TECHNICAL NOTE

Effect of tidal volume on the output and particle size distribution of hypertonic saline from an ultrasonic nebulizer

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Effect of tidal volume on the output and particle size distribution of hypertonic saline from an ultrasonic nebulizer. J. Riedler, C.F. Robertson. ©ERS Journals Ltd 1994.
ABSTRACT: The purpose of the present study was to measure the output and particle size distribution of hypertonic saline from an ultrasonic nebulizer over the range of tidal volumes (V_T) used in an epidemiological survey of asthma in children.

A Starling pump was used to generate different V_Ts from 250 to 500 ml, at different respiratory rates of 12 and 20 breaths·min⁻¹, to cover the normal range of respiratory pattern of children aged 7–14 yrs. The Starling pump was connected to a Timeter Compuneb Ultrasonic Nebulizer Model MP 500 with 24 cm of corrugated aerosol tubing, ID 2.2 cm, and a two-way non-rebreathing valve. Nebulizer output was measured by weighing the nebulizer chamber plus tubing and valve before and after each nebulization. To measure particle size distribution, a Malvern Particle Sizer M 3.0 (laser diffraction) was used, with a special adapter attached between valve and Starling pump.

Nebulizer output increased linearly from 1.6 to 2.5 ml·min⁻¹ for V_T 250 to 500 ml, with little influence by the respiratory frequency. Furthermore, we found that in the range of V_T=300–500 ml the mass median aerodynamic diameter (MMAD) was 2.61 µm, with 100% of the particles less than 5 µm, whereas at V_T=150–250 ml the MMAD was 8.89 µm, with 90% larger than 5 µm.

As output from this ultrasonic nebulizer correlates linearly with tidal volumes, size correction may not be necessary in hypertonic saline challenge tests in children. Above a V_T of 300 ml, the MMAD is in the respirable range, with 100% of particles less than 5 µm. However, in children with a V_T less than 250 ml, this equipment may be unsuitable to perform hypertonic saline challenge tests.
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The prevalence of reported asthma in children varies widely between countries, with high rates reported from countries in the Southern Hemisphere [1, 2], and lower rates in the Northern Hemisphere [3]. Epidemiological surveys of the prevalence of asthma in children have traditionally relied on questionnaires completed by parents, and have not used an objective measure of asthma. Different questionnaires have been used in different surveys. The International Study of Asthma and Allergies in Childhood (ISAAC) has developed a standard questionnaire for use internationally, but this does not overcome the problem of different languages and different interpretation of the concept of wheeze in different communities. In addition, a flaw in such questionnaires is that the parent's response may be influenced by their own prior exposure to the condition and the level of awareness of the condition in the community. It is therefore important to establish some objective measure of asthma in the community to allow comparisons of asthma prevalence over time and between geographic regions.

In an attempt to provide an objective measure of asthma, previous workers have used pharmacological challenges, such as methacholine or histamine [4–6]. As pharmacological challenges become less acceptable to some communities, there has been considerable interest in the use of non-isotonic aerosols as a more clinically relevant stimulus for the diagnosis of asthma [7–11]. For epidemiological studies, the test has to be simple, safe, reliable and reproducible.

Results of inhalation challenge tests are quantitative and are influenced by a number of factors, such as characteristics of the aerosol [12], type and output of the nebulizer [13–18], breathing patterns [8, 12, 15], lung function [19, 20], age of subjects [15, 21], and measurement and expression of results [22].

The aim of this study was to assess the effect of tidal volume (V_T) on the output and particle distribution of hypertonic saline from an ultrasonic nebulizer used in an epidemiological survey of asthma in children.

Methods

A Starling (piston) pump (C.F. Palmer, London, UK) was used to generate different V_Ts over the range 250–500 ml, at different respiratory rates of 12 and 20 breaths·min^{-1}, to cover the normal range of respiratory pattern of children aged 7–14 yrs. The accuracy of the pump was checked by connecting it to a bell-spirometer (Expirograph, Godard).

Nebulizer output

The pump was connected to a Timeter Compuneb Ultrasonic Nebulizer Model MP 500 with 24 cm of corrugated aerosol tubing (smooth interior surface, ID 2.2 cm) and a two-way non-rebreathing valve (Hans Rudolph, Kansas City, No. 1400). The nebulizer solution was 4.5% hypertonic saline (HS), and the nebulizer canister was filled with 200 ml of this solution and refilled after nebulization of more than 50 ml. This was done because the level of fluid in the canister was found to influence output when there was less than 150 ml of solution in the nebulizer chamber. The output was set to maximum position. The function of the valve was carefully observed throughout nebulization, as improper valve function also had an impact on output. Airflow, generated by the blower, through the nebulizer system without the inspiratory valve and the Starling pump attached was measured with a pneumotachograph (Jaeger, Flowmate) and was 24 l·min^{-1}.

At each V_T (500, 450, 400, 350, 300 and 250 ml) three nebulizations, each lasting for 2 min, were performed. The output of the nebulizer per minute was determined by weighing the nebulizer canister with tubing and valve before and after each nebulization and dividing the difference by two (Mettler balance, Switzerland). The results were expressed as the mean (SD) of these measurements at each tidal volume. We compared the output at respiratory rates of 12 and 20 breaths·min^{-1}.

Particle size distribution

The particle size distribution at each V_T was measured by laser diffraction using a Malvern Particle sizer M 3.0. As we were interested in the particle size distribution of the aerosol through tubing and valve, we developed a special adapter to attach between valve and tubing on the one side and the Starling pump on the other side (fig. 1). The laser beam passed through this adapter, which was sealed between detector lens and a special holder for fluid samples. The nebulizer was switched on for a period of one respiratory cycle at V_T 150, 200, 250, 300, 350, 400, 450 and 500 ml. Three measurements were made for each V_T and the results were expressed as the mean (SD). Particle size distribution of the aerosol through the tubing but without valve and Starling pump attached was also measured. The cumulative particle size distribution and the mass median aerodynamic diameter (MMAD), together with the geometric standard deviation (GSD), were determined for each V_T.
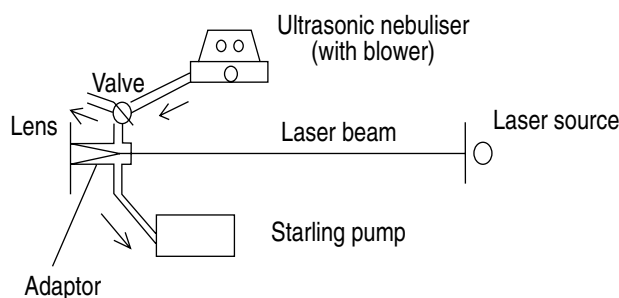

Fig. 1. – Schematic representation of the Malvern Particle Sizer (system for measurement of particle size distribution) with special adapter between inspiratory valve, aerosol tubing and nebulizer on one side, and the Starling pump on the other side. Arrows indicate direction of flow.

Statistical analysis

Regression analyses were made to determine the magnitude of the effect of V_T on nebulizer output and MMAD. A general linear model (ANCOVA for unbalanced data) was used for comparison of the nebulizer output at different V_Ts at pump frequencies 12 and 20 breaths·min^{-1}, as well as for comparison of the output at low and high fluid levels in the nebulizer canister. The level of statistical significance was chosen as $p < 0.05$. All calculations were made on an IBM Computer, using Minitab software programme.

Results

Nebulizer output

Nebulizer output was linearly and significantly correlated to V_T at respiratory rate 12 and 20 breaths·min^{-1} (table 1 and fig. 2). The two regression lines at 12 and 20 breaths·min^{-1} were parallel and significantly different ($p < 0.0001$).

The level of fluid in the nebulizer canister influenced output substantially. At a volume fill of 130 ml, the output was 2.00 ml·min^{-1} (V_T 500 ml) and 1.53
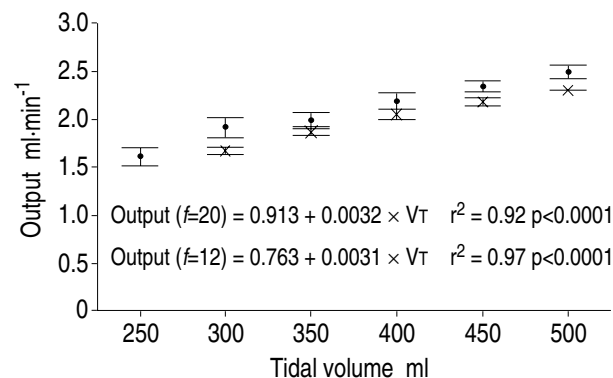

Fig. 2. – Effect of tidal volume on the nebulizer output of hypertonic saline at two respiratory rates. Data are represented as mean±SD. ●: respiratory rate = 20 breaths·min^{-1}; × : respiratory rate = 12 breaths·min^{-1}; f: respiratory rate; V_T: tidal volume.

Table 1. – Nebulizer output and particle size distribution at different tidal volumes

		Tidal volume ml							
		150	200	250	300	350	400	450	500
Output	ml·min⁻¹ at f=20			1.60 (0.09)	1.90 (0.10)	1.98 (0.08)	2.18 (0.08)	2.33 (0.09)	2.49 (0.06)
	at f=12				1.67 (0.03)	1.88 (0.03)	2.05 (0.05)	2.18 (0.03)	2.30 (0.01)
MMAD	µm	9.10 (0.10)	9.10 (0.10)	8.48 (0.53)	2.87 (0.21)	2.97 (0.21)	2.57 (0.42)	2.33 (0.25)	2.33 (0.25)
GSD	µm	1.09 (0.01)	1.10 (0.05)	1.11 (0.05)	1.20 (0.03)	1.21 (0.04)	1.21 (0.05)	1.21 (0.08)	1.28 (0.08)

Data are presented as mean, and SD in parenthesis. f: respiratory rate (breaths·min⁻¹); MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation.
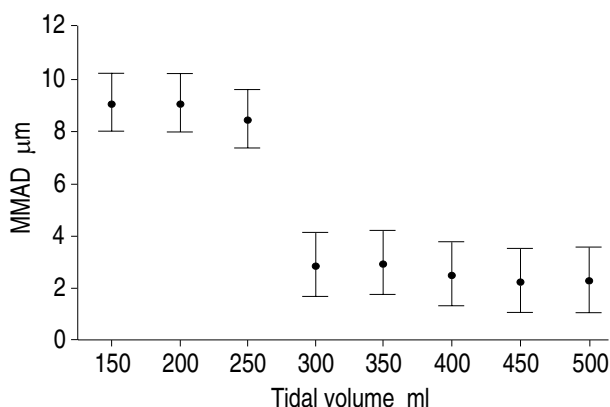

Fig. 3. – Mean±GSD. Effect of tidal volume on particle size distribution of hypertonic saline. MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation.

ml·min⁻¹ (VT 250 ml). When the volume fill was increased to 200 ml, the output also increased to 2.49 ml·min⁻¹ (VT 500 ml) and 1.70 ml·min⁻¹ (VT 250 ml) (p<0.001).

A fluttering valve decreased the output at VT=500 ml from 2.49 to 0.62 ml·min⁻¹.

Particle size distribution

In the range of VT=300–500 ml, the MMAD was 2.61 (0.29) µm and the GSD was 1.22 (0.03) µm, whereas at VT=150–250 ml the MMAD was 8.89 (0.36) µm and the GSD was 1.10 (0.01) µm (table 1 and fig. 3).

The MMAD of the aerosol through tubing but without valve and Starling pump attached was 4.93 (0.15) µm with a GSD of 1.58 (0.10) µm.

Discussion

The results of this study demonstrate that different tidal volumes can be important determinants of output and particle size distribution from an ultrasonic nebulizer used to nebulize hypertonic saline. This is of importance,

especially for inhalation challenge tests in children, as results of the response to these tests are usually quantitative. Standardization of inhalation provocation tests have been developed for various pharmacological agents, exercise tests, cold and dry air hyperventilation and non-isotonic aerosols. Jet nebulizers are used for nebulization of pharmacological agents, whereas non-isotonic aerosols are inhaled *via* ultrasonic nebulizers.

An increase in nebulizer output from 1.3 to 2.3 ml·min⁻¹ improved the accuracy of challenge with 4.5% HS from 75 to 90% in children with mild asthma and in control children [13].

Output of an ultrasonic nebulizer may be influenced by the acoustic frequency of the transducer [23], component tolerance [23], line voltage [23], and the solution level [23, 24]. The latter determinant was confirmed in this study. The output of the same nebulizer also varies with the length of the tubing to the valve. With the delivery system attached, maximum output was reduced from 3.5 to 1.2 ml·min⁻¹ [7]. These measurements were performed without the respiratory valve, whereas we measured output and particle size distribution with the valve attached to the tubing. We were able to measure output more precisely by including the respiratory valve in the gravimetric procedure because, with the use of the Starling pump, there were no problems with salivation. The HS that condensed in the valve was included in the weighing. Measurements without the valve overestimate the output, because they miss the solution that condenses in the valve. A proper function of the valve is imperative, since any "fluttering" increases condensation and reduces output. Output is also determined by the rate and depth of respiration [25]. Therefore, the actual density of the aerosol within each breath varies according to the VT. We were able to show that VT and output were linearly correlated over a range of 250–500 ml for respiratory rate 12 and 20 breaths·min⁻¹. However, the same increase in minute ventilation, brought about by increasing VT, resulted in a greater increase in nebulizer output than by increasing respiratory rate.

We speculate that, with increasing flows at higher respiratory rates, more aerosol particles impact on the walls

of the tubing and at the inspiratory valve, which reduces output. This is also in keeping with the decrease of the MMAD at higher tidal volumes, because the larger particles are more likely to impact at higher flows. This is in contrast to the concept of air entrainment in jet nebulizers from which all children over the age of 12 months inspire the same dose, because after that age inspiratory flow exceeds nebulizer flow and the entire nebulizer output is inhaled during inspiration [15]. Most jet nebulizers operate with flow rates between 6–10 $l \cdot min^{-1}$, whereas we measured a flow rate of 24 $l \cdot min^{-1}$ from the ultrasonic nebulizer used in this study. The peak inspiratory flow at V_T=500 ml was 30 $l \cdot min^{-1}$ and at V_T=250 ml was 15 $l \cdot min^{-1}$. Therefore, peak inspiratory flow rates exceeded nebulizer flow rates only at a V_T of more than 400 ml. In clinical practice, this means that the smaller children are taking smaller breaths and, thus, receive appropriately smaller doses, which may render size or weight correction unnecessary. On the other hand, it indicates the importance of weighing the nebulizer unit plus tubing to precisely assess nebulizer output when intersubject comparisons are made in bronchial challenge tests with HS in children.

The particle size distribution may vary with the acoustic frequency of the transducer, the viscosity and vapour pressure of the nebulizer fluid and the flow rate generated [25]. It may, however, also vary with the tubing and valve through which the aerosol passes. A heterodispersed aerosol with a MMAD of 5.6 µm became homodispersed with a smaller MMAD of only 3.6 µm when delivery circuit attached [7]. We measured particle size distribution with tubing and valve attached at V_T 150–500 ml in 50 ml steps, and found the mean MMAD over V_T 300–500 ml to be 2.61 µm compared to 8.89 µm over V_T 150–250 ml. There was a trend for the MMAD to increase slightly from V_T 500 ml to 300 ml which was clinically unimportant. However, at V_T 250 ml or less the MMAD increased into the nonrespirable range. As we did not alter the inspiratory time, it was the inspiratory flow that changed with changing V_T. We speculate that with higher flow rates at higher V_Ts more larger particles impact on the walls of the tubing and the valve. This can explain the increase in MMAD from 2.33 µm at V_T 500 ml to 2.97 µm at V_T 300 ml. However, it does not explain the sharp and sudden increase in particle size below V_T 300 ml. As these measurements were performed in a random order, a systematic effect is unlikely. It is more likely that there is a critical inspiratory flow between V_T 250 and 300 ml below which particle sizes get out of the respirable range. It might be that this low flow does not sufficiently open the inspiratory valve. This leads to an increase in resistance, which decreases nebulizer flow in the aerosol tubing to such an extent that the particles clump together. Hence, we think that the inspiratory valve in the delivery circuit might be the critical place where this substantial change in particle size distribution occurs. Evaporation is another factor affecting particle size distributions of aerosols generated by jet nebulizers, where compressed cold air cools and concentrates nebulizer solutions. With ultrasonic nebulizers, however, there is no compressed and cool air. Temperature of the solution increases with time and output may increase, although, due to the relatively large volumes, the effect appears to be negligible. The only open contact that the ultrasonic nebulizer plus tubing and inspiratory valve has to the ambient air, is the air inlet. However, the aerosol coming from the nebulizer chamber is not pushed back to the air inlet during tidal breathing. Even if there was some evaporation it would not explain the sudden and sharp increase in MMAD below V_T 300 ml.

The MMAD of the aerosol through tubing but without valve was 4.93 µm compared to 2.61 µm at V_T 300–500 ml with the valve attached. It is most likely that larger droplets impacted on the valve and, thus, were filtered out, leading to a decrease in MMAD with the valve attached.

In conclusion, this study demonstrates that nebulizer output from an ultrasonic nebulizer was linearly correlated to tidal volumes. For most children aged 7–14 yrs their inspiratory flow rates would not exceed the nebulizer flow rate. Hence, there is no need for weight or size correction in HS challenge tests using this type of ultrasonic nebulizer, because the smaller children get less aerosol to their lungs in proportion to their V_T. Furthermore, it shows that different equipment is necessary for smaller children with a V_T less than 250 ml, because the MMAD is outside the respirable range. Therefore, aerosol characteristics need to be assessed in studies looking at bronchial response to HS in children of different age groups.

References

1. Jones DT, Sears MR, Holdaway MD, *et al*. Childhood asthma in New Zealand. *Br J Dis Chest* 1987; 81: 332–340.
2. Robertson CF, Heycock H, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne school children: changes over 25 years. *Br Med J* 1991; 302: 1116–1118.
3. Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old school children and association with asthma. *Arch Dis Child* 1989; 64: 1118–1125.
4. Burney PGJ, Britton JR, Chinn S, *et al*. Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. *Thorax* 1987; 42: 38–44.
5. Peat JK, Salome CM, Sedgwick CS, Kerrebijn J, Woolcock AJ. A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian school children. *Clin Exp Allergy* 1988; 19: 299–306.
6. Paoletti P, Viegi G, Carrozzi L. Bronchial hyperresponsiveness, genetic predisposition and environmental factors: the importance of epidemiological research. *Eur Respir J* 1992; 5: 910–912.
7. Smith CM, Anderson SD. Inhalation challenge using hypertonic saline in asthmatic subjects: a comparison with response to hyperpnoea, methacholine and water. *Eur Respir J* 1990; 3: 144–151.
8. Anderson SD. Bronchial challenge by ultrasonically nebulized aerosols. *Clin Rev Allergy* 1985; 3: 427–439.
9. Smith CH, Anderson SD. Hyperosmolarity as the stimulus to asthma induced by hyperventilation? *J Allergy Clin Immunol* 1986; 77: 729–736.

10. Anderson SD, Schoeffel RE, Finney M. Evaluation of ultrasonically nebulised solutions for provocation testing in patients with asthma. *Thorax* 1983; 38: 284–291.

11. McFadden ER Jr. Heat and water exchange in human airways. *Am Rev Respir Dis* 1992; 146: S8–S10.

12. Ryan G, Dolovich MB, Eng P, *et al*. Standardization of inhalation provocation tests: influence of nebulizer output, particle size, and method of inhalation. *J Allergy Clin Immunol* 1981; 67: 156–161.

13. Araki H, Sly P. Inhalation of hypertonic saline as a bronchial challenge in children with mild asthma and normal children. *J Allergy Clin Immunol* 1989; 84: 99–107.

14. Dennis JH, Stenton SC, Beach JR, *et al*. Jet and ultrasonic nebuliser output: use of a new method for direct measurement of aerosol output. *Thorax* 1990; 45: 728–732.

15. Collis CG, Cole CH, Le Souef PH. Dilution of nebulised aerosols by air entrainment in children. *Lancet* 1990; 336: 341–343.

16. Callaghan CO, Clarke AR, Milner AD. Inaccurate calculation of drug output from nebulisers. *Eur J Pediatr* 1989; 148: 473–474.

17. Dennis JH, Avery AJ, Walters EH, Hendrick DJ. Calibration of aerosol output from the Mefar dosimeter: implications for epidemiological studies. *Eur Respir J* 1992; 5: 1279–1282.

18. Cockroft DW, Hurst TS, Gore B. Importance of evaporative water losses during standardized nebulized inhalation provocation tests. *Chest* 1989; 96: 505–508.

19. Backer V, Groth S, Dirksen A, *et al*. Sensitivity and specificity of the histamine challenge test for the diagnosis of asthma in an unselected sample of children and adolescents. *Eur Respir J* 1991; 4: 1093–1100.

20. Bakke P, O'Conner G, Enarson D, Gulsvik A. Nonspecific challenge test for the diagnosis of asthma in a general population sample (letter to the editor). *Eur Respir J* 1992; 5: 644.

21. Avital A, Noviski N, Bar-Yishay E, *et al*. Nonspecific bronchial reactivity in asthmatic children depends on severity but not on age. *Am Rev Respir Dis* 1991; 144: 36–38.

22. Chinn S, Britton JR, Burney PGJ, *et al*. Estimation and repeatability of the response to inhaled histamine in a community survey. *Thorax* 1987; 42: 45–52.

23. Compu-Neb, Electronic Nebulizer MP 500 Manual; Timeter Instrument Group. 1987; 3.

24. Anderson SD, Schoeffel RE. The inhalation of ultrasonically nebulized aerosols as a provocation test for asthma. *In*: Hargreave FE, Woolcock AJ eds. Airway Responsiveness: Measurement and Interpretation. Proceedings of a Workshop. Ontario, Canada, Astra Pharmaceuticals Canada Ltd, 1985; pp. 39–50.

25. Anderson SD, Smith CM, Rodwell LT, du Toit JI. The use of nonisotonic aerosols for evaluating bronchial hyperresponsiveness. *In*: Spector SL, ed. Provocative Challenge Procedures. New York, Marcel Decker, 1994; (in press).