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Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation

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Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation. C.J. Harvey, M.J. O'Doherty, C.J. Page, S.H.L. Thomas, T.O. Nunan, D.F. Treacher. ©ERS Journals 1997.

ABSTRACT: Increased delivery of aerosol to a model lung (attached to a mechanical ventilator) has been demonstrated with an ultrasonic nebulizer as compared to a jet nebulizer. This study examined whether the increased aerosol deposition with an ultrasonic nebulizer could also be demonstrated *in vivo*.

Seven patients (6 male and 1 female) were studied during mechanical ventilation (Siemens Servo 900C, Middlesex, UK) after open heart surgery. Two studies were performed in each patient. In the first study, aerosol was delivered *via* a Siemens Servo 945 nebulizer system (high setting) driving a System 22 Acorn jet nebulizer (Medic-Aid, Sussex, UK) containing 3 mL ^{99m}technetium-labelled human serum albumin (^{99m}Tc-HSA) (50 µg; activity 74 MBq). In the second study, a DP100 ultrasonic nebulizer (DP Medical, Meylan, France) containing 12 mL ^{99m}Tc-HSA (50 µg; activity 185 MBq) was used. Pulmonary deposition was quantified using a gamma camera. The humidification of the circuit and the ventilator settings were kept constant according to the patient's clinical requirements.

The total lung aerosol deposition (mean±SD), as a percentage of initial nebulizer activity, was greater using the ultrasonic nebulizer than using the jet nebulizer (5.3±1.4 *vs* 2.3±0.9 %; p<0.002). The ultrasonic nebulizer was also associated with a reduction in the time required to complete nebulization (9 *vs* 21 min, respectively) (p<0.0001).

Use of the DP100 ultrasonic nebulizer more than doubled lung deposition compared with the System 22 jet nebulizers in mechanically-ventilated patients. Their efficiency, speed of drug delivery, and compatibility with mechanical ventilator circuits make ultrasonic nebulizers potentially attractive for use during mechanical ventilation.

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The use of nebulized drugs during mechanical ventilation is increasing, but it is important to ensure that adequate quantities of drug reach their site of action. Previous studies have shown pulmonary aerosol deposition to be poor *in vivo*, with only 1.2–2.9% of the nebulizer dose reaching the lungs [1–3]. A number of factors have been identified which improve aerosol delivery *in vitro* [4–6], and lung deposition *in vivo* [7, 8]. In particular, the type of nebulizer has been shown to be important, since greater aerosol delivery can be achieved from a large capacity ultrasonic nebulizer when compared to a jet nebulizer during mechanical ventilation *in vitro* [5]. Ultrasonic nebulizers have another advantage, in that delivery is completed more rapidly than with jet nebulizers. Use of ultrasonic nebulizers has not previously been studied *in vivo* in adults. *In vitro* studies in infant ventilator circuits have also demonstrated advantages with ultrasonic devices [9]. They do not produce better delivery than metred-dose inhalers [10], but the latter are not available for all drugs.

The present study compares the pulmonary deposition from a jet and an ultrasonic nebulizer in mechanically-ventilated adult patients.

Methods

Patient selection

Seven patients (6 males and 1 female; 5 ex-smokers and 2 lifelong nonsmokers) were studied during volume-cycled mechanical ventilation following open heart surgery. Informed consent was obtained from all patients, and the study was approved by the Ethics Committee of West Lambeth Health Authority. Patients with pre-existing respiratory symptoms or disease were excluded as the intention of the study was to measure aerosol deposition in normal lungs. Lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR)) was measured preoperatively (table 1). Patients were only studied if they required ventilation on clinical grounds. Studies were commenced within 4 h of the completion of the operation.

Experimental protocol

All patients were intubated and ventilated using a Siemens Servo 900C mechanical ventilator in volume

Table 1. – Patient details, respiratory function and ventilator settings (n=7)

	Mean	Range
Preoperative assessment		
Age yrs	68	56–76
FEV_1 L	2.6	1.4–4.2
% pred	105	93–124
FVC	3.4	1.7–4.7
% pred	102	91–121
PEFR $L \cdot min^{-1}$	472.3	320–678
Mechanical ventilation settings		
Respiratory rate $breaths \cdot min^{-1}$	15.2	14–16
Minute volume $L \cdot min^{-1}$	8.1	7.3–8.8
Inspiratory time %	24	15–25
Pause time %	10	–

FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; FVC: forced vital capacity; PEFR: peak expiratory flow rate.

control mode. Prior to each study, the ventilator settings were adjusted to optimize the patient's blood gas values and, thereafter, were kept constant, as was the humidification of the inspiratory gas (table 1). Pulmonary deposition was measured using a gamma camera fitted with a diverging collimator (IGE Portacamera, (SFOV); IGE Medical Systems, Berkshire, UK) as verified previously [3]. Tissue attenuation was measured using a 47 cm diameter cobalt-57 flood source, with the gamma camera positioned anteriorly, as described previously [3]. The use of the attenuation correction method has been compared previously with build-up factor methods and shown to provide a similar degree of accuracy in quantitation [11].

Before administration of aerosol, a xenon-133 (^{133}Xe) breathhold image was obtained to define lung edges and regions. This was achieved by injection of 10 mL (110 MBq) of gas through the proximal end of the endotracheal tube (ET), immediately before the inspiratory phase. Ventilation was stopped for 10 s at the end of the inspiratory cycle, whilst an anterior image was acquired *via* the gamma camera. The expired ^{133}Xe was collected *via* the expiratory port of the ventilator until wash-out was complete.

Two studies were performed on each patient, the first using a System 22 Acorn jet nebulizer (Medic-Aid, Sussex, UK), followed by a DP100 ultrasonic nebulizer (DP Medical, Meylan, France). It was decided not to randomize the order of study, as there was concern that after use of the jet nebulizer the incremental increase in lung technetium-99m (^{99m}Tc) activity might be too small to detect reliably if the more efficient ultrasonic nebulizer [6] had already been studied. Previous research has shown that no systematic error is produced by this approach [1]. A solution of ^{99m}Tc-labelled human serum albumin (^{99m}Tc-HSA 50 µg) in 3 mL saline fill for the jet nebulizer and 12 mL fill for the ultrasonic nebulizer (run at high setting) was administered, with activities of 74 MBq in Study 1 and 185 MBq in Study 2. Study 2 was performed immediately after Study 1 using the same ventilator settings. A Siemens Servo 945 nebulizer system (Middlesex, UK) (high setting) was used in conjunction with the jet nebulizer. Since a volume of gas is necessary to drive the jet nebulizer, this must be taken into account when the tidal volume is set, and the respiratory minute volume, therefore, has to be adjusted manually. The jet nebulizer was positioned in the inspiratory limb of the ventilator circuit *via* a T-piece, 12 cm proximal to the Y-piece, whilst the ultrasonic nebulizer was inserted in the inspiratory limb *via* a 35 cm length of elephant tubing (fig. 1).

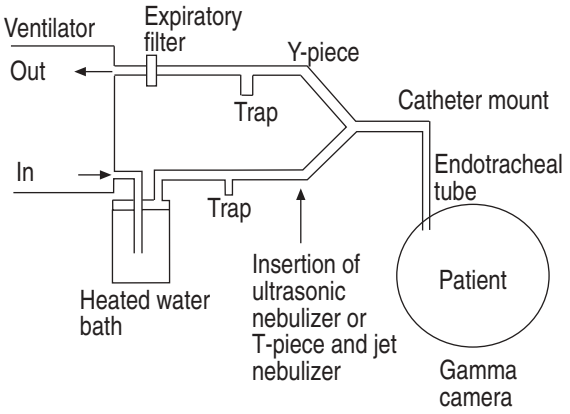

Fig. 1. – Diagram of the experimental arrangements of the ventilator circuit and the position of the nebulizers.

During the period of aerosol administration, pulmonary deposition of ^{99m}Tc-HSA was continuously monitored *via* the gamma camera (anterior projection) in 15 s frames. After completion of nebulization, 300 s static scans of the lungs were taken in the anterior and posterior projections. Activity in the nebulizers was measured before and after nebulization. The gamma camera was also used to measure activity in the T-piece, tubing and exhalation filter postnebulization. The deposition in each lung and tracheal region was computed. Lung edges were defined by the 20% isocount contour obtained from the ^{133}Xe image. The deposition in the lung from Study 2 was corrected for deposition from Study 1 by subtraction, after correction for decay and background activity.

In vitro measurements of the aerosol particle sizes were performed with both nebulizers using a Malvern Master laser particle sizer (Worcs, UK) and a model independent calculation. The sizes were measured at the T-piece, where the nebulizer connected to the ventilator circuit, and at the tip of the ET. The measurements were repeated on three occasions. The results are presented as the mass median aerodynamic diameter (MMAD) and the span. The span represents the ratio: dimension of the 90th percentile particle - dimension of the 10th percentile particle)/dimension of the 50th percentile particle.

Statistical analysis was performed using the paired two-tailed t-test. A p-value of less than 0.05 was considered significant.

Results

Studies were performed on seven patients, who had undergone either coronary artery bypass grafting or cardiac valve replacement (table 1). All were intubated with 8 or 9 mm cuffed ETs. The mean±SD attenuation coefficient measured was $0.09 \pm 0.004 \cdot cm^{-1}$.

Table 2 shows aerosol deposition expressed as a percentage of initial nebulizer activity. The DP100 ultrasonic nebulizer produced more than double the lung

Table 2. – Aerosol deposition in seven ventilated patients with a jet (System 22 Acorn) and ultrasonic nebulizer (DP100).

	Jet %	DP100 %
Pulmonary deposition		
Both lungs	2.3±0.9	5.3±1.4*
Right lung	1.4±0.5	3.8±1.6$
Left lung	0.9±0.5	1.5±0.8
Extrapulmonary deposition		
Trachea and ET	3.1±2.1	11.6±3.9ϕ
Exhalation filter	18.7±5.4	7.5±1.7*
T-piece or tubing	1.6±0.8	18.7±2.0#
Nebulizer retention	49.7±8.7	29.6±4.4*
Time to completion of nebulization min	21±1.0	9±1.0‡

Values are presented as mean±SD. ET: endotracheal tube. *: $p<0.002$; $: $p<0.005$; ϕ: $p<0.001$; #: $p<0.00001$; ‡: $p<0.0001$, compared to jet nebulizer (two-tailed paired t-test).

deposition compared with the System 22 Acorn jet nebulizer ($p<0.002$). The ultrasonic nebulizer was also associated with a significant reduction in aerosol loss down the expiratory limb of the ventilator circuit and in the retention of aerosol solution in the nebulizer after use. Nebulization was also completed more rapidly, in 9 min compared to 21 min ($p<0.0001$) (fig. 2). Approximately 25% of the initial nebulizer activity was unaccounted for using both types of nebulizer. This is presumed to be deposited within the ventilator circuit. This was not quantified due to practical difficulties in scanning long lengths of tubing and water baths. The distribution of ^{133}Xe and aerosol deposition after jet and ultrasonic nebulization is shown in figure 3.

In vitro measurements of the particle sizes of the aerosols were recorded at the point of entry into the ventilator circuit (T-piece) for the system 22 jet nebulizer as MMAD mean±SD (span±SD) 5.2±0.4 (2.2±0.6) µm and for the DP100 as 4.6±0.3 (2.0±0.1) µm, respectively. The similar recordings at the tip of the ET tube were: for the System 22 3.5±0.2 (2.0±0.1) µm and for the DP100 2.7±0.1 (1.3±0.05) µm, respectively.

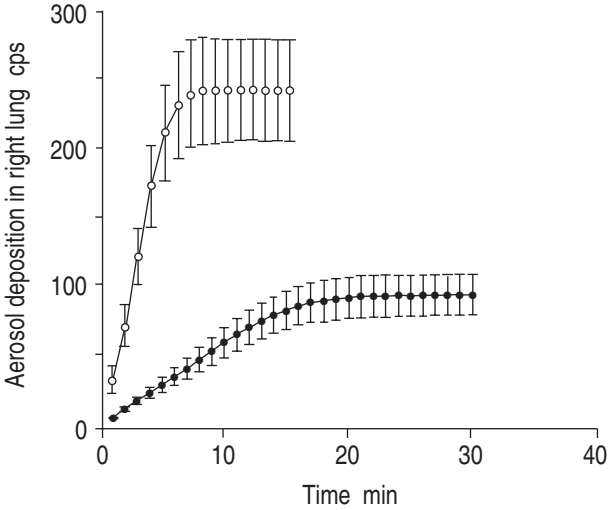

Fig. 2. – The dynamic deposition of aerosol from the jet nebulizer (System 22 Acorn) and the ultrasonic nebulizer (DP100). Values are presented as mean±SD. ●: Acorn; ○: DP100. cps: counts per second.

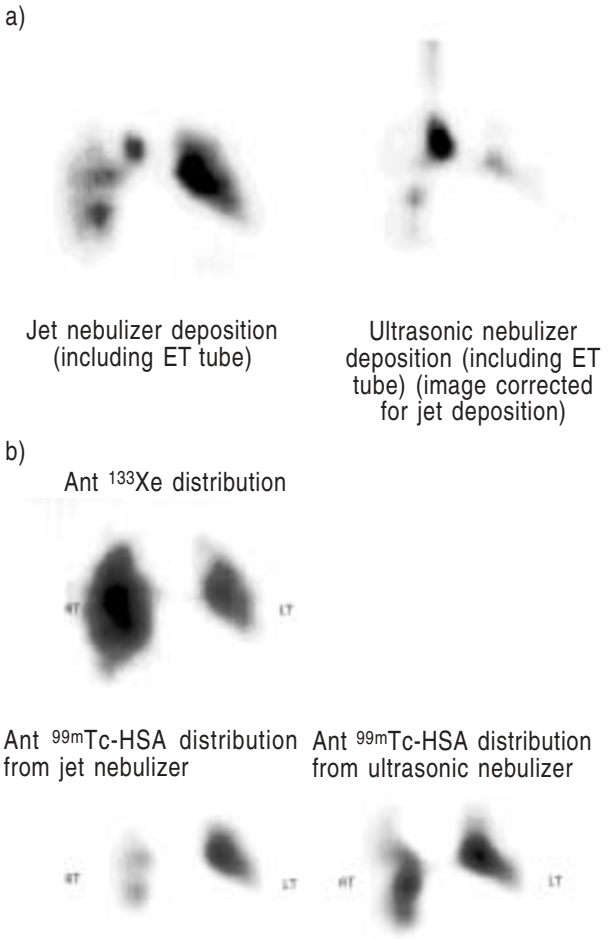

Fig. 3. – The distribution of ^{133}Xe, and ^{99m}Tc-human serum albumen aerosol (^{99m}Tc-HSA) from the jet nebulizer (System 22 Acorn) and the ultrasonic nebulizer (DP100). The ultrasonic deposition images shown are after subtraction of the jet nebulizer deposition image: a) including the trachea and endotracheal tube (ET) deposition; and b) without the trachea and ET deposition.

Discussion

Direct delivery of drug aerosols to the lungs of mechanically-ventilated patients is increasingly used. The most common methods of administration are by metered-dose inhalers and jet nebulizers. Administration of metered-dose inhaler is limited to bronchodilators, cromoglycate and inhaled steroids, but has been demonstrated to be efficient, with delivery ranging 3.9–5.6% [2, 12]. Nebulized drug aerosol administration during mechanical ventilation is of increasing importance because of the increasing number of drugs for which metered-dose inhalers are not available. Following the demonstration that lung deposition with jet nebulizers was poor *in vivo* [1–3], a number of researchers identified factors that affect aerosol delivery *in vitro* [4–6]. These include: the type and position of the nebulizer; the ventilator settings, particularly the inspiratory time; the gas flow to the nebulizer; humidity; and nebulizer fill; and the use of a spacer [8]. O'DOHERTY *et al*. [5] compared aerosol delivery

from jet and two ultrasonic nebulizers *in vitro*, and found that large capacity ultrasonic nebulizers can deliver more aerosol through an ET tube during simulated mechanical ventilation.

Using the same volume of fill and similar ventilator settings as in the present study, our previous *in vitro* studies have produced aerosol delivery values of 5.4 and 14.5% of initial nebulizer activity for the Acorn jet nebulizer and DP100 ultrasonic nebulizer, respectively, [6]. *In vitro* work produces a higher aerosol delivery than can be expected *in vivo*, since the filters used in the model lung entrap all inhaled particles, including those that would be deposited in the major airways or exhaled. Indirect methods of measuring deposition (using inspiratory and expiratory filters) also overestimate deposition for the same reasons, and this partially explains the high delivery reported in other studies [7]. The deposition that occurs in the inspiratory limb filter includes activity deposited in the ET and the trachea, which may not be the site of action of the drug in question.

The present study demonstrated a large increase in pulmonary deposition with the DP100 ultrasonic nebulizer. The relative increase in lung delivery of 230% agrees well with the increase in total aerosol delivery of 250% measured *in vitro*. This underlines the value of preliminary *in vitro* trials to test nebulizer systems before they are studied *in vivo*. Although this study is small, it is of sufficient size to detect these large improvements in aerosol delivery with an ultrasonic nebulizer.

There are several possible reasons why aerosol deposition, during mechanical ventilation, is increased by using an ultrasonic nebulizer. The large chamber capacity allows use of a larger dilution volume, which is associated with more efficient aerosol delivery [6]. Ultrasonic nebulizers produce aerosol continuously, and aerosol fills the nebulizer chamber (acting as a small storage chamber during expiration) and the ventilator circuit prior to lung inflation. In contrast, a jet nebulizer is activated only during inspiration, and we have observed that much aerosol production occurs towards the end of lung inflation and too late for delivery from the nebulizer to the lung. As a result, more aerosol is lost down the expiratory limb, as evidenced by the higher exhalation filter deposition observed as a percentage of total lung deposition.

The design of the current ultrasonic device also encourages increased aerosol delivery because of the small aerosol storage volume within the chamber and inspiratory tubing prior to the Y-piece [6]. This particular ultrasonic nebulizer produces a particle at the end of the ET tube of 2.7 µm (MMAD) [5, 6], which is within the so-called "respirable" range. However, the jet and the ultrasonic nebulizers deliver larger particles into the ventilator circuit; this suggests that there is deposition of larger particles in the circuit, Y-piece, catheter mount and the ET tube prior to delivery to the lung. It is possible that some of the lung deposition observed is due to aerosol trickling from the ET tube into the trachea and larger airways. This may not be useful for treating various disease processes in the small bronchioles and lung parenchyma. The left lung base is poorly ventilated following cardiopulmonary bypass and, therefore, changes in deposition of aerosol in the left lung are less marked than the right.

The results of this study will not necessarily reflect the situation in patients with lung disease. For example, peripheral airway deposition may be less efficient with obstructive or reversible airways disease. The nature of the disease may encourage deposition more centrally when the bronchi are constricted, and may allow deeper penetration of the particles in the 1–2 µm range as therapy starts to work. In addition, different aerosols may have different aerodynamic characteristics; we have demonstrated that the use of different antibiotic solutions in a jet nebulizer can change the particle size [13].

Improved lung aerosol delivery may increase the efficacy of nebulized therapy in ventilated patients or allow a reduction in the nebulizer dose of drug. For expensive agents, this may afford an important cost-saving. Other advantages over jet nebulizers are that treatments take a significantly shorter time to complete and it is not necessary to alter ventilator settings. On the other hand, some ultrasonic nebulizers are expensive or bulky. Some drug solutions may not be stable under conditions of ultrasonic nebulization because of the ultrasonic stimulation and the temperature rise of the nebulized solution; although this has not been demonstrated in currently used drugs delivered by nebulization. To our knowledge, ultrasonic nebulizers are not currently used in this way in adult intensive therapy units in the UK, and we could find no other studies of their use during adult mechanical ventilation *in vivo*. Deposition studies in neonates and children are likely to have different deposition characteristics because of differences in the volume and pressure ventilation used.

This study shows that the DP100 ultrasonic nebulizer provides improved pulmonary aerosol deposition during mechanical ventilation compared with a conventional System 22 Acorn jet nebulizer. There was no need to adjust ventilator settings in manually-operated ventilators using the ultrasonic device. Although the deposition of aerosol is still poor, further studies to establish the types of ultrasonic nebulizers and the conditions of use that are most efficient would be helpful. In particular, it will be important to confirm, in clinical trials, that the use of ultrasonic nebulizers to deliver drugs improves physiological measurements and/or patient outcome.

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