

Measuring Nebulizer Output*

Aerosol Production vs Gravimetric Analysis

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Study objectives: The function of jet nebulizers has been measured traditionally by gravimetric methods, *ie*, by weighing nebulizers before and after nebulization. Newer techniques measure aerosol output directly by analyzing aerosolized drug or tracer, *ie*, radioactive ^{99m}Tc . Because of evaporation, the equivalence of these methods is uncertain. The aim of this study was to determine if the gravimetric method is an accurate measure of aerosol production under different conditions of aerosol generation (*ie*, nebulizer type, flow rate, pressure, volume fill, and concentration of solution used to nebulize a drug).

Methods: In the first phase of the study, we measured the aerosol output of nine commercially available jet nebulizers (AvaNeb; Up-Draft-Hudson RCI; Cirrus-Intersurgical Inc; DeVilbiss 646-DeVilbiss; Powermist-Hospitak, Inc; Respirgard II-Marquest Medical Products; Seamless-Seamless/Dart Respiratory; Salter; Salter Labs; AirLife-Baxter Health Care) run under commonly used conditions (2.5 mL volume fill, 2.0 mL normal saline solvent, 0.5 mL albuterol, flow of 6 L/min, and pressures averaging 15.0 ± 2.3 [mean \pm SD] pounds per square inch [on the] gauge [psig] provided by a DeVilbiss PulmoAide compressor) with simultaneously measured gravimetrics and filtered radioactivity. Each nebulizer was run to dryness with data acquired every 2 min. The change in the weight of the nebulizer and radioactivity captured on the filter were expressed as percentages of the total in the nebulizer solution. In the second phase of the study, the experiments were repeated using the same nebulizers with a volume fill of 5 mL (diluted to half normal saline solution plus albuterol), flow of 10 L/min, and pressures of 35.6 ± 8.8 psig.

Results: The cumulative (sum of all 2-min runs) weight loss for each individual nebulizer ranged from 25.00 to 64.55% and cumulative aerosol captured varied from 12.63 to 38.76%. While different, the weight loss and aerosol captured were closely correlated ($y = -0.62 + 0.62x$; $r = 0.961$, $p < 0.0001$). Changing volume fill and concentration of solvent did not affect this correlation ($p = 0.921$ and 0.373 , respectively). However, changing flow from 6 L/min to 10 L/min significantly ($p = 0.02$) affected the relationship ($y = -3.80 + 0.83x$; $r = 0.969$, $p < 0.001$).

Conclusions: When compared with direct methods such as filtering generated particles, the gravimetric method of assessing nebulizer function overestimates aerosol output by 1.8 ± 0.18 times, presumably because of the loss of solvent during nebulization. However, the relationship between methods is predictable and appears unaffected by changing the type of nebulizer, volume fill, and concentration of solvent. Changes in nebulizer flow and pressure significantly affected the correlation. Gravimetric methods can be used as simple and convenient screening techniques for comparing jet nebulizers under a wide range of experimental conditions.

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Abbreviations: ANCOVA=analysis of covariance; psig=pounds per square inch (on the) gauge

The increasing number of jet nebulizers available commercially and the recognition that their function may differ¹⁻³ has led to comparative studies of aerosol production. For example, Loffert et al⁴ recently compared 17 commercially available jet

nebulizers. Their data and data from previous studies⁵⁻⁷ convey a common message, that the function of jet nebulizers varies considerably between brands. However, comparison between studies is hampered by technical differences and possible uncertainties relating to techniques estimating production of aerosol. The two most common methods of measuring nebulizer output are the "gravimetric method" (*ie*, weighing the nebulizer before and after nebulization and assuming that weight loss represents the aerosol produced) and "direct measurement of aerosol" which uses a radioactive tracer or drug assay⁸⁻¹⁰ to measure the actual aerosol produced. Most studies,

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including that of Loffert et al,⁴ used the gravimetric method. It is known that the gravimetric method overestimates the “nebulizer output” as compared with direct measurement of aerosol, due to concomitant loss of nebulizer solution by evaporation.¹⁰⁻¹² What remains unclear, however, is whether there is a predictable relationship between methods and if so, how is it affected by different conditions used to nebulize drugs. To our knowledge, there have been no studies designed to answer this question. If the relationship among aerosol produced, weight change, and evaporative loss varies between devices, then gravimetric comparison may not be useful. The purpose of this study was to measure simultaneously the aerosol produced and gravimetric changes for a variety of nebulizers under various experimental conditions of flow and driving pressure, volume fill, and the concentration of solvent used.

MATERIALS AND METHODS

Nebulizer Selection

Nine commercially available jet nebulizers were studied utilizing a modified protocol outlined by Loffert et al.⁴ These nebulizers are as follows:

- (1) Airlife (Baxter Health Care Corp; Valencia, Calif);
- (2) Respigard II (Marquest Medical Products; Englewood, Colo);
- (3) DeVilbiss 646 (DeVilbiss; Somerset, Pa);
- (4) AvaNeb (Hudson RCI; Temecula, Calif);
- (5) Up-Draft (Hudson RCI; Temecula, Calif);
- (6) Cirrus (Intersurgical Inc; Liverpool, NY);
- (7) Powermist (Hospitak Inc; Farmingdale, NY);
- (8) Salter (Salter Labs, Arvin, Calif); and
- (9) Seamless (Seamless/Dart Respiratory; Wallingford, Conn).

During nebulization, compressor-driven systems attain a flow and pressure (upstream to the nebulizer orifice) that depend on the characteristics of the compressor and the resistance of the tubing and nebulizer orifice. To define these variables, we measured the pressure and flow upstream to the nebulizer orifice with a mechanical pressure gauge and flowmeter (Checkmate; Bourns Medical Systems Inc; Riverside, Calif). The compressor (DeVilbiss PulmoAide) provided a driving pressure of 10.5 to 19 (mean±SD; 15.0±2.3) pounds per square inch (on the) gauge (psig) at a flow of 5.5 to 7 (5.9±0.5) L/min, depending on the type of nebulizer (Table 1). To increase flow and pressure, another compressor (Aridyne 3500; Timeter Instrument Corp; Lancaster, Pa) was used that provided flows of 6 and 10 L/min at pressures ranging from 9.0 to 27.5 (mean 17.5±5.1) psig at 6 L/min and 18.5 to 51.0 (mean 35.6±8.8) psig at 10 L/min (Table 2). In addition to the increase in flow and pressure, the effects on aerosol production of the volume fill (2.5 and 5.0 mL) and concentration of saline solution (normal 0.9%, and 0.45%) were measured.

Experimental Technique

In the first stage of the protocol, single examples of each nebulizer were run under similar conditions to those used by

Table 1—Flow and Pressure Data for Jet Nebulizers Run by DeVilbiss PulmoAide Compressor

| Nebulizer | Flow, L/min | Pressure, psig |
|---------------|-------------|----------------|
| DeVilbiss 646 | 7.0 | 10.5 |
| Powermist | 6.0 | 16.0 |
| Cirrus | 6.0 | 15.0 |
| Respigard II | 5.5 | 16.0 |
| Airlife | 6.0 | 15.0 |
| Up-Draft | 5.0 | 19.0 |
| Seamless | 6.0 | 15.5 |
| Salter | 6.0 | 15.0 |
| AvaNeb | 6.0 | 13.0 |
| Mean±SD | 5.94±0.52 | 15.0±2.30 |

Loffert et al⁴ (*ie*, DeVilbiss PulmoAide compressor, 2.5 mL volume fill and normal saline solution diluent) at ambient conditions of temperature and relative humidity. The exit port of the nebulizer was connected to a low-resistance absolute filter that captured the aerosol particles (Fig 1). This technique is called “standing cloud” and is described elsewhere.¹³ Each nebulizer was weighed using an electronic analytical balance (FX-40; A&D Company Ltd; Tokyo; accuracy of 0.0001 g) when empty and when fully charged with 2.5 mL of solution (0.5 mL albuterol plus 2 mL normal saline solution and ^{99m}Tc). The nebulizer was subsequently weighed at 2-min intervals while being run to the end point. The filter was changed at 2-min intervals and radioactivity deposited on the filter was measured with a radioisotope calibrator (CRC-10R; Capintec; Montvale, NJ). Appropriate “decay time” corrections were applied for measuring radioactivity. Experiments performed in our laboratory have shown that the amount of radioactivity deposited on the filter follows a linear relationship of identity with the amount of albuterol aerosolized.¹⁴ Therefore, the radioactivity deposited on the filter was used as a direct measure of aerosolized albuterol. The loss in weight of the nebulizer and the radioactivity captured on the filter for every “2-min segment” of the “nebulizer run” were expressed as percentages of the original weight of nebulizer solution or the amount of total radioactivity placed in the nebulizer at the beginning of the experiment. A total of 51 pairs of data points, each representing a 2-min nebulizer run, were collected and analyzed. Nebulization was considered to be complete when the nebulizer became “silent” and no visible aerosol was generated. Following the initial set of experiments

Table 2—Pressure Data for Jet Nebulizers Run With Aridyne Compressor at Different Flows*

| Nebulizer | Pressure at 6 L/min (psig) | Pressure at 10 L/min (psig) |
|---------------|----------------------------|-----------------------------|
| Devilbiss 646 | 9.0 | 18.5 |
| Powermist | 17.0 | 35.0 |
| Cirrus | 17.0 | 35.0 |
| Respigard II | 21.0 | 42.5 |
| Airlife | 17.5 | 36.0 |
| Up-Draft | 27.5 | 51.0 |
| Seamless | 19.0 | 38.5 |
| Salter | 16.5 | 34.5 |
| AvaNeb | 13.0 | 30.0 |
| Mean±SD | 17.50±5.10 | 35.6±8.7 |

*For this device, flows are set by rotameter and pressures were measured upstream to nebulizer orifice.

COMPRESSOR &
AIR FLOWMETER

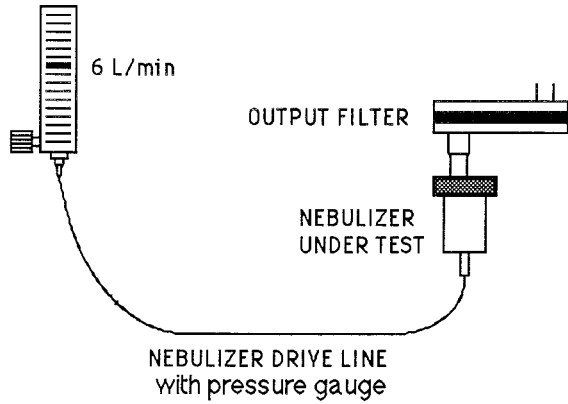


FIGURE 1. The "standing cloud" technique. Aerosol particles leaving the nebulizer were captured by a filter. Drug activity on the filter was determined by using a radioactive tracer or drug assay.

that represented the conditions of Loffert et al,⁴ the variables listed above were changed and an additional 83 data points were collected.

Statistical Analysis

Linear regression by the least squares method was used to analyze the relationship between the two methods of measuring nebulizer output. The slopes of the regression lines were compared using one-factor analysis of covariance (ANCOVA). A p value of <0.05 was considered significant. All statistical analyses were done using SuperANOVA (Abacus Concepts; Berkley, Calif).

RESULTS

Flow and pressure data for different nebulizer/compressor combinations are listed in Tables 1 and

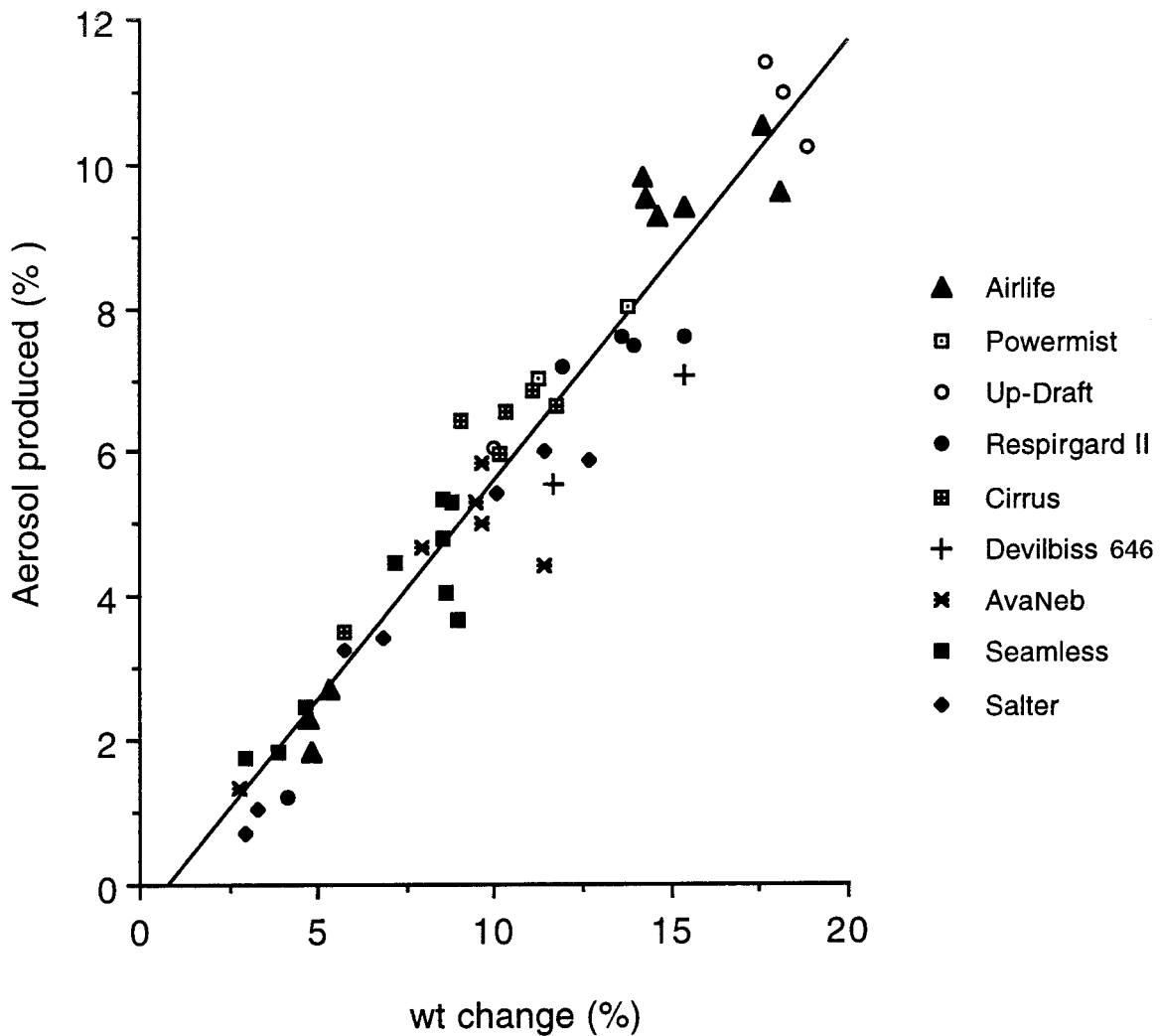


FIGURE 2. "Wt change (%)" vs "aerosol produced (%)" for nine jet nebulizers; different brands are represented by different symbols. Each data point represents a 2-min run. Those nebulizers with more points had longer running times. Linear regression is represented as $y = -0.62 + 0.62x$; $r = 0.961$; $p < 0.0001$.

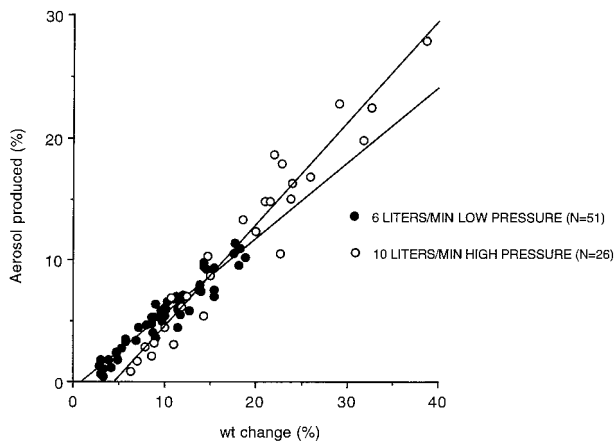


FIGURE 3. Effect of flow (and pressure) on the relationship between weight (wt) change (%) and aerosol produced (%); the 10 L/min flow points are represented by $y = -3.80 + 0.83x$; $r = 0.969$; $p < 0.0001$. The change in relationship was significant by ANCOVA ($p = 0.022$).

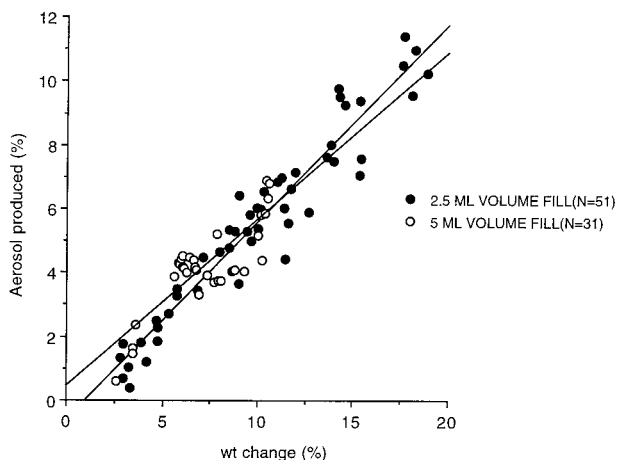


FIGURE 4. The effect of volume fill represented by $y = 0.43 + 0.52x$; $r^2 = 0.714$; $p < 0.0001$. Changes from 2.5 mL volume fill were not significant (ANCOVA, $p = 0.921$).

2. Depending on the nebulizer, the compressor (DeVilbiss PulmoAide), with flow fixed at 6 L/min, generated pressures ranging from 10.5 to 19 psig (Table 1). On another system (Aridyne), at 6 L/min, pressures were similar to the DeVilbiss PulmoAide (Table 2). At 10 L/min, pressures increased significantly. These data suggest that for commercial compressors, defining the flow also defines the pressure in the line upstream to the nebulizer orifice.

Figure 2 illustrates the data for the first set of experiments that paralleled those of Loffert et al.⁴ Each data point represents a 2-min run. The different symbols represent different nebulizer brands. Those nebulizers with more points had longer running times. The vertical axis depicts the captured aerosol as a percentage of the initial amount placed in the nebulizer. The horizontal axis represents the

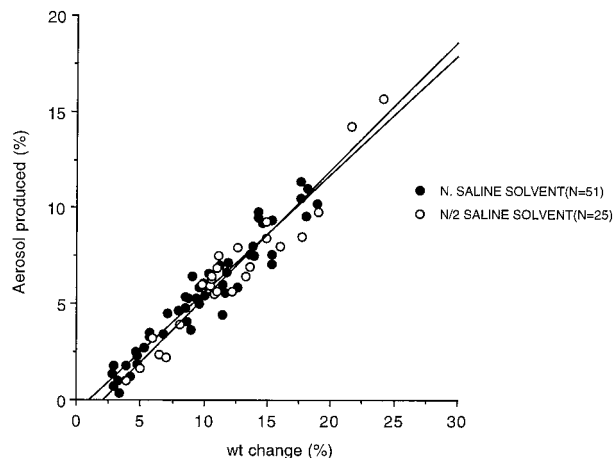


FIGURE 5. Half normal saline solution data represented by $y = -1.42 + 0.67x$; $r^2 = 0.926$; $p < 0.0001$. Differences were not significant ($p = 0.373$).

change in nebulizer weight as a percentage of the original solution weight. As shown in Figure 2; there is an obvious correlation between aerosol produced and the change in weight for all nebulizers ($y = -0.62 + 0.62x$; $r = 0.961$; $p < 0.0001$). While significant, the slope 0.62 is not unity demonstrating that, even though predictable, fewer particles are produced than estimated by the change in weight. It is important to note that the data points in Figure 2 do not reveal information regarding aerosol produced over time. All points are serial data from 2-min observations over the entire period of nebulization. After the initial period of nebulization, aerosol generation tends to fall off with obvious sputtering of the nebulizer until aerosol production ceases. All of those points were included in the data.

The same data are plotted in Figure 3 (filled circles). Superimposed are data points (open circles) from experiments run at “high pressure and flow” conditions (10 L/min of flow and pressures 18.5 to 51

Table 3—Cumulative Gravimetric and Aerosol Output for Different Nebulizers

| Nebulizer | Weight Change, % | Aerosol Produced, % | Ratio, Weight/Aerosol |
|---------------|-------------------|---------------------|-----------------------|
| Powermist | 25.001 | 15.037 | 1.663 |
| DeVilbiss 646 | 26.939 | 12.631 | 2.133 |
| AvaNeb | 50.821 | 26.603 | 1.910 |
| Salter | 52.851 | 25.766 | 2.051 |
| Airlife | 54.401 | 32.522 | 1.673 |
| Cirrus | 57.983 | 36.041 | 1.609 |
| Respirgard II | 59.024 | 31.109 | 1.897 |
| Seamless | 62.088 | 33.761 | 1.839 |
| Up-Draft | 64.554 | 38.761 | 1.665 |
| Mean \pm SD | 50.40 \pm 14.52 | 28.02 \pm 9.04 | 1.81 \pm 0.18 |

psig depending on nebulizer). Again, there is an excellent correlation but the slopes are significantly different ($p=0.022$). Figure 4 depicts a similar comparison between the first set of experiments run with a volume fill of 2.5 mL (filled circles) and data from the volume fill of 5.0 mL (open circles). No significant differences were detected ($p=0.921$). Similarly, Figure 5 demonstrates that dilution of the original solvent to half normal saline solution had no detectable effect ($p=0.373$).

Cumulative changes in weight and aerosol produced by the different nebulizers are listed in Table 3 in the order of aerosol production. There was a wide range in aerosols produced, but the differences were detected by the gravimetric measurements ($y=2.33+0.52x$; $r=0.918$; $p<0.0005$). The cumulative data allow comparison of overall nebulizer function. The 2-min points shown in Figures 2 to 5 illustrate the effects of the listed variables over the entire time span of testing.

DISCUSSION

Our group has long advocated the direct measurement of aerosol actually presented to the patient (inhaled mass^{13,15}) as the best approach to the final assessment of a nebulizer delivery system, but that technique is relatively time consuming for screening large numbers of devices. Gravimetric analysis remains the simplest technique. While evaporation was known to contribute to changes in nebulizer weight, it was not known if these effects were device-specific and, if so, comparison between devices might be unreliable. The present article demonstrates that for a large number of devices and conditions, there is a good correlation between production of aerosol and change in weight. Under the conditions used by Loffert et al,⁴ all tested nebulizers fell along the same overall regression line indicating that gravimetric estimates could predict differences in aerosol production. Of the commonly changed variables in clinical practice, only flow had a measurable effect. The slopes of the regression lines suggest that evaporation accounts for 30 to 40% of the change in weight with differences resulting primarily from changes in flow and pressure.

We did not measure particle distributions, which can be important in the final evaluation of a delivery system. Several techniques are available to assess the diameters and aerodynamic behavior of nebulized particles, but those techniques do not readily provide

a measure of the mass of nebulized drug unless all of the nebulized particles are captured. Under those circumstances, the data would be similar to our filter measurements that capture all of the aerosol particles actually produced.

In conclusion, gravimetric testing of nebulizers overestimates aerosol generation by a significant but predictable amount. For typical jet nebulizers, under usual conditions of therapy (flow rates of 6 to 10 L/min and pressures of 9.0 to 51 psig, aqueous solutions and volume fill of 2.5 ml to 5.0 mL), bench comparison of function can be made with the gravimetric method to screen large numbers of jet nebulizers. Final testing by measurement of "inhaled mass" and the particle distribution is necessary to precisely define aerosol production before clinical testing.

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