad \text{area EFGH} = OF \times \left(\frac{1}{2f} - \left(\frac{\sin^{-1} \left(\frac{OF}{\pi f V_T} \right)}{\pi f} \right) \right)$$

This equation can be modified to calculate the aerosol inhaled with a breath-actuated nebulizer rather than a constant-flow or breath-enhanced (vented) nebulizer, as assumed in the analyses above. For a breath-actuated nebulizer, nebulization begins when the inspiratory flow reaches the nebulizer's trigger threshold and then proceeds at the nebulizer output flow rate. Thus, substituting trigger flow for OF in Appendix Equation 3 and carrying forward the derivations to Appendix Equation 15 we get:

(16) inhaled aerosol with breath-actuated nebulizer

$$= OF \times \left(\frac{1}{2f} - \left(\frac{\sin^{-1} \left(\frac{TF}{\pi f V_T} \right)}{\pi f} \right) \right)$$

where \sin^{-1} is the arcsine of a number, in radians, of a number in the range of $-\pi/2$ to $\pi/2$, OF is nebulizer output flow (mL/s), TF is breath-actuated trigger flow (mL/s), π is approximately 3.14, V_T is in mL, and f is in cycles/s. This equation gives the gaseous volume of aerosol inhaled per breath for a breath-actuated nebulizer only.

Total inhaled aerosol volume per breath is derived by adding Appendix Equations 13 and 15:

(17) (See equation below)

where inhaled aerosol (in mL) is the gaseous volume of aerosol inhaled during the one inspiration, V_T is in mL, \cos is the cosine function (evaluated in radians rather than degrees), OF is nebulizer output flow (in mL/s), π is approximately 3.14, and f is in cycles/s.

D. Calculate the final breathing pattern efficiency. Breathing pattern efficiency is calculated as the proportion of aerosol volume output by the nebulizer that is inhaled. We have calculated the inhaled aerosol volume for one ventilatory cycle (ie, one inspiration and expiration). Thus, we need to know the output aerosol for the same period. The gaseous output aerosol volume is simply the product of the nebulizer output flow and the ventilatory period:

$$(18) \quad OA = \frac{OF}{f}$$

where OA is output aerosol (in mL), OF is output flow (in mL/s) and f is in cycles/s.

The breathing pattern efficiency is:

(19) (See equation below)

$$(17) \quad \text{inhaled aerosol} = \left(-V_T \cos \left(\sin^{-1} \left(\frac{OF}{\pi f V_T} \right) \right) \right) + V_T + OF \times \left(\frac{1}{2f} - \left(\frac{\sin^{-1} \left(\frac{OF}{\pi f V_T} \right)}{\pi f} \right) \right)$$

$$(19) \quad BE = \frac{IA}{OA} = \frac{f \times \left(\left(-V_T \cos \left(\sin^{-1} \left(\frac{OF}{\pi f V_T} \right) \right) \right) + V_T + OF \times \left(\frac{1}{2f} - \left(\frac{\sin^{-1} \left(\frac{OF}{\pi f V_T} \right)}{\pi f} \right) \right) \right)}{OF}$$

where BE is breathing pattern efficiency, IA is inhaled aerosol, OA is aerosol output by the nebulizer, V_T is in mL, \cos is the cosine function (evaluated in radians rather than degrees), OF is nebulizer output flow (in mL/s), π is approximately 3.14, and f is in cycles/s. Note that this equation is only valid if the peak inspiratory flow is greater than the nebulizer output flow.

It is interesting to note that the breathing pattern efficiency is dependent on only 3 variables: nebulizer output flow, V_T , and f . This can be appreciated intuitively by examining Appendix Figure 3. Recall that breathing pattern efficiency is represented by the ratio of 2 areas: area AFGJ (aerosol volume inhaled) divided by area ABCD (aerosol volume output by nebulizer). We need only consider one breath cycle, because the breathing pattern is represented by a sine wave, where every cycle is identical in shape.

Appendix Equation 19 shows that for a given breathing pattern (ie, V_T and f), the breathing pattern efficiency decreases as the nebulizer output flow increases. This makes sense because, as output flow increases (ie, line BC rises), the wasted aerosol (area ABF plus area JGCD) grows faster than the inhaled aerosol (area AFGJ). That is, areas ABF and JGCD increase in size while the potential inhaled volume (area FPG) decreases in size.

Appendix Equation 19 also shows that for a given nebulizer output flow, breathing pattern efficiency decreases as V_T decreases or f increases. If V_T decreases while f is

held constant, peak flow (point P) decreases (see Appendix Equation 4), and the inhaled volume decreases (ie, line FG shortens and, thus, area AFGJ decreases). If V_T is held constant and f decreases, again peak inspiratory flow (point P) decreases with the same result: a decrease in both inhaled volume and breathing pattern efficiency. Conversely, as either V_T or f increase, peak inspiratory flow increases and efficiency increases toward the limit of 50% (ie, area AFGH approaches rectangular shape as areas AFE and HGJ approach zero while area EFGH increases toward the limit of half of area ABCD).

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