Assessing New Technologies:
Patient-Device Interactions and Deposition

Gerald C Smaldone MD PhD

As our understanding of aerosol therapy matures, advances in technology afford the potential for solving the major problems in clinical aerosol delivery: control of variability in dosing, and targeting of therapy to different regions of the lung. As "interactive" devices are developed, testing on the bench becomes more sophisticated and demanding. The present review begins with simple in vitro testing techniques and addresses their ability to predict in vivo deposition. Advances in technology are reviewed and control of delivery in vivo is demonstrated. *Key words: aerosol, bench test, cascade impactor, scintigraphy, gamma camera, face mask, drug delivery.* [Respir Care 2005; 50(9):1151–1158. © 2005 Daedalus Enterprises]

Introduction: Principles

Assessing effects of an aerosolized drug requires understanding 3 major factors: the aerosol delivery system, the quality of the aerosol produced, and the quantification of deposition within the lungs. The latter measurement is performed in vivo and is time-consuming, costly, and involves some degree of risk and uncertainty to the patient. The other components of the aerosol delivery process can be well characterized and studied in vitro. The field of aerosol delivery has substantially advanced in the last 10 years, such that device characteristics and aerosol behavior can be optimized on the bench before exposure to patients.[1,2]

The Inhaled Mass

Figure 1 depicts a simple in vitro setup for measuring the quantity of aerosol produced by a nebulizer.[3] An absolute filter that captures the aerosolized particles has replaced the mouthpiece. This system does not require an understanding of nebulizer function from first principles. Because the nebulizer is attached to a breathing device, the

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Gerald C Smaldone MD PhD presented a version of this article at the 36th RESPIRATORY CARE Journal Conference, Metered-Dose Inhalers and Dry Powder Inhalers in Aerosol Therapy, held April 29 through May 1, 2005, in Los Cabos, Mexico.

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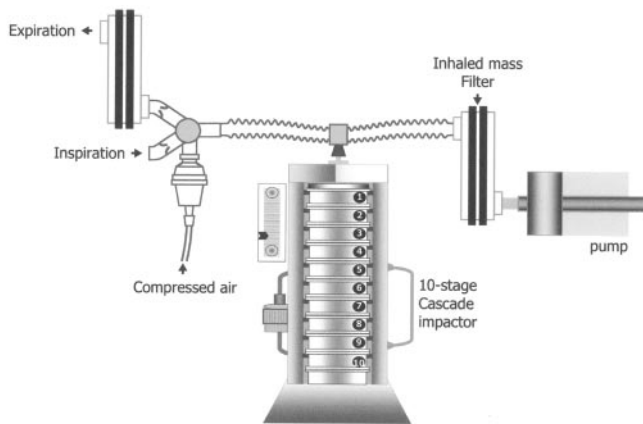
Fig. 1. Technique for bench measurements of inhaled mass and particle distribution. The breathing pattern is defined by settings on the pump. Particles presented to the "patient" are captured on the inhaled mass filter. In separate experiments, the cascade impactor measures "inspired" aerosol. (From Reference 3, with permission.)

conditions of delivery, such as routine tidal breathing, can be duplicated. The quantity of drug captured on the inspiratory filter represents the amount that passes the patient's lips. To distinguish that quantity from a "dose" or deposited drug, the term "inhaled mass" has been coined.[4] The inhaled mass represents *delivery* of drug to the patient, constrained by conditions that should mimic actual clinical delivery.

The Aerosol

A cascade impactor can be inserted into the circuit depicted in Figure 1 and can provide information regarding the aerodynamic distribution of a given aerosol (mass median aerodynamic diameter [MMAD] and geometric standard deviation). Depending on circumstances, the MMAD and geometric standard deviation can predict the behavior of particles in the lungs. Figure 2 depicts deposition images for 3 subjects following inhalation of interferon gamma aerosol generated by Misty-Neb (Allegiance, McGraw Park, Illinois) and AeroEclipse (Trudell Medical International, London, Ontario, Canada) nebulizers. All 3 patients show better lung deposition with the AeroEclipse, as evidenced by increased activity in the lung fields, and less deposition in the oropharynx (reduced stomach activity). With the Misty-Neb, lung deposition was 28–32% (mean ±
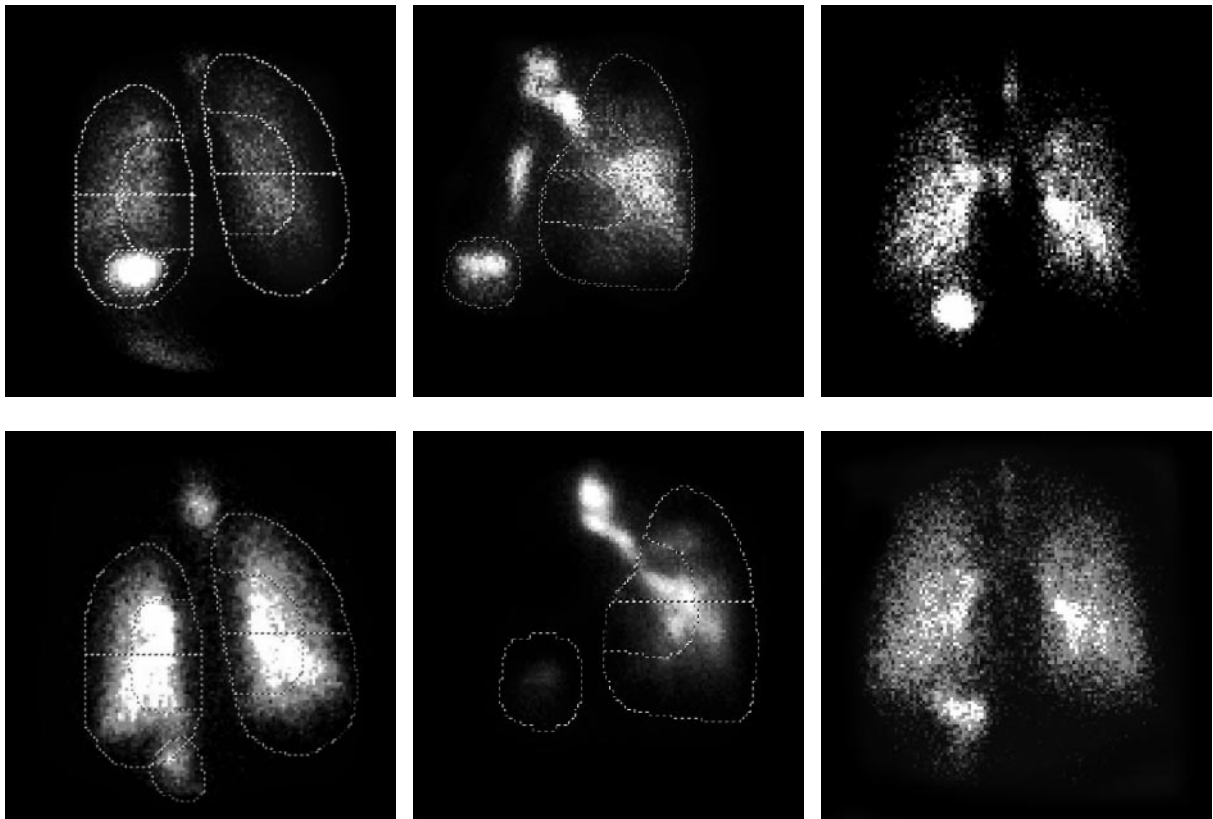

Fig. 2. Deposition scans of the lungs of 3 patients who received aerosolized interferon gamma for tuberculosis, from a Misty-Neb nebulizer (above) and from an AeroEclipse nebulizer (below). The dotted lines (^{133}Xe equilibrium scan) indicate the outlines of the lungs and stomachs of the first 2 patients. Oropharyngeal deposition is less with the AeroEclipse. (From Reference 5, with permission.)

Table 1. In Vitro Assessment of Interferon Gamma Aerosol*

Nebulizer	Misty-Neb	AeroEclipse
MMAD (μm)	3.10	2.20
Particles < 6 μm (%)	55	77
Particles < 3 μm (%)	49	73†
Particles < 2 μm (%)	30†	53

*Aerosol particle size distribution determined with cascade impaction. The values in this table are from the in vitro cascade studies.
MMAD = mass median aerodynamic diameter
†This value represents the mean lung deposition (see text) measured from deposition images in vivo for the 3 subjects.
(Adapted from Reference 5, with permission.)

SD = 30.9 ± 0.03%) of the total aerosol deposited in the patient. With AeroEclipse, lung deposition was 59–73% (mean ± SD = 68.1 ± 0.08%) of total deposition.[5] Table 1 shows the Misty-Neb and AeroEclipse distribution of particles between the oropharynx and the deep lung, plus the aerodynamic size distributions from cascade impaction measurements. By inspection, one can see that a cutoff of approximately 2.5 μm defines particles that pass the oropharynx and deposit in the lung. With the Misty-Neb, approximately 30% of the particles are ≤ 2.5 μm, and this corresponds to the lung depositions seen in the images for the 3 patients studied. With the AeroEclipse, which produces a smaller particle distribution, the 2.5-μm cutoff predicts that approximately 70% of the particles will deposit in the lung, versus the upper airways.[5] It is not the purpose of this paper to summarize the nuances of cascade

impaction in detail. Our results are a strong function of the design and control of the experimental setup. However, for certain devices, knowledge of the MMAD measured on the bench can assist in the design of appropriate aerosol delivery systems prior to in vivo testing.

Deposition

The term "deposition" begins to imply a "dose" to the patient. The term "deposition" needs to be further refined in a given situation, for example, oropharyngeal versus parenchymal deposition, or central versus peripheral deposition within the lung. Each of these terms may be important, depending upon the disease entity to be treated. Obviously, the measurement of deposition requires an in vivo experiment. However, deposition can be related to variables that are measured in vitro, as shown in the equation:

deposition = aerosol inhaled – aerosol exhaled

Because the term "aerosol" is a little vague with respect to drug activity, the equation can be rewritten as:

deposition = inhaled mass – exhaled mass

Many experiments can be performed on the bench to define the variables that define the inhaled mass for different devices and experimental conditions.[2]
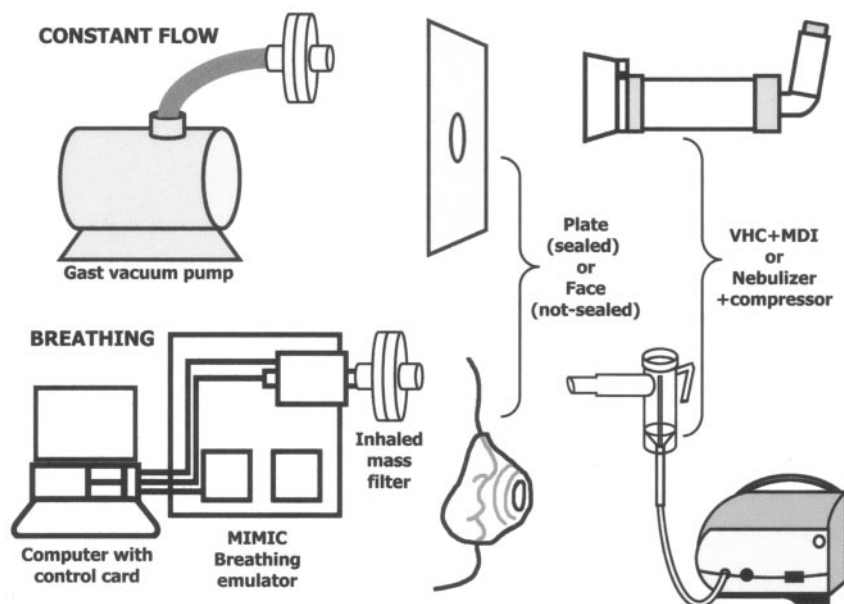

Fig. 3. In vitro setup: constant-flow experiment (upper), breathing simulator (lower). For each inhalation device (nebulizer, valved holding chamber), the connection with the flow-generating apparatus was made with a flat plate (sealed configuration) or a face (face configuration). (From Reference 6, with permission.)

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Table 2. Inhaled Mass As a Function of Breathing Pattern, Valved Holding Chamber Condition, and Presence of Face Mask

Nebulizer and Drug	V_T (mL)	Inhaled Mass (mean $\pm$ SD percent of label dose)			
		Sealed Configuration		Face Configuration	
Hudson Updraft II with budesonide	207	24.3 $\pm$ 3.06		19.3 $\pm$ 2.31	
	75	9.55 $\pm$ 0.65		4.14 $\pm$ 0.84	
Pari LC Plus with budesonide	207	18.7 $\pm$ 1.89		11.7 $\pm$ 1.09	
	75	9.95 $\pm$ 1.14		9.16 $\pm$ 1.88	
Valved Holding Chamber and Drug	V_T (mL)	Unwashed	Washed	Unwashed	Washed
pMDI with AeroChamber and fluticasone propionate	207	7.15 $\pm$ 2.00	53.3 $\pm$ 6.22	2.36 $\pm$ 0.71	13.6 $\pm$ 2.74
	75	2.90 $\pm$ 1.53	30.5 $\pm$ 3.17	3.10 $\pm$ 2.36	4.72 $\pm$ 0.73
pMDI with OptiChamber and fluticasone propionate	207	7.69 $\pm$ 1.60	50.2 $\pm$ 1.20	2.93 $\pm$ 0.34	28.6 $\pm$ 2.47
	75	0.68 $\pm$ 0.45	27.2 $\pm$ 1.40	1.01 $\pm$ 0.22	3.98 $\pm$ 1.61

pMDI = pressurized metered-dose inhaler
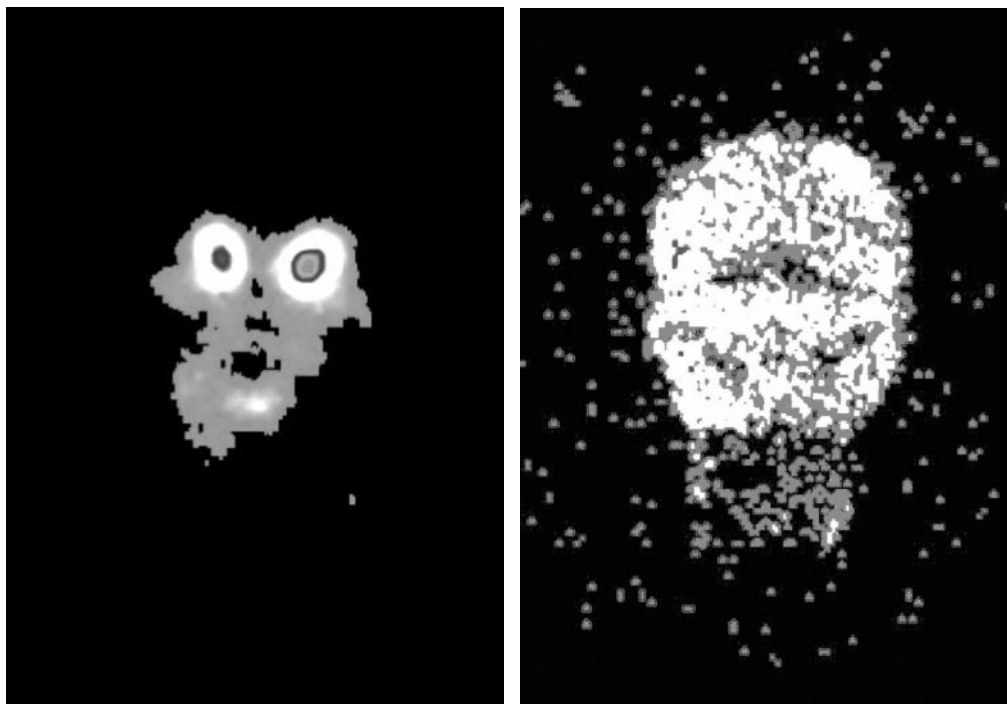(Adapted from Reference 6, with permission.)

Fig. 4. Preferential eye deposition with Laerdal and Pari LC Plus nebulizer (left) and diffuse facial pattern with Salter mask and AeroTech II nebulizer. (Adapted from Reference 7, with permission.)

Measurement of Inhaled Mass

Pediatric in Vitro Models

Figure 3 represents a more complex situation than that of Figure 1. A metered-dose inhaler (MDI) and a valved holding chamber are connected in series. For many patients the valved holding chamber is used with a mouthpiece, but younger patients require a face mask. Reported studies to date place the inhaled-mass filter on the valved holding chamber and capture particles using a suction device or a breathing machine (see Fig. 3). However, the principles illustrated above require the inhaled-mass filter to mimic particles that actually pass the lips. To complete the in vitro model, therefore, the face mask must be placed on a face. Finally, the face must "breathe" with a breathing
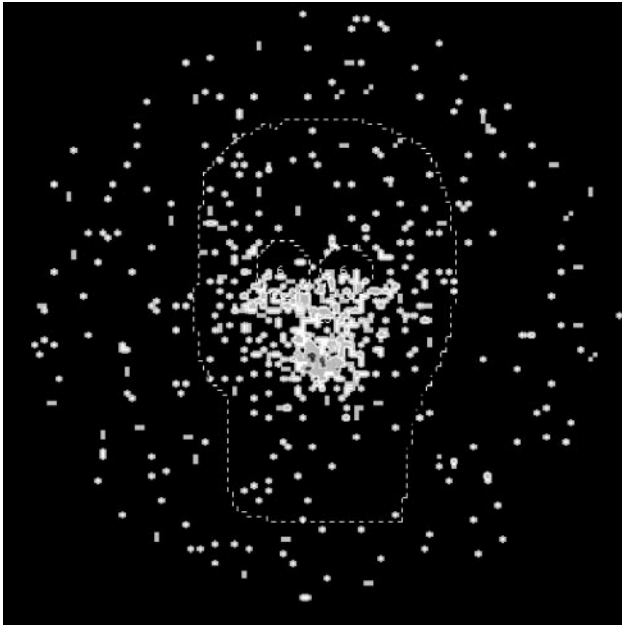
Fig. 5. Reduced facial and eye deposition with Pari nebulizer and prototype face mask designed to reduce particle acceleration in the region of the eyes. (From Reference 8, with permission.)

pattern representative of the patient population to be treated. As depicted in the lower part of Figure 3, the correct filter location is shown between the breathing simulator and the face facsimile.[6] Thus, all the components of the aerosol delivery system, including the MDI, the valved holding chamber, the face mask, and the pattern of breathing, will be reflected in the measured inhaled mass.

Table 2 shows summary data from a recent study that compared MDIs and nebulizers, using breathing patterns appropriate for pediatric patients using face masks.[6] The study tested the effects of the breathing pattern, the valved holding chamber employed, and the face mask and various nebulizers. Valved holding chambers were also washed with detergent to eliminate static charge. The influence of conditioning the valved holding chamber, combined with the effects of the breathing pattern, resulted in (mean $\pm$ SD) inhaled mass ranging from 0.7 $\pm$ 0.5% to 53.3 $\pm$ 6.2%. Nebulizers were less variable (9.6 $\pm$ 0.7% to 24.3 $\pm$ 3.1%). Detergent coating the holding chamber markedly increased inhaled mass and reproducibility of drug delivery (27.2 $\pm$ 1.4% to 53.3 $\pm$ 6.2%) for the combinations of pressurized MDI (pMDI) and valved holding chamber, but these effects were lost in the presence of face masks. Us-

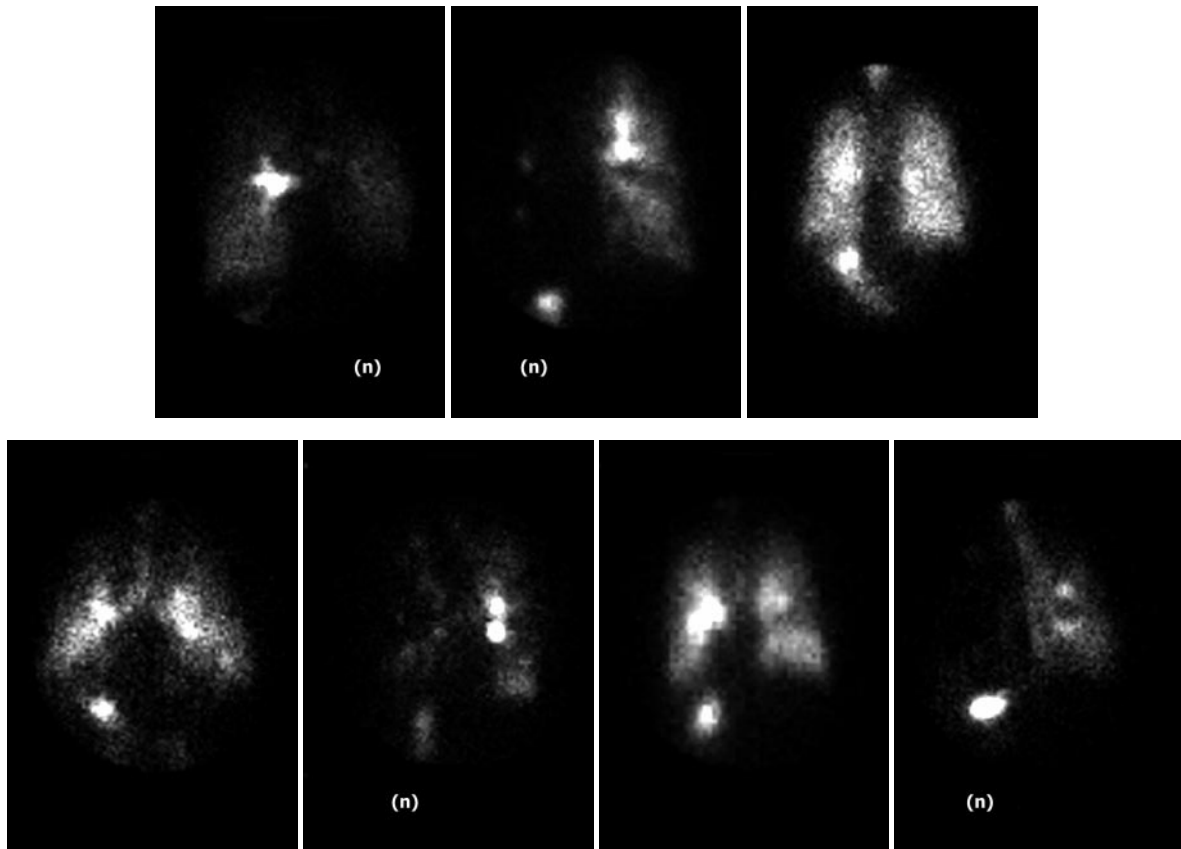
Fig. 6. Lung images from 7 patients following inhalation of cyclosporine aerosol labeled with technetium (^{99m}Tc human serum albumin). The "n" indicates native lungs (see text). There is considerable variation in regional particle deposition.
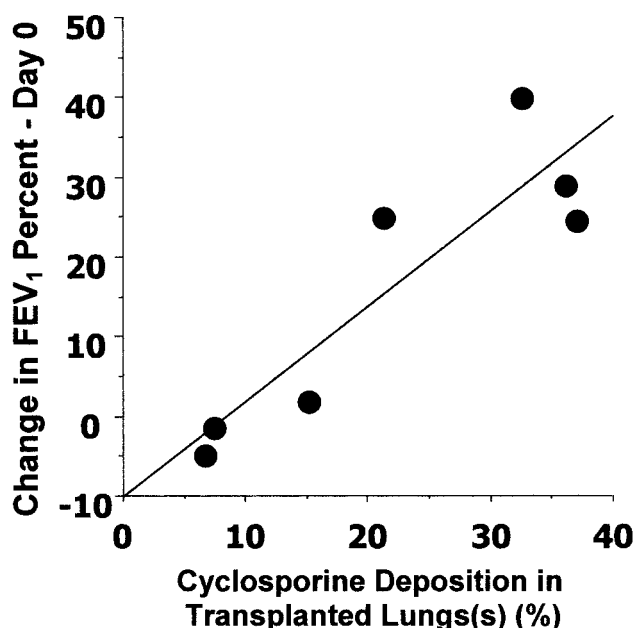
Fig. 7. Change in forced expiratory volume in the first second (FEV$_1$) (day 0) from the initiation of aerosol cyclosporine to approximately 200 days of therapy, as a function of cyclosporine deposited in transplanted lung(s). (From Reference 12, with permission.)
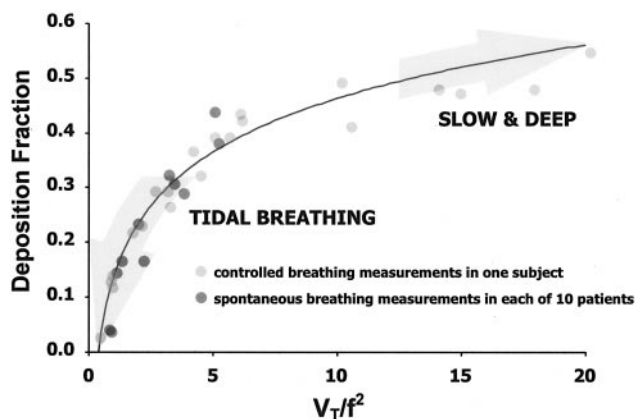

Fig. 8. Deposition fraction versus pattern of breathing, defined by a relationship that represents a measure of the period of breathing (tidal volume divided by breathing frequency squared [V$_T$/f^2]). Typical tidal breathing variables are found near the origin; slow and deep inspirations are away from the origin. (Adapted from Reference 13, with permission.)

ing pediatric breathing patterns, the nebulizer/face-mask combinations delivered $4.1 \pm 0.8\%$ to $19.3 \pm 2.3\%$ of the label dose, whereas a pMDI and detergent-coated valved holding chamber delivered $4.0 \pm 1.6\%$ to $28.6 \pm 2.5\%$. Face-mask seal was a key factor in drug delivery. Leaks around the face mask reduced drug delivery, and with the pMDI with valved holding chamber, leaks negated the effects of detergent coating.[6]

Face Masks and Facial Deposition

For pMDI with valved holding chamber, leaks around the face mask limit the exchange of tidal air with air in the chamber reducing the inhalation of aerosol. For nebulizers operated with compressors, the face mask can be kept filled with particles, despite leaks, because the compressor flow can exceed the child's minute ventilation. However, the very leaks that may preserve delivery to nebulizers result in deposition of drug on the face and eyes. Figure 4 demonstrates characteristic deposition patterns following nebulizer therapy via face mask, using a pediatric model of aerosol delivery with a tightly fitted face mask (left) and a straight-in nebulizer, and a commercially fitted mask with a straight-up nebulizer (right).[7]

Recent experiments indicate that deposition on the face, and particularly in the eyes, can be minimized if masks are designed such that linear velocity is reduced in the region of the leaks near the bridge of the nose. An example is

shown in Figure 5, which is a deposition image created under the same conditions as Figure 4 (left), using a modified mask design.[8] Deposition on the eyes and face was markedly reduced, while drug delivery to the patient (inhaled mass) was preserved.[9]

Deposition and Dose Versus Response

For conventional bronchodilators and steroids, the dose and response are not critical for clinical efficacy, because most delivery systems provide drug to the patient on the flat portion of the dose-response curve.[10] Safety of most preparations is enhanced because of the high potency of most drugs and a high threshold for toxicity. The situation for bronchodilators and steroids may not carry over to newer drugs. For example, aerosolized cyclosporine used in the treatment of lung-transplant rejection significantly reduces mortality.[11] In vivo measurements of deposition have been related to clinical effects (dose vs response). For example, Figure 6 shows gamma camera images of individual patients from an early study of the effects of inhaling cyclosporine. Analysis of cyclosporine deposition was related to clinical effects, as shown in Figure 7.[12] For patients with persistent acute rejection, 6 months of aerosolized cyclosporine improved FEV$_1$, and there was a suggestion of a dose-response relationship, because patients who received < 20 mg of drug per allograft had minimal response. A similar situation will exist for systemically absorbed drugs such as insulin, with which the dose to the lung parenchyma will be critical for disease management. Though clinical studies suggest that aerosolized cyclosporine is effective overall in a population of patients, the data from individual patients in Figure 7 suggest that conven-

Fig. 9. The I-Neb adaptive aerosol delivery system offers 2 breathing patterns. It is the first handheld device that regulates the pattern of breathing.
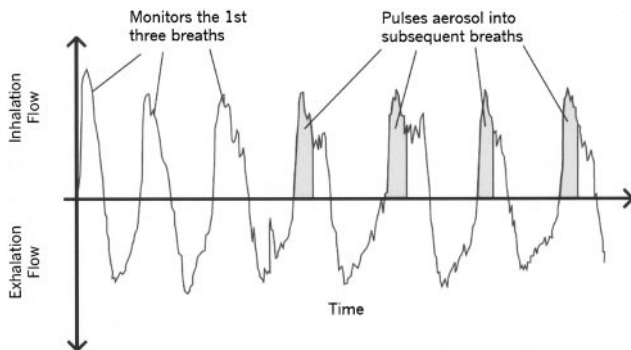

Fig. 10. The I-Neb's "tidal breathing mode" sets the device to deliver aerosol in the first 50% of the patient's inspiration. The patient inhales spontaneously during tidal breathing. The device measures flow (vertical axis) and time (horizontal axis). After the device determines the maxima and minima of 3 breaths, the software defines the start of the next breath (zero flow) and then injects aerosol into the inhaled gas as a series of pulses or boluses over 50% of the inhalation time. For each succeeding breath, the aerosol pulse is adjusted for the average of the 3 preceding breaths. The inhaled mass is determined by the sum of the aerosol pulses. (Courtesy of Profile Therapeutics, a Respironics company, Cedar Grove, New Jersey.)
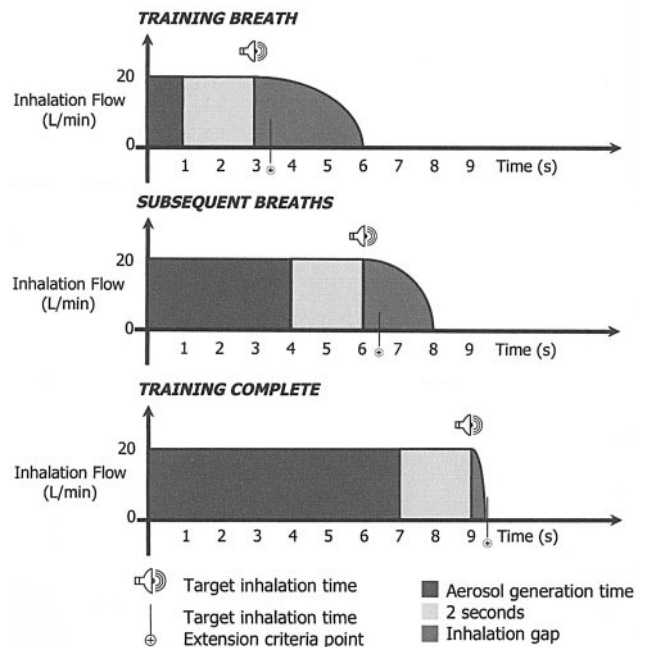

Fig. 11. The I-Neb's "target inhalation mode," or slow and deep breathing, is a new algorithm that guides the patient to a slow and deep inspiration. Typical inspiratory flows are reduced to approximately 20 L/min via a high-resistance mouthpiece (inhalation is upward). With each breath, the system trains the patient to lengthen inspiration via a vibration feedback. As shown in the upper panel of the figure, the patient inhales the first training breath, and after 3 seconds the system vibrates, signaling the patient to exhale. A bolus of aerosol was delivered for the first second of the breath. Because inspiration exceeded the so-called "target inhalation time" (vertical mark on horizontal axis), the device extends the target inhalation time in subsequent training breaths (middle panel) and the time of inspiration is gradually lengthened. After approximately 30 breaths the process is complete and the time of inspiration is set at approximately 9 seconds (lower panel). In this mode the aerosol pulse (darkly shaded area) begins with inspiration and lasts for 7 seconds. The device stops extending the target inhalation time at this point, because the length of the patient's inspiration is now approximately the same as the target inhalation time. The device remembers this pattern and gives the vibratory feedback at the same point in each succeeding breath and for all future treatments. (Courtesy Profile Therapeutics, a Respironics company, Cedar Grove, New Jersey.)

Control of Breathing Pattern and Deposition

As stated above, MMAD and geometric standard deviation can predict the deposition of particles in the lungs. However, for a given aerosol distribution, the major factor influencing deposition in normal subjects appears to be the pattern of breathing. As shown in Figure 8, the fraction of particles depositing in the lung can be closely related to the period of breathing.[13] In simplified form, points near the origin of the horizontal axis represent normal tidal

tional aerosol delivery systems leave some patients at risk for inadequate dose while others may be overdosed and exposed to potential toxicity.

volumes and breathing frequencies. As tidal volume increases and frequency decreases, the time of inspiration is prolonged (ie, slow and deep inspiration). The curve in Figure 8 represents maximum deposition with a slow and deep inspiration for monodisperse particles of 2.6 μm. The curve would be shifted upwards, with deposition approaching 100% for larger particles. Adaptive aerosol delivery technology analyzes variables of inspiration and provides feedback to guide the patient's inspiratory maneuvers.[14] The I-Neb adaptive aerosol delivery system (Respironics, Cedar Grove, New Jersey), a handheld device, combines the latest adaptive aerosol delivery technology with an optimized form of vibrating mesh technology (Fig. 9). The I-Neb system can deliver aerosol via 2 modes of inspiration: the "tidal breathing mode," which sets the device to deliver aerosol in the first 50% of the inspiration (Fig. 10), and the "target inhalation mode," which is a new algorithm that guides the patient to a slow and deep inspiration (Fig. 11). Testing of I-Neb prototypes has demonstrated that the target inhalation mode is capable of delivering between 19 and 20 times as much drug per breath as can simple tidal breathing. In addition, the target inhalation mode's slow and deep breath enhances deposition as much as 2–3-fold. Therefore, when compared to tidal breathing, in vivo measurements of deposition have indicated that the target inhalation mode is 51 times more efficient per breath in depositing particles in the lungs.[8]

Summary

Over the last 10 years it has become well established that comparisons between aerosol delivery devices can be carried out on the bench. With proper control of bench design and particular attention paid to the conditions of aerosol delivery (eg, breathing pattern and face mask), the inhaled mass of a given clinical scenario can be estimated. By combining inhaled mass measurements with the aerodynamic behavior of the aerosols produced, estimates can be made of the expected performance of the device in a given clinical situation. Breathing pattern, a major factor influencing deposition in the lungs, can be controlled with devices that measure the pattern of breathing and provide feedback to the patient, minimizing variability in drug delivery and deposition.

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Discussion

MacIntyre: Gerry, you showed a slide on aerosolized cyclosporine. That's the first time I have ever seen an aerosol treatment affect mortality, and you stressed that the dosing is critical. Should you assess patients carefully, maybe with gamma scanning, prior to starting them on these kinds of therapies, to see if you're going to get the drug to where you want it to go, and adjust the dose accordingly?

Smaldone: Cyclosporine may be marketed, and it's effective, but while the aerosol is a new kind of aerosol, the technology used to deliver it is old technology. If I had a patient on cyclosporine and who failed, I would do a gamma scintigraphy study, because the chances are the patient failed because of the dose. I think that, for modern studies, scintigraphy dose control and the standardization of the dose-response curve is going to be critical. Cyclosporine was kind of a transition drug, and it will be approved without that kind of control.

MacIntyre: You showed some scintigraphy of transplant patients in whom the deposition is quite variable from one

patient to the next. Might different breathing patterns be better for different types of deposition, and should patients be screened with gamma scans prior to doing that, to make sure they've got the right kind of breathing pattern for their particular disease anatomy?

Smaldone: At the time those studies were performed, control of breathing was not possible for clinical aerosol delivery. The technology to do that is now available, and I think that question will have to be applied to future markets. How does the disease affect the deposition? How does the formulation and the device affect it? I think those questions should be answered at the "phase zero" level, meaning *before* the clinical trial.

Martonen: I want to compliment Gerry's presentation, and the comment that Neil MacIntyre offered. This integration of computer modeling with the clinical administration of drugs is something that John Fleming and I are doing right now at Southampton General Hospital. Gerry's presentation showed real-time ventilatory patterns for patients, so the aerosol instrumentation could be programmed to know when to deliver drugs. That's certainly the basis for what Neil said. Perhaps for other patients you might want to have breathing patterns that you regulate, even though they're spontaneous, by having different tidal volumes. What we're trying to do at Southampton General Hospital and University of North Carolina is integrate our mathematical modeling with inhalation therapy so that physicians can administer drugs based on principles of physics. Of course, this is research right now, but that would be the next step in getting this science into the medical arena.

Smaldone: That's a very important point. Soon computer modeling will be able to reflect variables from a given individual. A model will be validated when you can correctly predict the change in deposition from a given change in breathing pattern of that individual. I think that's the challenge for the immediate future for modeling; then we can move into disease scenarios, where the physiology is different than in normals.

Newman: I have a question about nebulizer therapy. The data you showed relating to different breathing patterns is very persuasive, in that nebulizer therapy seems to be going in the direction of using controlled breathing patterns to optimize delivery. But one of the traditional advantages of the nebulizer is that you don't have to use any particular breathing pattern; you just use relaxed tidal breathing and there's no breathing pattern for the patient to learn. With the move toward more controlled breathing with nebulizers, is there a down side in terms of the patient's ability to use the nebulizer as successfully?

Smaldone: That's an excellent question. I think the best way to view that is to answer it like a physician. There are many ways to treat different kinds of diseases, and, depending on the disease state or the need, you have to choose a therapy that's appropriate for that condition.

First, some of the most sophisticated aerosol delivery systems can be used with patients who are sick, and they provide feedback to the patient. The Akita and I-Neb systems do that, and it's been demonstrated in their own clinical trials that patients who have substantial disease but are stable can be trained to use different breathing patterns by feedback from the machine. However, I think that, for example, in an emergency room situation it's probably unlikely that those systems would work. You would have to tailor use to the circumstances.

There is no one ideal system for all therapies. As we move into a modern treatment era, we need to talk about the disease—we need to know the pathophysiology, the stability of the

patient, the breathing pattern, the airway geometry—and then come up with a delivery system that will satisfy the need. I've tried to briefly illustrate today some of the ways we're beginning to think about doing that.

Rau: Regarding your delivery and deposition data with the breathing pattern you showed, Steve [Newman] said—if I understood correctly—that the breathing pattern with slow, deep inhalation is moving toward what we've been telling patients (somewhat unsuccessfully) to do with MDIs. Since the advent of the MDI in 1956 it seems we have been evolving toward a nebulizer that delivers a highly concentrated dose that could be inhaled with that slow, deep inhalation over a time period that might be substantially less than the 3½ minutes you showed, with better lung delivery. Myrna Dolovich coined the term "metered-dose liquid spray" or "metered-dose liquid inhaler" to describe the convergence of MDI and nebulizer delivery. But if you look at the different concepts along with the data you gave and extrapolate them, that seems to be where this is going.

Smaldone: Right. I agree in general with everything you just said. But, again, there is no one ideal breathing scenario in general for everybody; it depends on the disease. To treat bronchospasm in a patient who has emphysema—a disease that maximizes deposition in the central airways—I would give them a cheap nebulizer and tell them to breathe tidally and go about your business. But to give them alpha-1 antitrypsin to treat the parenchyma, I would use an expensive, fancy device to make sure that this expensive drug gets to the lung region it's supposed to, which, over 20 or 30 years, could mean the difference between life and death. Each scenario requires a different understanding, and this is what doctors are going to have to learn to become modern aerosol specialists.

Laube: Would you comment on the use of CPAP and aerosol delivery?

Smaldone: I don't have any experience giving aerosols to patients with CPAP, so I can't answer that question very well, but I can say that CPAP may keep airways open, it may relieve dyspnea, and, depending on the circumstances, the patient might be able to breathe an aerosol more effectively with CPAP, which might enhance deposition. On the other hand, all other things being equal, CPAP would make the airways larger, so deposition might be diminished.

Fink: I noticed that in your new information on breathing patterns there were some substantial differences in particle size. What causes that? Also, I would caution that as we look at new techniques and new devices, we need to validate how these new measurements relate to those previously made with more standard methods. The value of these measurements is really based on how well we empirically validate the methods.

Smaldone: That's an excellent question. To validate our measurements we tend to do scintigraphy when we think it's important. For example, in the original studies that I showed, where we measured the 2.5-μm particle fraction cutoff, those are scintigraphy images that correlated with cascade-impactor data. If we had gone with some other aerosol characterization technique, we might have gotten a different MMAD, and that's why if I get a certain MMAD in my laboratory, I confirm it by making a measurement in a human subject. That's why I did those I-Neb measurements I presented. When I got those particle-size measurements I wasn't sure that any of those particles would make it past the oropharynx into the lungs; slow-and-deep breathing might do it, but I decided to do a scintigraphy study to make sure. That's the kind of validation I'm talking about.

Anderson: More is not always better, and as we manipulate particle size and breathing patterns, depending on the drug, now that we're not just using bronchodilators, we need to have some measures of toxicity, to ensure we're not doing harm.

Smaldone: I agree completely. I think none of these devices, or even concepts, would exist if we were just administering bronchodilators and corticosteroids. The newer techniques apply to new drugs.

Hickey: Regarding facial deposition, are there other adverse effects than simply not delivering the dose? Are there adverse effects from getting aerosol particles in the eyes and on the face? I imagine that some particles could deposit on the face during exhalation too.

Smaldone: These systems were all mimicking inhalation and expiration, because they were ventilated models. But they're only models and they have limitations. There is anecdotal clinical literature on the effects of facial and eye deposition.[1-3] There is adult literature indicating that atropine-like drugs can cause pupil dilation and glaucoma and that sort of thing.[4] However, there is a lot of general clinical data that indicate that in pediatrics the drugs are generally safe, but I think that anecdotal data and individual patient data are not out there. Our job is to try to understand these variables as much as possible. I'd rather use a mask that was designed for the specific therapy rather than just slap one on the patient's face.

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Hickey: It seems to me that that has implications for MDIs and DPIs too.

Smaldone: Our current data would suggest that delivery aspects are more important than facial deposition aspects for those types of devices.[1-3]

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