Comparison of Lung Deposition in Two Types of Nebulization*

Intrapulmonary Percussive Ventilation vs Jet Nebulization

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Background: So-called intrapulmonary percussive ventilation (IPV), frequently coupled with a nebulizer, is increasingly used as a physiotherapy technique; however, its physiologic and clinical values have not been rigorously assessed.

Study objective: To compare in vitro and in vivo characteristics of the nebulizer of the IPV device (Percussionaire; Percussionaire Corporation; Sandpoint, ID) with those of standard jet nebulization (SST) [SideStream; Medic-Aid; West Sussex, UK].

Design: Aerodynamic particle size was studied by a cascade impactor. The deposition of 99mTc-diethylenetriaminepenta-acetic acid was measured in 10 healthy subjects by tomoscintigraphy during spontaneous breathing with both nebulizers.

Measurements and results: The mass median aerodynamic diameter (0.2 μm vs 1.89 μm for IPV and SST, respectively) and the fine-particle fraction (16.2% vs 67.5%, respectively) were significantly smaller with IPV. In vivo, respiratory frequency (RF) was lower with the IPV device (10.1 ± 3.4 breaths/min vs 14.6 ± 3.4 breaths/min, p = 0.002). Whole-body deposition was significantly higher with IPV (15.63% vs 9.31%), but it was due to a higher extrapulmonary deposition. Although intrapulmonary deposition (IPD) was not different with both devices (4.20% for SST vs 2.49% for IPV), it was much more variable with IPV, compared to SST. The penetration index into the lung was higher with IPV than SST when normalized for RF (0.045 ± 0.018 breaths/min vs 0.026 ± 0.013 breaths/min, p = 0.007).

Conclusion: The two techniques showed comparable lung deposition despite a large difference in particle size. However, IPV IPD was too variable and thus too unpredictable to recommend its use for drug delivery to the lung.

Key words: intrapulmonary percussive ventilation; lung deposition; nebulization; respiratory therapy; 99mTc diethylenetriaminepenta-acetic acid

Abbreviations: CD = central deposition; ED = emitted dose; FPF = fine-particle fraction; ID = initial dose; IPD = intrapulmonary deposition; IPV = intrapulmonary percussive ventilation; MMAD = mean median aerodynamic diameter; PD = peripheral deposition; PI = penetration index; RF = respiratory frequency; ROI = region of interest; RW = residual weight; SST = standard jet nebulization; Ti = inspiratory time; Vt = tidal volume; WBD = whole-body dose

Nebulizers are widely used in the treatment of pulmonary diseases such as asthma, COPD, and cystic fibrosis. Many patients find nebulizations attractive. However, deposition of nebulized medications may be highly variable. The therapeutic effect depends on the quality of the nebulization, on the drug solution, on the conditions of the nebulization, on the individual patient (pattern of breathing, anatomy, underlying lung pathology), and on the device characteristics. All those variables influence the nebulization.5

Jet nebulization has been studied with different devices in various groups of patients and in different

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Lung deposition by jet nebulization was also studied using different drugs.3–7 By contrast, intrapulmonary percussive ventilation (IPV) has been poorly studied from this point of view.10 The device was designed by F.M. Bird in 1979. It consists of a high-frequency percussive ventilation method combined with a nebulizer. It delivers rapid minibursts of air and aerosol solution through a unique sliding Venturi, and it was originally designed, according to the manufacturer, to increase the mucociliary clearance, to improve the gas exchange, to stabilize airway patency, to humidify the airway, and to improve the lung mechanics. Aerosolized antibiotics are used in patients with cystic fibrosis and, combined with albuterol aerosolization, IPV may help to mobilize airway secretions in these subjects.11 However, there is no published study on deposition properties of the IPV. There is therefore a need for validation studies.

The aim of this study was to compare IPV combined with nebulization to a validated jet nebulizer. Comparison of particle deposition with both devices can give important information on their respective efficacy and indications. The aerodynamic particle size analysis was performed, and the lung deposition was investigated by tomoscintigraphy.

### MATERIALS AND METHODS

#### Subjects

Ten healthy men, all nonsmokers (mean age, 28 years; range, 23 to 43 years), were investigated. All subjects underwent standard spirometry according to American Thoracic Society guidelines.12 The Ethics Committee of our institution approved the study, and a written, informed consent was obtained from the volunteers.

#### Nebulizers

Both devices were driven by the same pressure: 3.5 bars of compressed air. For standard jet nebulization (SST), we chose a well-studied nebulizer (SideStream; Medic-Aid; West Sussex, UK). Since the collector device is made up of two pieces, we abraded the borders to optimize the sealing of the collector and avoid leaks to the atmosphere. For IPV, an IPV apparatus (Percussionaire; Percussionaire Corporation; Sandpoint, ID) with an operating pressure of 20 cm H2O for a frequency of 250 cycles per minute was used. The same collector and top of both nebulizers were used throughout all the in vitro and in vivo measurements.

#### In Vitro Measurements

Particle size was measured by a cascade impactor (1 ACFM Eight Stage NonViable Cascade Impactor; Graseby Andersen; Atlanta, GA) at ambient temperature (23°C). Each stage of the impactor (10 to 0.7 μm) was coated with a hydroxypropylcellulose gel (22.5% weight/volume in water).

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22005/ on 06/26/2017)

The drug quantities found on each stage were added to determine the emitted dose (ED). The cumulative mass of nebulized solution retained in the successive stages of the cascade impactor was calculated and plotted on a log-probability scale (as percentage of total mass recovered in the impacter) against the effective cutoff diameter. According to Clark and Borgstrom,13 the experimental mass median aerodynamic diameter (MMAD) of the particles was defined from this graph as the interpolation of the regression line at 50%. The percentage of particles with a size between 1 μm and 5 μm, defined as the fine-particle fraction (FPF), was calculated.

Output flow of both nebulizers was measured using a spirometer (Expirograph; Godart; Bilthoven, the Netherlands). The nebulizers were connected to the tubing of the spirometer, and the volume of the nebulized solution was measured as a function of time to calculate flow. The measurements were done in triplicate and the mean values are reported.

#### In Vivo Measurements

For SST, a Hans Rudolf 1410 valve (Hans Rudolf; Kansas City, MO) was inserted between the filter and the mouthpiece to avoid rebreathing (Fig 1). We added a filter on the expiratory airway of both systems to avoid atmospheric contamination by radioactive particles. The subjects breathed spontaneously through the same mouthpiece with a nose clip in place. According to manufacturer of the IPV device, 1 mL of solution is nebulized per minute. However, after preliminary testing, we noticed that 4 mL of solution were nebulized in 3 min with IPV. We therefore reduced the nebulization time to 3 min for IPV with continuous percussions. For SST, the duration of nebulization was fixed at 4 min.

All the nebulizations were done in the same room at ambient temperature (mean, 22.9°C ± 1.1°C; range, 22°C to 25°C) at the same time of the day (2 pm). All the subjects were submitted to both nebulization systems. The first six subjects started with SST followed by IPV 3 days later, whereas the last four volunteers performed the maneuvers in the reverse order.
Data Acquisition and Treatment

The collectors of SST (element 1 in Fig 1) and IPV were filled with 4 mL of a final solution of 99mTc-diethylenetriaminepenta-acetic acid aerosol for nebulization, prepared with ethanol according to the recommendations of the provider (Mallinkrodt, Petten, Holland). 99mTc-diethylenetriaminepenta-acetic acid aerosol is a diagnostic radiopharmaceutical specially designed for administration by inhalation. As determined by chromatography, the labeling efficiency is > 95% and the complex is stable during 6 h in vitro. The absence of modification of the radioactive background in the tissues surrounding the lungs (except the digestive tract) indicated that the radioactive marker was not released during the data acquisition process. Thus, the regional quantification of radioactivity in the lungs is a reliable means for studying aerosol distribution.

Radioactivity of the collector was measured before (initial dose [ID]) and after nebulization with a radiosotope calibrator (Capintec CRC-12, Capintec, Ramsey, NJ). By subtraction of both measurements, the nebulized dose was calculated and expressed in megabecquerels after calibration of the detector by the head of the camera as detector. Activity in cycles per minute was expressed in megabecquerels after calibration of the detector by the head of the camera as detector. Activity in cycles per minute was expressed in megabecquerels after calibration of the detector by the head of the camera as detector. Activity per second per pixel was determined as follows: Activity = megabecquerels per pixel = counts per second per pixel.

Data Acquisition and Treatment

Maximum 43 91 187 106 107 104

Table 1 presents average anthropometric and lung function data of the subjects. All volunteers had spirometric values in the normal range.

Statistical Methods

The RW and radioactivity of both collectors were compared using an unpaired Student t test. A Student paired t test was used with a level of significance of p < 0.05 for the comparisons of ventilatory and scintigraphic parameters. We compared respiratory parameters and deposition results between the two methods. Each subject was his own control. We also compared the IPV-first group with the SST-first group to assess an eventual training effect. A standard linear regression analysis was used to examine the relationship between ventilatory and scintigraphic variables, as well as between gravimetric parameters. The coefficient of variation was used to evaluate the variability (SD/mean × 100).

RESULTS

Lung Function Tests

Table 1 presents average anthropometric and lung function data of the subjects. All volunteers had spirometric values in the normal range.

Aerodynamic Particle Size Analysis

The FPFs were 67.5% and 16.2% for SST and IPV, respectively. The EDs were 13.4% and 1.45%
for SST and for IPV, respectively. MMADs were 1.89 μm for SST and 0.2 μm for IPV. Output flow of the nebulizers was 10.3 L/min for SST and 70.6 L/min for IPV.

### Pattern of Breathing During Nebulization

Table 2 summarizes the data of ventilation. Average RF was significantly lower with IPV than with SST. Average Vt was higher with IPV, though not significantly. There was no significant difference between the two groups for the Ti (p = 0.396), while the duration of nebulization was shorter in the IPV group. The ratio of Ti to total time did not show any significant difference (p = 0.261).

### Scintigraphy

As shown in Table 3, the mean dose of radioactive aerosol WBD was significantly higher with IPV than with SST. However, interindividual variations were lower with SST than with IPV. Inversely, the mean dose of aerosol deposited in both lungs (IPD) was lower with IPV than with SST. Although this difference was not significant, it should be noted that individual data illustrated in Figure 2 show that IPD was higher with SST in 7 subjects (subjects 1, 2, 4, 5, 6, 8, and 10) of 10. The coefficient of variation of IPD was 35% for SST and 104% for IPV. The IPD/WBD ratio was significantly higher with SST than with IPV (p = 0.003) [Table 3].

The PI was different between both nebulization systems. The coefficient of variation was comparable for the PI in the two groups (37% and 29% for SST and IPV, respectively) [Table 3]. The amount of aerosol (μCi/100 pixels) deposited in both central (central deposition [CD]) and peripheral (peripheral deposition [PD]) areas of the right lung was also comparable between SST and IPV (Table 3).

The pattern of breathing during nebulization (Table 2) was not influenced by the system used except for RF, which was 45% higher with SST than with IPV. Vt was also increased with IPV, albeit not significantly because of a large variability.

There was no significant relationship between RF and IPD for both devices. By contrast, we found a significant correlation between RF and PI for SST (r = 0.65, p < 0.05) but not for IPV (Fig 3). There was no significant training effect between the subjects starting with the SST or the IPV in terms of WBD, IPD, or PI.

We normalized the results for RF (Table 4) because this parameter showed a significant difference between the two groups. Normalized PI was significantly higher for IPV (p = 0.007) but IPD showed no difference (p = 0.882). WBD remained significantly higher with IPV (p = 0.005).

### Gravimetric Measurements

The emitted weight was comparable with the two devices (p > 0.05), but the RW in the collector was significantly higher with the SST (1.58 ± 0.44 g) than with the IPV (1.13 ± 0.40 g, p = 0.028). Accordingly, residual radioactivity measured in the

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### Table 2—Pattern of Breathing for the Two Groups During Nebulization

<table>
<thead>
<tr>
<th>Variables</th>
<th>VE, L/min</th>
<th>RF, min</th>
<th>Vt,* L</th>
<th>Ti, s</th>
<th>Ti/Total Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SST</td>
<td>IPV</td>
<td>SST</td>
<td>IPV</td>
<td>SST</td>
</tr>
<tr>
<td>Mean</td>
<td>12.02</td>
<td>11.11</td>
<td>14.61</td>
<td>10.09</td>
<td>0.85</td>
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<tr>
<td>SD</td>
<td>4.53</td>
<td>4.25</td>
<td>4.13</td>
<td>3.39</td>
<td>0.34</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>0.38</td>
<td>0.38</td>
<td>0.26</td>
<td>0.34</td>
<td>0.40</td>
</tr>
<tr>
<td>p Value</td>
<td>0.568</td>
<td>0.0021</td>
<td>0.090</td>
<td>0.396</td>
<td>0.261</td>
</tr>
</tbody>
</table>

*Body temperature and pressure, saturated.
†Indicates significance.

### Table 3—Comparison of SST and IPV in Terms of Radioactivity Deposition Parameters and PI

<table>
<thead>
<tr>
<th>Variables</th>
<th>WBD, % ID</th>
<th>IPD, % ID</th>
<th>IPD/WBD Ratio</th>
<th>CD, μCi/100 Pixels</th>
<th>PD, μCi/100 Pixels</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SST</td>
<td>IPV</td>
<td>SST</td>
<td>IPV</td>
<td>SST</td>
<td>IPV</td>
</tr>
<tr>
<td>Mean</td>
<td>9.31</td>
<td>15.63</td>
<td>4.2</td>
<td>2.49</td>
<td>0.46</td>
<td>0.17</td>
</tr>
<tr>
<td>SD</td>
<td>1.57</td>
<td>4.24</td>
<td>1.2</td>
<td>2.59</td>
<td>0.15</td>
<td>0.18</td>
</tr>
<tr>
<td>Coefficient of variation, %</td>
<td>17</td>
<td>27</td>
<td>35</td>
<td>104</td>
<td>0.106</td>
<td>0.106</td>
</tr>
<tr>
<td>p value</td>
<td>0.002*</td>
<td>0.0006</td>
<td>0.003*</td>
<td>0.185</td>
<td>0.528</td>
<td>0.287</td>
</tr>
</tbody>
</table>

*Indicates significance.
collector, dead space, and filter was higher with SST than IPV (11.98 ± 2.11 mCi vs 8.08 ± 1.14 mCi, p < 0.001). There was a significant correlation between the residual radioactivity and RW with SST (r = 0.85 p < 0.01) but not with IPV (r = 0.03).

DISCUSSION

We have found that nebulization combined with IPV resulted in a higher WBD than SST. This was due to a higher extrapulmonary deposition with the IPV. This device delivered intrapulmonary aerosols irregularly in a group of naive healthy subjects. Although in vitro testings present some limitations and may give an overestimation of the lung deposition measured in vivo, it remains nevertheless an acceptable way to compare two methods in a standardized protocol. FPF was small, and particle size distribution was theoretically less favorable for IPD with IPV than with SST. The aerodynamic data of the SideStream device reported here are consistent with the literature (FPF, 67.5% vs 71.9%; MMAD, 1.89 μm vs 2.1 μm). Then we postulated the validity of the comparison of the aerodynamic characteristics (FPF, ED, and MMAD) of the two devices.

The design of the dead space of IPV might have explained part of the differences in aerodynamic properties, because the larger particles could have remained in the instrumental dead space before reaching the impactor. However, the residual radioactivity measured in the devices, including their dead space, was significantly less with IPV than with SST, ruling out this hypothesis.

Classically, using a jet nebulizer, <10% of a nebulized drug deposits in the lung. Lung deposition depends on particle size distribution, which is under the influence of air flow, filling volume, drug solution, and ambient temperature. In this study, those parameters were kept constant to avoid variability. We used a fixed driving pressure of compressed air for both nebulizers that corresponded to the minimal pressure recommended by the IPV manufacturer (3.5 bars).

The pattern of breathing is also important, as lung deposition depends principally on inspiration. In our study, the T1 was comparable in the two groups, and thus the potential influence of the inspiration on deposition was minimized. As shown by previous reports, the mouthpiece may influence the results. We therefore used an identical mouthpiece with the two devices. The same nebulizers were reused during all measurements. Because each subject was his own control, we avoided the effect of anatomical and mechanical variability as confounding factors. The disease can modify the pattern of breathing, but the subjects were all healthy volunteers.

We did not calculate the dose retained in the body from the difference between the weight of the ID and the RW. Indeed, we had to take into account the dead space of the devices, which were different (36 mL with SST and 76 mL with IPV), and the loss of solvent during nebulization by the concomitant process of evaporation. Scintigraphy of the dead space and the collector enabled us to measure the

<table>
<thead>
<tr>
<th>Variables</th>
<th>WBD, % ID/RF</th>
<th>IPD, % ID/RF</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SST</td>
<td>0.69</td>
<td>0.31</td>
<td>0.026</td>
</tr>
<tr>
<td>IPV</td>
<td>1.73</td>
<td>0.30</td>
<td>0.045</td>
</tr>
<tr>
<td>SST</td>
<td>0.22</td>
<td>0.14</td>
<td>0.013</td>
</tr>
<tr>
<td>IPV</td>
<td>0.87</td>
<td>0.33</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*p Indicates significance.

Figure 2. Individual data of IPD obtained with SST and IPV showing the difference of interindividual variability.

Figure 3. Relationship between PI and RF for both devices.

Table 4—Comparison of SST and IPV Radioactivity Deposition Parameters and PI After Normalization for RF
Besides the different aerodynamic properties and the pattern of breathing, percussions could also explain the observed lung deposition. They could slow down inhaled small particles in the respiratory tract and could have the same effect as a postinspiratory pause. The superimposed percussions of IPV could also enhance turbulence in the carrier gas stream. These turbulences could increase the coalescence of aerosolized particles, increasing their size and promoting their impaction in the upper airway.

Our subjects were not trained before the study. Contrary to a classic nebulizer, the IPV could be rather surprising for a naive subject, and could influence the breathing pattern. But we did not find any difference between the SST-first group and the IPV-first group. However, to verify this hypothesis, a similar study with a previous training or with a fixed RF could be useful.

In conclusion, we have found large differences in the aerodynamic properties of IPV and SST nebulizers. The Percussionaire IPV device presents a potential interesting property in terms of a higher PI when normalized for RF, but our study demonstrates that IPV cannot replace a standard nebulizer if a pharmacologic agent must be delivered to the lung. However, our results cannot be extrapolated to patients with COPD or cystic fibrosis. These diseases are characterized by totally different respiratory mechanics and respiratory muscle functions. Because of the high cost of IPV and the large interindividual variability of its IPD, we cannot recommend this device as a first choice for inhaled drug therapy.

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