Regional Deposition and Regional Ventilation During Inhalation of Pentamidine*  
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In most patients, the deposition of aerosolized pentamidine (AP) is less in the apex of the lung relative to the base. As the apex of the lung is relatively less ventilated than the base, it is possible that reduced regional ventilation may explain the inhomogeneity in regional drug deposition. The purpose of this study was to measure the relationship between regional deposition of AP and regional ventilation, and the influence of particle size and airway caliber on this relationship. Ten subjects with HIV infection who were receiving prophylaxis with AP were recruited. Using krypton (186Kr) we measured regional ventilation during treatment with AP, labeled with 99mTc. Two nebulizers were used (Respirgard II and Fisoneb) that produced particles of different size. In addition, patients were studied with and without a bronchodilator because changes in airway geometry can affect sites of particle deposition. There was no significant correlation between regional ventilation and regional particle deposition (r = 0.00, linear regression). Particle deposition in the upper lobes relative to the lower lobes was less than would be predicted by regional ventilation, by a ratio of 0.84 ± 0.03 (mean ± SE). Using two-way analysis of variance (ANOVA), the upper to lower zone deposition pattern was not affected by either nebulizer or by the use of albuterol. The Fisoneb had significantly more central deposition relative to the jet nebulizer (mean ± SE, s_c/Tc: Fisoneb 1.3 ± 0.1, Respirgard 1.1 ± 0.1, p = 0.005, two-way ANOVA). The use of a bronchodilator did not significantly affect the central/peripheral deposition pattern. We conclude that differences in deposition between upper and lower lung regions are not accounted for simply by differences in regional ventilation in patients undergoing prophylaxis with AP. In assessing the cause of regional inhomogeneities of pharmaceutical aerosol deposition (and in devising strategies to achieve more uniform distribution), regional ventilation should be measured directly rather than be inferred from the deposition pattern of the aerosol.  

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Aerosolized pentamidine (AP) is used as prophylaxis of Pneumocystis carinii pneumonia in patients infected with human immunodeficiency virus (HIV) infection.1 However, in addition to its role in preventing P carinii, AP may serve as a paradigm for a new generation of aerosolized therapies. In contrast to most preexisting nebulized medications, it was intended for delivery to the alveoli, rather than to the airways. Furthermore, its delivery and efficacy could not be judged by simple clinical criteria, in contrast to bronchodilators, which are currently the most commonly administered aerosolized drugs. Efforts to optimize AP therapy have yielded new techniques of administering therapeutic aerosols and a greater understanding of the principles governing the measurement of their deposition and clinical efficacy, developments that are likely to influence the future design and assessment of other aerosolized medications.8-11  

An issue that has stimulated much discussion during the evaluation of AP has been its regional distribution. Less aerosol is deposited in the upper lobes relative to the lower lobes5-7 and it has been suggested that this may contribute to localized recurrence.12,13 Regional variation in ventilation between the upper and lower lung regions has been proposed as a possible mechanism for the observed inhomogeneities in deposition.6,12 This hypothesis prompted some investigators to suggest ways of improving upper lobe distribution: for example, administering therapy with the patient in a supine position or modifying the aerosol delivery system.5-7 Although these maneuvers undoubtedly improve upper lobe deposition, it is not clear if the improvements are due to a change in regional ventilation or to a change in some other factor (eg, the caliber of airspaces in a particular region). The uncertainty over the relationship between ventilation and deposition has implications for future efforts to regionally target aerosolized drugs. For example, if regional ventilation is the sole determinant of regional deposition of small pharmaceutical aerosols (mass median aerodynamic diameter [MMAD] = 1 μm), then optimization of regional ventilation would result in optimization of regional drug deposition. However, if

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ANOVA = analysis of variance; AP = aerosolized pentamidine;  
DTPA = diethylenetriamine pentacetate; g = geometric  
standard deviation; MMAD = mass median aerodynamic  
diameter; s_c/(C/P) = central to peripheral ratio of 99mTc  
counts normalized for ventilation; s_t/(U/L) = upper to lower  
ratio of 99mTc counts normalized for ventilation; 99mTc-  
DTPA = technetium bound to diethylenetriamine  
pentacetate; 99mTc-HSA = technetium bound to human  
serum albumin  

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regional ventilation is not the sole determinant of regional deposition, then more complex strategies may be needed to optimize deposition.

In this study, we decided to measure regional ventilation using krypton $^{81m}$Kr contemporaneously with the deposition of AP and see if they correlated. Further, because the choice of aerosol delivery system has been shown to influence regional deposition of AP, we administered AP to each subject using two types of nebulizer—an ultrasonic device (Fisoneb, Fisons, Rochester, NY) and a jet nebulizer (Respirgard II, Marquest, Englewood, Colo). These are the two most commonly used devices for the administration of AP in North America. Because these devices produce aerosols of different sizes, we can assess the effect of changing particle size on the relationship between regional ventilation and deposition. The Fisoneb produces larger particles and was the device used in an important clinical study that reported increased upper lobe relapse. In addition, we decided to assess the effects of routinely administering an aerosolized $\beta$-agonist with each of these nebulizers on regional deposition and ventilation in HIV-infected patients.

METHODS

Patients

Ten male subjects who had positive serologic tests for HIV infection were recruited. All subjects had been receiving primary or secondary prophylaxis with AP. The study had been approved by the hospital ethics committee and informed written consent was obtained from all subjects.

Nebulizers and Solutions

On the first study day, 180 $\mu$g of albuterol (Proventil, Schering, Kenilworth, NJ) was administered by metered dose inhaler prior to inhalation of pentamidine. Then, spirometry was performed (after albuterol but before the administration of pentamidine). On a second day, the patients underwent the same protocol as on day 1 except that no albuterol was given. The prepentamidine spirogram on the albuterol day was compared with the prepentamidine spirogram on the control day.

All patients were studied using a Respirgard II and a Fisoneb nebulizer on each of the two study days. The dose and concentration of pentamidine placed in each nebulizer were in accordance with the manufacturer’s recommendations for each device. The Respirgard II contained 300 mg of pentamidine (Pentamidine, Lyphomed, San Francisco), which was dissolved in distilled water to make up 6 ml and labeled with 5 mCi of technetium bound to human serum albumin ($^{99m}$Tc-HSA). Patients breathed tidally for 5 min. The Fisoneb contained 3 ml of a solution containing 60 mg of pentamidine that was also labeled with 5 mCi of $^{99m}$Tc-HSA. The Fisoneb ran continuously and was run to dryness in approximately 5 min.

Five of the subjects inhaled from the Fisoneb before using the Respirgard and five did the converse. An interval of at least 6 h elapsed between the two pentamidine inhalations. The patients received the complete recommended monthly dosage using the Fisoneb and because the patients inhaled from the Respirgard II for only 5 min, they received only a small additional dose of pentamidine, thereby avoiding the danger of pentamidine overdosage by giving two treatments in one day. Subject 8 did not undergo a Respirgard trial without albuterol for technical reasons. Subjects 9 and 10 refused studies without albuterol because of histories of airway irritation during pentamidine therapy.

Generation of Images

Subjects were seated in front of a posteriorly positioned gamma camera (Picker Dyna camera, Northford, Conn., wide field of view, low energy, parallel hole collimator) that was in line with a computer that stored images (Advanced Medical Computer, Sunnyvale, Calif). As soon as the patient had settled into a stable breathing pattern, the nebulizer was switched on. Then, Krypton gas $^{81m}$Kr, at a constant flow rate, was introduced into the inspiratory tubing of the nebulizer with the camera set to read only the higher energy corresponding to $^{81m}$Kr. An equilibrium image was obtained after 3 to 5 min (at 80 to 100K counts/min). Following ventilation measurements, the camera was adjusted to read only $^{99m}$Tc and a deposition image was obtained (25 to 50k counts/min of $^{99m}$Tc activity). Therefore, for each individual aerosol deposition study (four in most patients), a separate $^{81m}$Kr ventilation scan was performed. Serial studies performed on the same day were proceeded by a repeated $^{99m}$Tc background image that allowed subtraction of residual activity.

Analysis of Regional Deposition and Ventilation

When administered by continuous inhalation, the regional $^{81m}$Kr counts are propionate to the relative regional ventilation during tidal breathing, and measurements of regional ventilation, using $^{81m}$Kr, are similar to regional ventilation measurements made using $^{133}$Xenon washout (with the exception of measurements made in certain subjects with severe airway obstruction, which was not the case with the patients in the present study). We express the pulmonary distribution of deposited particles in terms of regions of interest that are illustrated in Figure 1. These computer-generated regions are based on lung outlines that are delineated by the $^{81m}$Kr ventilation image. Based on the $^{81m}$Kr outlines, we can divide the lung into central and peripheral regions and into upper and lower regions. By convention, using irregular regions of interest, we set the central lung region to 33 percent of the total two-dimensional lung area on the $^{81m}$Kr scan. The upper and lower zones were delineated by a horizontal line at the level of 50 percent of the height of the $^{81m}$Kr image, defining simple rectangular regions.

By superimposing the $^{99m}$Tc deposition image on the $^{81m}$Kr regions, the aerosol deposition pattern can be normalized for ventilation. That is, the regional distribution of deposited particles (labeled by $^{99m}$Tc) divided by the ventilation (labeled with $^{81m}$Kr) can be expressed as the ratio of the activities measured in a particular region. For the upper/lower lung regions (Fig 1), the aerosol distribution can be expressed as follows:

![Figure 1. Central/peripheral and upper/lower regions of interest generated from the $^{81m}$Kr equilibrium scan. All calculations are based on the right lung.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21689/ on 06/26/2017)
Particle Distribution

Particle size distributions were estimated using cascade impaction in circuit with a pump (Harvard) in a manner described in detail previously. The MMAD and geometric standard deviation (σg) of the particles produced by the Respigrard II were 0.76 μm (1.9), and by the Fisoneb, 2.5 μm (2.0).

Statistics

Paired Student's t tests were used to compare spirometric measurements before and after albuterol. Linear regression analysis was used to test the significance of the relationship between regional ventilation (U/L)_kr and regional particle deposition (U/L)_kr. Two-way analysis of variance (ANOVA) was used to assess the effect of the choice of nebulizer and the use of bronchodilator on the ratios of upper to lower deposition normalized for ventilation (s_U/L) and the central to peripheral deposition ratios normalized for ventilation (s_C/P). To test the hypothesis that the s_U/L was less than 1.0 (the value at which regional ventilation and regional deposition would be matched), binomial tests were used.

RESULTS

On the first study day, the mean (± SE) FEV₁/FVC percent after administration of albuterol but prior to receiving pentamidine was 80.5 ± 2.9 percent. On the second day, when no albuterol was given, the prepentamidine FEV₁/FVC percent was similar: 81.6 ± 3.1 percent. Similarly, the mean FEV₁ was not significantly different regardless of whether albuterol was received (3.2 ± 0.2 with albuterol, 3.1 ± 0.2 without albuterol; paired Student's t test, p = NS).

In Figure 2, the ratio of upper to lower zone deposition, (U/L)_kr, shown on the vertical axis, is plotted against the ratio of ventilation, (U/L)_kr, on the horizontal axis for the Respigrard II and the Fisoneb, each with and without albuterol. For all the studies, no correlation was apparent, using linear regression analysis (r = 0.00, p = NS).

If particles deposit uniformly throughout the alveoli, peripheral and central airways in a manner proportional to ventilation, the regional meanTc distribution would be similar to the equilibrium meanTc distribution, and the 1/C/P ratio would equal 1.0. As particles deposit in more central airways, the 1/C/P ratio becomes greater than 1.0. Because of stomach activity from swallowed particles, only the right lung data were analyzed.

Table 1—Regional Deposition Normalized for Regional Ventilation for Upper and Lower (s_U/L) and Central to Peripheral (s_C/P) Regions for Respigrard II and Fisoneb, With and Without Albuterol

<table>
<thead>
<tr>
<th></th>
<th>Jet Nebulizer (Respigrard)</th>
<th>Ultrasonic Device (Fisoneb)</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>s_U/L</td>
<td></td>
<td></td>
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<tr>
<td>With albuterol</td>
<td>9</td>
<td>0.87</td>
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<tr>
<td>Without albuterol</td>
<td>8</td>
<td>0.78</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>0.83</td>
</tr>
<tr>
<td>s_C/P</td>
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<td></td>
</tr>
<tr>
<td>With albuterol</td>
<td>9</td>
<td>1.06</td>
</tr>
<tr>
<td>Without albuterol</td>
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<td>1.03</td>
</tr>
<tr>
<td>Total</td>
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<td>1.05</td>
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L = 1.0). Most of the points fall below the line, with a mean (± SE) of 0.84 ± 0.03 for all the data points in Figure 3, indicating that relatively fewer particles were deposited in the upper zone than would be proportionate to regional ventilation. Further, the median $s_U/L$ of the four individual groups was less than 1.0, achieving statistical significance (using binomial tests)\(^7\) for three of the groups: the Respigrad with albuterol (median = 0.78, p = 0.02), Respigrad II subjects without albuterol (median = 0.84, p = 0.004), Fisoneb with albuterol (median = 0.78, p = 0.01), Fisoneb without albuterol (median = 0.86, p = NS).

Similar findings occurred regardless of the choice of nebulizer or the presence or absence of the bronchodilator. Using two-way ANOVA, neither the choice of nebulizer nor the presence/absence of albuterol affected the $s_U/L$.

In Table 1, mean data describing the central to peripheral distribution patterns of deposited particles are shown. The pattern of distribution using the Respigrad II is closer to the pattern predicted by regional ventilation (mean ± SE: 1.1 ± 0.1, predicted $s_C/P = 1$), than that of the Fisoneb whose $s_C/P$ is greater (mean ± SE: 1.3 ± 0.1). Using two-way ANOVA, the choice of nebulizer was significantly associated with the $s_KC/P$ (p = 0.005), but the relationship between the use of a bronchodilator and the $s_C/P$ was not significant.

Discussion

In this study, we simultaneously measured regional ventilation and regional drug deposition during inhalation of AP. We found that in upright subjects, upper lobe drug deposition was less than would have been predicted from the ventilation data. In addition, for individual subjects, drug deposition, normalized for regional ventilation, did not correlate with regional ventilation ($r = 0.00$, $p = NS$). Reduced upper lobe deposition of pentamidine, after inhalation in an upright position, has been reported previously by several studies.\(^3\).\(^5\).\(^6\).\(^13\) It had been assumed that inadequate regional ventilation would explain the regional variations in deposition because previous investigators had demonstrated that regional ventilation is reduced in the upper lobes of normal subjects who had been studied in an upright position.\(^16\) However, the findings of the present study demonstrate that regional ventilation alone cannot explain the deposition data and that other factors must also influence regional deposition of inhaled pentamidine.

Our findings complement those of a previous study from this laboratory\(^3\) that demonstrated that in HIV-positive patients, the upper zone of the lung receives less ventilation and less deposition relative to the lower zone but found no correlation between these parameters for individual subjects. However, because the principal objective of Smaldone et al\(^3\) was to study intersubject differences in pentamidine deposition, they had used $^{133}$Xe to normalize for intersubject differences in lung volume. Hence, their regional ventilation data were gleaned from $^{133}$Xe washout data, which cannot be collected at the same time as an aerosol inhalation. In contrast, the use of $^{81m}$Kr enables contemporaneous measurements of regional ventilation and regional particle deposition to be made. This difference is important because an individual's pattern of regional ventilation is not necessarily constant over time and can be influenced, for example, by changes in inspiratory muscle groups during tidal breathing,\(^19\) especially if the individual is being asked to inhale through different gas and aerosol delivery systems. Further, because the $^{81m}$Kr gas and $^{99m}$Tc particles were inhaled at the same time for each experiment, the possibility of patient movement between studies affecting the results is eliminated. The most important implication of the findings of the present study and those of our previous study\(^3\) is that in assessing the etiology of regional inhomogeneities of pentamidine deposition (or that of other pharmaceutical aerosols), regional ventilation should be measured directly rather than be inferred from the deposition pattern of the aerosol.

Our findings in HIV-positive subjects inhaling pentamidine are consistent with the results of previous studies in other clinical settings. Susskind et al.\(^20\) in coal miners, measured regional ventilation using $^{81m}$Kr and compared it with the regional deposition of
diethylenetriamine pentacetate (DTPA) aerosols. They found that the distribution of regional ventilation and the distribution of the deposited DTPA particles did not correlate. Alderson et al. studied patients with suspected pulmonary emboli and after imaging with both DTPA aerosols and a radioactive gas (either \(^{81m}\)Kr or \(^{133}\)Xe), they observed, in patients who had been studied in an upright position, markedly uneven apex to base gradients of deposited DTPA that were not explained by the distribution of regional ventilation as measured by radioactive gas. In contrast, these marked apex to base gradients were not observed in patients who had inhaled the DTPA aerosol while supine. Finally, Trajan et al. demonstrated that in normal subjects, decreased regional ventilation could be associated with increased regional deposition and suggested that this phenomenon was due to prolonged residence time of aerosol in slowly ventilated areas.

The absence of a significant correlation between regional ventilation and regional particle deposition is consistent with the fact that different physiologic processes govern regional ventilation and particle deposition. For example, in healthy subjects, regional ventilation is dependent on regional compliance and regional resistance. During tidal breathing in the upright position, the upper portion of the lung is less compliant, resulting in reduced regional ventilation. The factors influencing regional particle deposition are more complex. Regional ventilation is required to deliver a particle to a particular region but the tendency of a region to retain that particle is determined by three processes that can cause particles to deposit: gravitational sedimentation, inertial impaction, and to a lesser extent, diffusion. The relative importance of these processes is, in turn, determined by the density, diameter, and diffusion coefficient of the inhaled particle, its residence time in the airway, the anatomy and dimensions of the airway, and the volumetric flow rate of air. Nevertheless, despite the fact that the processes governing ventilation and deposition are different, they are both associated with increasing apex to base gradients in the upright position (i.e., both ventilation and deposition are less in the upper lobe relative to the lower). Hence, the lack of correlation may be apparent only if regional quantification of deposition and ventilation for specific regions of interest are compared in individual patients.

The findings of Baskin et al. together with those of a similar study by O’Doherty et al. illustrate a potentially important role for manipulation of body position in optimizing the regional delivery of pharmaceutical aerosols. However, ventilation was not measured in those studies and our data indicate that direct measurement of ventilation is necessary to assess its contribution to the outcome of these maneuvers. While our results were obtained in a sitting position, they nevertheless suggest on a theoretical basis that the changes in distribution of deposited pentamidine when shifted to a supine position may be related to factors other than simple changes in regional ventilation. This concept is further supported by the failure of Baskin et al. to shift deposition using measures specifically designed to improve regional ventilation in the upright position (e.g., abdominal binding). Our data placed in the context of the findings of Baskin et al. and O’Doherty et al. suggest that regional deposition is significantly affected by gravity through its effects on regional anatomy. For example, Glazier et al. using a rapid freezing technique in dogs demonstrated that the alveoli in the apex became larger than those in the bases in the erect position while no such differences were apparent in the horizontal position. It is possible that such changes may affect the rate of sedimentation of small particles.

The distribution of deposited particles between upper and lower regions, normalized for regional ventilation, was similar for the two nebulizers. We had considered the possibility that the high incidence of upper lobe “radiological FCP” reported in the study of Jules-Elysee et al. may have been due to failure of the Fisonet to deliver its larger particles to the upper lobes. However, the present study makes that possibility unlikely. Similarly, it is unlikely that the findings of Jules-Elysee et al. were due to changes in breathing pattern induced by the Fisonet, as regional ventilation was not significantly different between nebulizers (Fig 2).

The central to peripheral distribution pattern of deposited aerosols (s,C/P) with the Respirgard II is closer to the pattern predicted by regional ventilation than that of the Fisonet. This indicates that factors other than ventilation, probably the larger particle size, are more important for the Fisonet than the Respirgard, in determining central to peripheral distribution. Similar findings have been reported by Ilowite et al.

Prior administration of an inhaled bronchodilator agent did not change the central to peripheral distribution pattern of deposited aerosols (s,C/P) with either nebulizer. Therefore, while the benefits of inhaled beta-agonists include the amelioration of airway irritation and bronchospasm in individual subjects, our data suggest that bronchodilators do not produce a more peripheral deposition pattern in the average patient with AIDS who tends to have restrictive rather than obstructive lung disease.

The demonstration that aerosol deposition is disproportionately reduced in the upper zone relative to regional ventilation does not establish a cause and effect relationship with failure of prophylaxis. Recent studies have found that while there is considerable intersubject variation in the dose of pentamidine deposited in the lungs, neither the dose deposited nor the levels of pentamidine in bronchoalveolar lavage (BAL) fluid correlate with success or failure of pentamidine prophylaxis. Further, using regional BAL, we have shown that
differences in regional levels of pentamidine do not account for relapse in patients receiving AP prophylaxis.\textsuperscript{25}

In conclusion, this study demonstrates that if the importance of ventilation in determining the regional deposition of pentamidine is to be assessed, then regional ventilation must be measured directly and not simply inferred from the distribution of deposited particles. Our findings have implications for future studies analyzing the etiology of regional inhomogeneities of pharmaceutical aerosol deposition and in devising strategies to achieve more uniform distribution.

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