Droplets Produced by Medical Nebulizers*  
Some Factors Affecting Their Size and Solute Concentration  

Paul R. Phipps, B. Pharm.; and Igor Gonda, B.Sc., Ph.D.

The effect of nebulizer solution temperature and dilution air humidity on the size and solute concentration of aqueous aerosol droplets was studied. Four combinations of jet-nebulizers with air compressors or oxygen sources and one ultrasonic nebulizer were tested. The temperature to which the nebulizer solution of each system fell during generation was measured. The nebulizers were then kept at set temperatures, generated aerosols collected and either droplet size or solute concentration measured. The droplet solute concentration was found to increase. The droplet size decreased along with the droplet solute concentration increase. The ultrasonic nebulizer also was tested: its high output made the concentration of the solution in the droplets much more stable. However, the proportion of droplets depositing in the tubing and valves changed markedly with aerosol flow rate. The potential for large changes in droplet solute concentration, droplet size and output during nebulization should be considered in therapeutic and diagnostic applications of nebulized aerosols.

(Chest 1990; 97: 1327-32)

Nebulized aerosols are used extensively in therapy and diagnosis of respiratory diseases. This mode of administration also has proven useful in ventilation imaging as an aid in the diagnosis of pulmonary embolism. In fact, it is the ease with which solutions or suspensions of therapeutic and diagnostic agents can be nebulized which makes the use of this type of aerosol so widespread.

The importance of the characterization of nebulizer systems for clinical applications has been recognized by a number of authors. The clinical efficacy of nebulized aerosol treatment depends primarily on the amount of active substance depositing at various sites in the respiratory tract, which in turn is dependent on the droplet size and output from the nebulizer as well as patient parameters such as inspiratory flow rate, respiratory tract morphology and disease state of the lungs. The wide variation in performance of nebulizer delivery systems makes it likely that a failure in therapy often may be explained by poor aerosol delivery rather than by a poor response to the drug therapy.

It is well known that the nebulizer solution cools and concentrates during nebulization, and it has been reported that the humidity of the air inhaled along with the aerosol affects droplet characteristics. We wished to look directly at the effects of nebulizer cooling and dilution air humidity on (a) the size and (b) the concentration of solutes in the aerosol droplets generated by a number of different medical nebulizer systems.

METHODS

The following products were assessed: Cadema nebulizer (Cadema Medical Products Inc., Middletown, NY) with compressed oxygen at 8 L/min; Up-Draft nebulizer (Hudson Up-Draft Oxygen Therapy Sales Co., Temecula, CA) with compressed oxygen at 8 L/min; Up-Draft with Flatus Mk.V air compressor (Maymed, Anees- theoretic Supplies Pty, Ltd, Sydney, Australia)—this system is equivalent to Tote-A-Neb, Hospital Inc., Lindenhurst, NY (private communication, Laura Martinzzi); Up-Draft with Aerosol-One air compressor (Medical Industries America, Des Moines, IA); Mist-O2-Gen ultrasonic nebulizer (Model EN143A, Timeter, PA). These systems are representative of equipment used in the diagnosis of pulmonary embolism (Cadema nebulizer), non-isotonic challenge testing in asthma diagnosis (Mist-O2-Gen) or for drug delivery in the treatment of various respiratory diseases (Up-Draft nebulizer, Up-Draft with Flatus Mk.V air compressor and Up-Draft with Aerosol-One air compressor). The flow rate produced by the Flatus Mk.V and the Aerosol-One air compressors through the Up-Draft nebulizer containing 5 ml normal saline solution was found to be 6.3 and 5.0 L/min, respectively as measured by rotameter (Platon Ltd, Basingstoke, Harts, UK).

The change in temperature of each system was measured with an esophageal theremistor probe (YSI series 400, temperature recorder model 46TUC, Yellow Springs Instruments Co. Inc, Yellow Springs, OH) placed in the nebulizer solution, and the temperature was recorded at set times during aerosol generation until the temperature had reached a steady value (Tc). The initial volume of solution in the nebulizer was 5 ml (jet nebulizers) or 200 ml (ultrasonic nebulizer). The ambient temperatures varied between 23 and 24°C.

The concentration of sodium chloride in the aerosol droplets generated by the jet nebulizers was measured for different, constant, nebulizer solution temperatures. The lowest temperature used for each nebulizer was approximately the value reached after running the nebulizer without heating to a steady temperature Tc, determined as described previously. The nebulizer bowl, containing 5 ml normal saline solution, was cooled to a nominated temperature by immersion in a cold water bath. The aerosol was then generated and the nebulizer solution temperature kept at the nominated value by immersion in a warm water bath. The temperature of the nebulizer solution was monitored with the miniature esophageal theremistor probe. The temperature was controlled to ± 0.3 degrees during a generation time of 10 to 25 min and generated volume of 1 to 3 ml. The aerosol was passed via a short length of tubing (30 cm) through the last two stages of a cascade impactor (DCI6, Delron, Columbus, OH) and collected in a small container of similar dimensions to a cascade impactor slide. The flow through the impactor stages was 12.5 L/min, and the dilution air necessary to supplement the flow through the nebulizer was supplied either at ambient temperature (23 to 24°C) and humidity (63 to 75 percent) or fully humidified at ambient temperature via a Douglas bag. After collection of the aerosol droplets, the containers were re-weighed and droplets diluted with normal saline solution if their volume was...
The solute concentration of the aerosol droplets generated by the Mist-O₂-Gen nebulizer was measured by the previously noted methods, except that aerosol droplets were collected in 30-s samples at set times during continuous nebulization.

The output of nebulizer solution from the jet nebulizer systems was measured by weighing after generation for different periods of time, whereas for the ultrasonic nebulizer it was measured continuously. The output from the mouthpiece with a two-way valve (model 2700, Hans Rudolf Inc, Kansas City, MO) in line, also was tested at various flow rates.

The droplet size of the jet nebulizers at a number of operating solution temperatures was measured in separate experiments. The nebulizer was cooled to a set temperature and aerosol generated as in the concentration measurements for 2 min. The nebulizer solution contained approximately 100 MBq/ml of ⁹⁹mTcO₄⁻ in normal solution. The aerosol was sized by cascade impaction as described previously.

The size of the droplets produced by the ultrasonic nebulizer was measured with and without the two-way valve in line, using the same methods as previously described.

**RESULTS**

The fall in temperature with time of nebulization for each of the nebulizer-generator systems is shown in Figure 1. For the jet nebulizers, the temperature falls to a steady value $T_s$ which is 5 to 6°C below the ambient temperature at the lower flow rates of the air compressors, and 11 to 15°C at 8 L/min flow rate from a gas cylinder. Most of this temperature change occurs in the first 4 min of aerosol generation. By contrast, the ultrasonic nebulizer increases in temperature by approximately 18°C and over a longer period of time (approximately 20 min [Fig 2]).

The total outputs of the jet nebulizer systems are plotted against generation time in Figure 3. The total output fell during nebulization for all of the jet nebulizer systems tested. The magnitude of the fall was similar for both the Cadema and Up-Draft with reductions in total output of approximately 45 to 65 mg/min for temperature falls of 11 to 15°C (over 6 min of generation).

The reduction in output with generation time for the two air compressor-driven systems was lower; approximately 15 and 27 mg/min for the Aerosol-One and the Flatus, respectively, after a temperature fall of 5 to 7°C during 6 min of generation.

The ultrasonic nebulizer solution output is much larger than that of the jet nebulizers. The output vs time graph is shown in Figure 4. The output without tubing or valve was found to be approximately constant at 4.8 ml/min over the time period tested. The output through the two-way valve was found to be greatly reduced and was dependent on the flow rate of the aerosol through it (Fig 4).

The change in concentration of solution in the nebulized aerosol droplets can be seen for each nebulizer system in Figure 5. The solute concentration contained in the aerosol produced by the jet nebulizers increases significantly with the fall in nebulizer temperature and with the reduction in the dilution air humidity. At the steady temperature $T_s$ the droplet solution reaches 5.8 and 9.2 percent sodium chloride for the Cadema and Up-Draft nebulizers, respectively.
using 8 L/min of compressed oxygen as the generation gas. The Flatus/Up-Draft system reaches a little less than 5 percent and the Aerosol-One/Up-Draft reaches approximately 36 percent saline solution after the same generation time.

The effect of dilution air humidity alone on the droplet solute concentration with the nebulizer at room temperature for each jet nebulizer system can be seen in Table 1.

The droplet solute concentration reaches 1.1 to 1.5 percent with saturated dilution air at ambient temperature. Ambient dilution air with relative humidity of 65 to 75 percent at ambient temperature increased the droplet solute concentration to 1.86 and 2.46 percent for the Up-Draft and Cadema, respectively, generated with compressed oxygen. The effect with the air compressors was greater with the Up-Draft, the Flatus compressor producing a concentration of 3.45 percent and the Aerosol-One, 13.5 percent.

The droplet solution concentration generated from the ultrasonic nebulizer changes very little with time. The maximum effect is seen at the start of generation (0.93 percent saline from 0.9 percent initial value), and as nebulization progresses, the concentration returns toward isotonic, reaching it after approximately 13 min.

The droplet size distributions of the jet-nebulizer

![Graph of nebulizer output vs generation time for the four jet-nebulizer systems: Up-Draft/Aerosol-One (squares), Up-Draft/Flatus (diamonds), Cadema/compressed oxygen (circles) and Up-Draft/compressed oxygen (triangles).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21614/)

![Graph of output vs generation time for the Mist-O2-Gen ultrasonic nebulizer: no tubing or valve (circles), Bennett tubing and valve (model 2700, Hans Rudolf Inc., Kansas City, MO) attached; 10 L/min flow rate (triangles), 20 L/min (squares), 30 L/min (diamonds) and 50 L/min (crosses).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21614/)

![Graph of droplet solute concentration (solid symbols, % W/V) and mass median aerodynamic diameter (open symbols, μm) vs nebulizer solution temperature for the four jet-nebulizer systems: Up-Draft/Aerosol-One (squares), Up-Draft/Flatus (diamonds), Cadema/compressed oxygen (circles) and Up-Draft/compressed oxygen (triangles). Note that the ambient temperature is the highest value on each graph.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21614/)
systems fall with reduced dilution air humidity and with the falling temperature in the nebulizer, in parallel with the increase in solute concentration in the aerosol droplets. Figure 5 shows the effect of nebulizer temperature on aerosol droplet size. The effect of temperature change is greater when compressed oxygen is used at 8 L/min, the droplet size falling by 33 and 36 percent of the size at ambient temperature for the Cadema and Up-Draft, respectively. With Flatus and Aerosol-One generation, the size change is smaller (19 and 11 percent fall from ambient temperature value, respectively). Conversely, the effect of dilution air humidity at ambient temperature is greater with the air compressor generation than with the compressed oxygen (Table 2). The changes that would be seen in practice with unheated nebulizers are shown in Table 3.

The ultrasonic nebulizer droplet size changes when a two-way valve is included in line but is not affected by changes in relative humidity of the dilution air (Table 4).

**DISCUSSION**

The fact that the nebulizer solution temperature of jet nebulizers falls during generation has been well documented. The heat loss is due to the evaporation of the nebulizer solution to saturate the gas used to generate the aerosol and some cooling due to adiabatic expansion of the generating gas. This evaporation also leads to an increase in solute concentration of the nebulizer solution. The gas from a compressed gas cylinder contains no water vapor, while an air compressor supplies air of ambient humidity. Less vapor is therefore required from the nebulizer solution to saturate the air from an air compressor and heat loss is therefore reduced. Of the energy imparted to the solution of an ultrasonic nebulizer, however, part is used to overcome the surface tension to disperse solution droplets and part to heat the solution itself. The nebulizer solution therefore warms during generation (Fig 2).

The initial output from the nebulizer depends on the type, the flow rate and the saturation of the generating gas. The change in jet nebulizer output measured during generation depends almost solely on the temperature of the nebulizer solution. The nebulizer solution provides both the solution output and the output of vapor necessary to saturate the generating gas with water vapor at the nebulizer temperature. Therefore, the amount of vapor carried by the generation gas decreases as the temperature falls and the reduction in total output mirrors these changes.

As the temperature of the ultrasonic nebulizer solution increases, the extra water needed to saturate the air is likely to come from the dense aerosol cloud within the nebulizer chamber. The output therefore is

**Table 1—Effect of Dilution Air Humidity on Droplet Solute Concentration at Ambient Temperature**

<table>
<thead>
<tr>
<th>Nebulizer/Generator System</th>
<th>100% Relative Solute Humidity</th>
<th>65-75% Relative Solute Humidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-Draft/Aerosol-One</td>
<td>1.5 ± 0.3</td>
<td>13.5 ± 1.8</td>
</tr>
<tr>
<td>Up-Draft/Flatus</td>
<td>1.1 ± 0.1</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>Up-Draft/Compressed O₂</td>
<td>1.3 ± 0.2</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Cadema/Compressed O₂</td>
<td>1.5 ± 0.2</td>
<td>2.5 ± 0.2</td>
</tr>
</tbody>
</table>

*Results expressed as mean ± range (number of determinations = 2 or 3).

**Table 2—Effect of Dilution Air Humidity on Droplet Size at Ambient Temperature**

<table>
<thead>
<tr>
<th>Nebulizer/Generator System</th>
<th>100% Relative Droplet Size</th>
<th>65-75% Relative Droplet Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-Draft/Aerosol-One</td>
<td>4.2 ± 0.3 (1.5)</td>
<td>2.7 ± 0.3 (1.5)</td>
</tr>
<tr>
<td>Up-Draft/Flatus</td>
<td>4.1 ± 0.2 (1.6)</td>
<td>3.1 ± 0.3 (1.6)</td>
</tr>
<tr>
<td>Up-Draft/Compressed O₂</td>
<td>4.2 ± 0.1 (1.4)</td>
<td>3.9 ± 0.2 (1.5)</td>
</tr>
<tr>
<td>Cadema/Compressed O₂</td>
<td>2.7 ± 0.1 (1.4)</td>
<td>2.4 ± 0.2 (1.4)</td>
</tr>
</tbody>
</table>

*Results expressed as mean ± range (number of determinations = 2 or 3).

**Table 3—Change of Concentration and Droplet Size Between Ambient and Steady State Temperature, T, (65-75% Relative Humidity Dilution Air)**

<table>
<thead>
<tr>
<th>Nebulizer/Generator System</th>
<th>Droplet Size, % Fall</th>
<th>Droplet Concentration, % Rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-Draft/Aerosol-One</td>
<td>11.1</td>
<td>170</td>
</tr>
<tr>
<td>Up-Draft/Flatus</td>
<td>5.2</td>
<td>39.1</td>
</tr>
<tr>
<td>Up-Draft/Compressed O₂</td>
<td>35.9</td>
<td>392</td>
</tr>
<tr>
<td>Cadema/Compressed O₂</td>
<td>2.4</td>
<td>244</td>
</tr>
</tbody>
</table>

*Calculated as:

\[ \left( \frac{X(T_{1}) - X(T_{2})}{X(T_{2})} \right) \times 100 \]

where X = droplet size or droplet solution concentration at ambient temperature T₁ or steady state temperature T₂ (lowest steady temperature reached by each system).

**Table 4—Size of Droplets Generated by the Mist-O₂-Gen Ultrasonic Nebulizer**

<table>
<thead>
<tr>
<th>Ambient Temperature, °C</th>
<th>Relative Humidity, %</th>
<th>Mouthpiece and Valve</th>
<th>Mass Median Aerodynamic Diameter (μm)</th>
<th>Geometric Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.5 ± 0.3</td>
<td>99.0 ± 1</td>
<td>Yes</td>
<td>3.6 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>19.0 ± 0.3</td>
<td>53.1 ± 1</td>
<td>Yes</td>
<td>3.5 ± 0.2</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>19.0 ± 0.3</td>
<td>53.5 ± 1</td>
<td>No</td>
<td>5.7 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
</tbody>
</table>

*Results expressed as mean ± range (number of determinations = 2 or 3).
not likely to change as the nebulizer temperature rises as suggested by the results (Fig 4). The two-way valve situated before the mouthpiece of the ultrasonic nebulizer filters a high proportion of the larger droplets from the aerosol stream. The effect therefore is to reduce the output and mass median aerodynamic diameter of the droplets. This effect depends on the flow rate of the aerosol stream and hence the velocity of the droplets. There is an optimum flow rate, however, due to opposing effects: At the lower flow rate, the droplets tend to settle into the nebulizer solution or within the tubing and the output is reduced. At the higher flow rates, the droplets are more likely to impact within the tubing and on the valve. The optimum flow rate for this system was found to be approximately 20 L/min (Fig 4).

Although it is known that the concentration of the solution in the jet nebulizer bowl increases with generation due to the release of vapor in addition to the liquid droplets,14,15 the changes in solution concentration in the droplets measured in the experiments reported here are generally much greater. This is because the cold aerosol droplets generated from the jet nebulizer solution will evaporate a substantial amount of water as they rapidly warm up to room temperature. Therefore, the concentration of solute in the droplets increases to a value determined by the difference between the ambient temperature and the temperature of the nebulizer solution and to a lesser extent due to the gradual increase of the concentration in the nebulizer.

The nebulizer solution equilibrates to a lower steady temperature $T_s$ when the dry gas from a compressed gas cylinder is used to generate the aerosol, compared with the air compressors. The droplet solute concentration thus increases to a greater extent (relative to the value at ambient temperature) as a result (Table 3).

The ambient air inhaled along with the aerosol that makes up the inspiratory flow is likely to have a lower relative humidity than that corresponding to the nebulizer solution; therefore, it has the effect of drying the aerosol droplets as it mixes before inhalation.7 This concentrating effect is quite marked, especially when the generation flow and the output of solution from the nebulizer is low. The consequence of the low output is that there is only a small volume of water present in the droplets to resaturate the aerosol stream (see results for Up-Draft/Flatus and especially the Up-Draft/Aerosol-One systems, Fig 5 and Table 1). The ambient relative humidity was comparatively high during these experiments (65 to 75 percent), and a lower ambient relative humidity, such as that found in air-conditioned rooms, would be expected to greatly enhance these effects.

The ultrasonic nebulizer has a higher output and larger droplet size, so more water is available for saturation of the dilution air and the concentration change of the droplet solution hence is much smaller than that of the jet nebulizers. The droplet concentration therefore starts off greater than isotonic, but as the tubing becomes saturated, this is able to supply the vapor necessary to saturate the dilution air. Although the nebulizer solution temperature is increasing, the droplets do not become hypotonic due to water vapor condensing on them as the aerosol stream cools; rather, the excess vapor will condense on the walls of the conducting tubing.19

Schoeffel et al20 found that small amounts of hypertonic (3.6 percent sodium chloride) aerosol caused bronchoconstriction in asthmatic subjects. Lewis and Tattersfield21,22 found that a number of asthmatic subjects had bronchoconstriction after inhaling a jet nebulized aerosol of isotonic saline solution, but not to an aerosol generated by a nebulizer heated to 37°C. This was explained in terms of a reduction in airway cooling by the warm aerosol, but it may have been due to a reduction in the concentrating effects that the nebulizer temperature fall imparted on the droplets. The possibility that initially isotonic, or even hypotonic, solutions may produce hypertonic aerosol droplets should therefore be accounted for when delivering therapeutic aerosols to patients with hyperreactive airways.

The necessity for nebulization to be reproducible for bronchial challenge testing, has led to some careful characterization of nebulizers;23-26 the nebulizer temperature change may, however, add to the variability in dose and site of delivery of challenge agents.

The size of the aerosol droplets falls with generation time in conjunction with the increase in concentration. The magnitude of this is variable but it is likely to affect the deposition pattern of aerosol within the lungs.8 Large differences in regional deposition as measured by “penetration index” on tomographic slices have been found in normal subjects inhaling aerosols with mass median aerodynamic diameters of 2.6 and 5.5 μm.28 The smaller droplet size showed a much higher relative deposition in the small airways and lung parenchyma. The change in droplet size, depending on the time since the start of generation and the humidity of dilution air (for example, from an initial droplet size of 4.2 μm with 100 percent relative humidity dilution air to 2.4 μm after the equivalent of 4 min generation for the Up-Draft/Aerosol-One system) may be important in therapeutic, diagnostic or experimental applications when reproducibility of aerosol deposition or clinical response is important.27,28 It is, of course, very likely that some subsequent adjustment of droplet size will take place in the respiratory tract.29

The Flatus compressor produces a droplet size
similar to the Aerosol-One, with the Up-Draft nebulizer, but with the higher flow rate of the Flatus, a smaller droplet size may be expected. The discrepancy may be due to the fact that the Aerosol-One droplets are evaporating to a greater extent than with the Flatus at ambient temperature and saturated dilution air (1.5 and 1.14 percent, respectively [Table 1]). The lower output of the Aerosol-One/Up-Draft system is likely to be responsible for this.

The effect of the increase in temperature of the ultrasonic nebulizer solution on the droplet solute concentration is small. Also, the effect of dilution air humidity on the droplet size (and presumably the droplet solute concentration) is small due to the much higher output from the Mist-O2-Gen nebulizer.

The larger droplet size generated by the ultrasonic nebulizer means that they are more easily deposited on the tubing and valves within the system.

To reduce the evaporation effects in jet nebulizers, the generating gas and dilution air should be saturated with water vapor at ambient temperature and the nebulizer solution should be maintained at ambient temperature. As these changes may affect the outcome of therapy, clinical studies to measure any alterations in response should be carried out.

The higher output and droplet size occurring with the Mist-O2-Gen ultrasonic nebulizer makes the droplet size and solute concentration less susceptible to large changes during nebulization. However, the presence of tortuous tubing, valves and high inhalation flow rate will cause a large reduction in the output available to the patient because the large droplets will deposit in the apparatus.

ACKNOWLEDGMENTS: The authors would like to thank Mr. Ian Spiers for the preliminary data on the Mist-O2-Gen ultrasonic nebulizer, colleagues in the Departments of Thoracic and Nuclear Medicine at the Royal Prince Alfred Hospital Camperdown for assistance and encouragement, and the Asthma Foundation of New South Wales for financial support.

REFERENCES
2 Newman SP, Pellow PGD, Clarke SW. Flow pressure characteristics of compressors used for inhalation therapy. Eur J Respir Dis 1987; 71:122-36
4 Matthys H, Kohler D. Pulmonary deposition of aerosols by different mechanical devices. Respiration 1985; 49:289-76
10 Hulwite JS, Corvoj JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987; 136:1445-49
11 Newman SP, Pellow PGD, Clarke SW. Drop-sizes from medical atomizers (nebulizers) for drug solutions with different viscosities and surface tensions. Atomisation Spray Technol 1987; 3:1-11
15 Mercer TT, Tillery MI, Chow HY. Operating characteristics of some compressed air nebulizers. Am Ind Hyg Assoc J 1968; 29:66-78
19 Mercer TT, Goddard RF, Flores RL. Output characteristics of three ultrasonic nebulizers. Ann Allergy 1968; 26:18-27
26 Phipps PR, Gonda I, Bailey DL, Borham P, Bautovich G, Anderson SD. Comparisons of planar and tomographic gamma scintigraphy to measure the penetration index of inhaled aerosols. Am Rev Respir Dis 1989; 139:1516-33
27 Clay MM, Clarke SW. Effects of nebulized aerosol size on lung deposition in patients with mild asthma. Thorax 1987; 42:150-94