

Pulmonary Drug Delivery Following Continuous Vibrating Mesh Nebulization and Inspiratory Synchronized Vibrating Mesh Nebulization During Noninvasive Ventilation in Healthy Volunteers

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Abstract

Background: A breath-synchronized nebulization option that could potentially improve drug delivery during noninvasive positive pressure ventilation (NIPPV) is currently not available on single-limb circuit bilevel ventilators. The aim of this study was to compare urinary excretion of amikacin following aerosol delivery with a vibrating mesh nebulizer coupled to a single-limb circuit bilevel ventilator, using conventional continuous (Conti-Neb) and experimental inspiratory synchronized (Inspi-Neb) nebulization modes.

Materials and Methods: A crossover clinical trial involving 6 noninvasive ventilated healthy volunteers (mean age of 32.3 ± 9.5 y) randomly assigned to both vibrating mesh nebulization modes was conducted: Inspi-Neb delivered aerosol during only the whole inspiratory phase, whereas Conti-Neb delivered aerosol continuously. All subjects inhaled amikacin solution (500 mg/4 mL) during NIPPV using a single-limb bilevel ventilator (inspiratory positive airway pressure: 12 cm H₂O, and expiratory positive airway pressure: 5 cm H₂O). Pulmonary drug delivery of amikacin following both nebulization modes was compared by urinary excretion of drug for 24 hours post-inhalation.

Results: The total daily amount of amikacin excreted in the urine was significantly higher with Inspi-Neb (median: 44.72 mg; interquartile range [IQR]: 40.50–65.13) than with Conti-Neb (median: 40.07 mg; IQR: 31.00–43.73), ($p = 0.02$). The elimination rate constant of amikacin (indirect measure of the depth of drug penetration into the lungs) was significantly higher with Inspi-Neb (median: 0.137; IQR: 0.113–0.146) than with Conti-Neb (median: 0.116; IQR: 0.105–0.130), ($p = 0.02$). However, the mean pulmonary drug delivery rate, expressed as the ratio between total daily urinary amount of amikacin and nebulization time, was significantly higher with Conti-Neb (2.03 mg/min) than with Inspi-Neb (1.09 mg/min) ($p < 0.01$).

Conclusions: During NIPPV with a single-limb circuit bilevel ventilator, the use of inspiratory synchronized vibrating mesh nebulization may improve pulmonary drug delivery compared with conventional continuous vibrating mesh nebulization.

Keywords: aerosol delivery, amikacin, bilevel ventilator, breath-synchronized nebulizer, healthy volunteers, nebulization, nebulization mode, noninvasive positive pressure ventilation, pulmonary drug delivery, single-limb circuit ventilator, vibrating mesh nebulizer

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Introduction

AEROSOL DELIVERY DURING NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV) has been little studied in human clinical trials, other than a few studies focusing specifically on the pulmonary delivery of drugs.^(1–4) Some clinical benefits have been reported in small trials^(5–8); however, the evidence is not sufficiently robust to recommend routine use of NIPPV for aerosol therapy.⁽³⁾ The effectiveness of nebulization is related to the mass of drug deposited in the lungs.^(9–11) During NIPPV, the fraction of the nominal dose actually administered depends on many factors, including the nebulizer device^(4,12,13) and its position in the ventilator circuit.^(3,12–15)

Recently, some technical issues regarding drug nebulization during NIPPV using a single-limb circuit bilevel ventilator were investigated and resolved with the help of bench studies.^(12,14,16–18) These studies concluded that the optimal position of the nebulizer device was between the patient and the passive exhalation port.^(3,12,14,15,18) Moreover, they showed that vibrating mesh nebulizer devices were more efficient than jet nebulizer devices.^(12,13,18)

Although the use of breath-synchronized nebulizers could potentially improve aerosol delivery during NIPPV,^(19–21) this technical aspect has been little studied because breath-synchronized nebulizers are currently not commercially available for use with bilevel ventilators.⁽³⁾ In a previous bench study,⁽²¹⁾ we showed that the respirable dose of amikacin from a vibrating mesh nebulizer coupled to a single-limb circuit bilevel ventilator could be increased by the use of an inspiratory synchronized nebulization mode, instead of the conventional continuous nebulization mode. However, due to the complexity of human airways,⁽²²⁾ the influence of ventilator-related factors (e.g., interface and settings),^(15,23–25) and patient-related factors (e.g., tidal volume, respiratory rate, and inspiratory time),^(15,17) a human clinical study is required to confirm the findings of our *in vitro* study.⁽³⁾

Monitoring the urinary excretion of a drug for 24 hours post-inhalation has been validated as a method to estimate the lung delivery of drugs^(26–28) as well as to compare different nebulizer devices in patients under mechanical ventilation.^(27,29–31)

On the basis of our previous *in vitro* study,⁽²¹⁾ we hypothesized that an inspiratory synchronized vibrating mesh nebulization mode would enhance aerosol drug delivery to the lungs of noninvasive ventilated patients, compared with a conventional continuous vibrating mesh nebulization mode. Therefore, the main aim of this study was to compare the urinary excretion of amikacin for 24 hours, following nebulization with a vibrating mesh device operating (1) in an inspiratory synchronized mode and (2) in the conventional continuous mode, in adult healthy volunteers undergoing NIPPV with a single-limb circuit bilevel ventilator. We also analyzed the pulmonary drug delivery rate, expressed as the ratio between total daily urinary amount of amikacin and nebulization time, and the elimination rate constant of amikacin, as an indirect measure of the depth of drug penetration into the lungs.

Materials and Methods

Subjects

After approval by the Ethics Committee of our institution (Comité d’Ethique Hospitalo-Facultaire, Université Cath-

olique de Louvain; Registration number: B403201524418), we recruited six non-smoking healthy male volunteers who gave their written informed consent after receiving complete protocol information (Clinical Trials: NCT01901497). Inclusion criteria included age between 18 and 65 years and no history of cardiovascular or lung diseases. Exclusion criteria included abnormal renal function, treatment with aminoglycosides within the previous 3 months, allergy to aminoglycosides, and inability to tolerate NIPPV. Each volunteer performed a spirometry test according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.⁽³²⁾ Subjects were excluded if forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) were <80% of the predicted value or they were unable to tolerate NIPPV.

Experimental aerosol delivery system and bilevel ventilator

As previously described in our bench study,⁽²¹⁾ we used an experimental aerosol delivery system, including an Aerogen[®] Solo vibrating mesh nebulizer powered by the Aerogen Pro Controller (Aerogen Ltd.; Dangan, Galway, Ireland), a prototype control module called Synchro-Neb (HEIG-VD and HESAV, Yverdon-les-Bains, Switzerland), and a pressure sensor (Honeywell Sensing and Control; model SSCSANN005PGAA5, Minneapolis, MN) connected to the outlet of the bilevel ventilator (between the circuit and the ventilator) through a T-piece adapter (Fig. 1).

The Synchro-Neb was developed to synchronize nebulization with the whole inspiratory phase of the bilevel ventilator. Based on an electrical signal from the pressure sensor, the control module detects a minimal positive or negative variation of pressure of 4 cmH₂O (above expiratory positive airway pressure [EPAP]) in the ventilator circuit (Inspiratory–Expiratory and Expiratory–Inspiratory cyclings) and switches on/off the Aerogen Pro Controller and hence the nebulizer device. In previous tests, a 20-millisecond delay has been measured between the onset of insufflation and the actuation of nebulization and between the end of insufflation and the interruption of nebulization (unpublished data). Moreover, Synchro-Neb has been found to respond perfectly to simulated breathing rates exceeding 45 breaths per minute (unpublished data).

Similarly to our *in vitro* study,⁽²¹⁾ we tested two different nebulization modes:

- Continuous nebulization mode (Conti-Neb), with the nebulizer operating continuously, irrespective of the inspiratory and exhalation phases (conventional mode).
- Inspiratory synchronized nebulization mode (Inspi-Neb), in which the nebulizer operated only during the whole inspiratory phase (experimental mode).

The experimental aerosol delivery system was coupled to a Philips Trilogy[®] 100 (Philips Respironics, Murrysville, PA) bilevel ventilator used with an adult single-limb circuit (180 cm length × 22 mm diameter), a passive exhalation port (Whisper Swivel II[®]; Philips-Respironics, Murrysville, PA), and a facial mask (Vygon[®] Schweiz GmbH, Niederwangen BE, Schweiz). No heating or humidification systems were used.

Study design

This double-blind, randomized crossover study was performed in the Department of Intensive Care and the

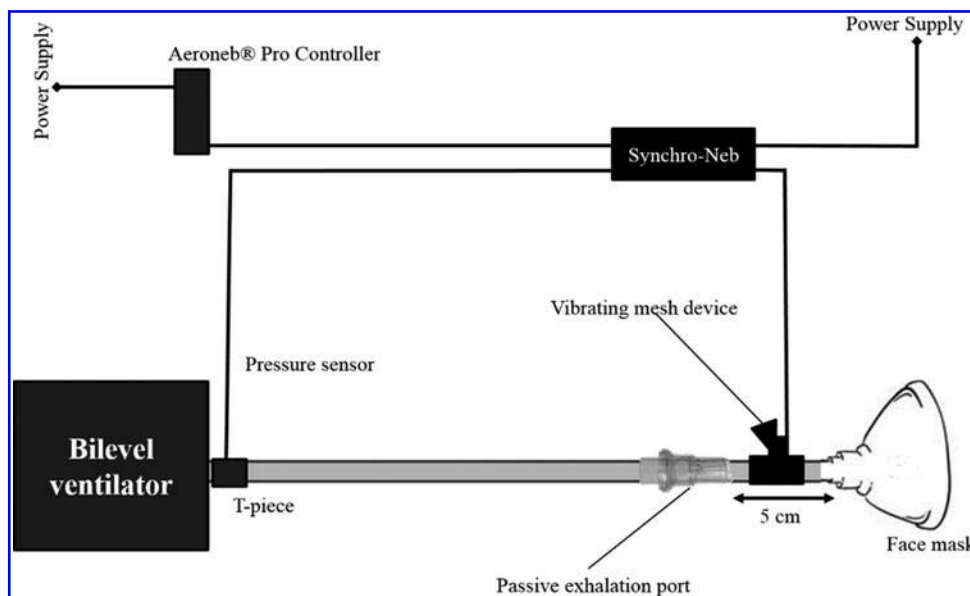


FIG. 1. Schematic showing our setup for nebulization during noninvasive ventilation. The experimental aerosol delivery system connected to a single-limb circuit bilevel ventilator.

Department of Pneumology at Saint-Luc University Hospital, Brussels, Belgium. All subjects were recruited by local advertisement. A schematic representation of the present study is illustrated in Figure 2.

Before beginning the experiment, all volunteers were fitted with the facial mask and trained to use the NIPPV. Computer software (www.randomizer.org/) was used to randomize the order of the nebulizer trials. Conti-Neb or Inspi-Neb was coupled to a bilevel ventilator set in spontaneous mode, with fixed levels of inspiratory positive airway pressure (IPAP) of 12 cmH₂O and EPAP of 5 cmH₂O, a flow trigger sensitivity of 9 L/min, an inspiratory cycle-off of 25%, and an inspiratory rise time set at level 3 (fastest response = 1 and slowest response = 6). These levels of IPAP and EPAP were already used in two previous studies.^(4,33)

A washout period of 1 week between the two trials was respected for each subject. This period allows eliminating all residual drug due to its short half-life.^(27,34) Each trial

was carried out in the same room at an ambient temperature (mean = 23.8°C ± 1.7) and at the same time of the day (2 p.m). All volunteers acted as their own controls, thus reducing the amount of error arising from anatomical (e.g., airway morphology and nasal-laryngeal airway volumes) and mechanical (e.g., airway resistance) differences between individuals.^(34,35)

The nebulizer device was connected to the ventilator circuit with specific adapters (recommended by the manufacturer) positioned between the face mask and the passive exhalation port. The device was filled with 500 mg of amikacin (Amukin, Bristol-Myers Squibb, Braine-l'Alleud, Belgium) diluted in 4 mL of normal saline solution.

For each subject, a new nebulizer device and complete ventilator circuit, including the facial mask and passive exhalation port, were used. The specific adapters were cleaned, disinfected, and dried after each test according to the manufacturer's instructions.

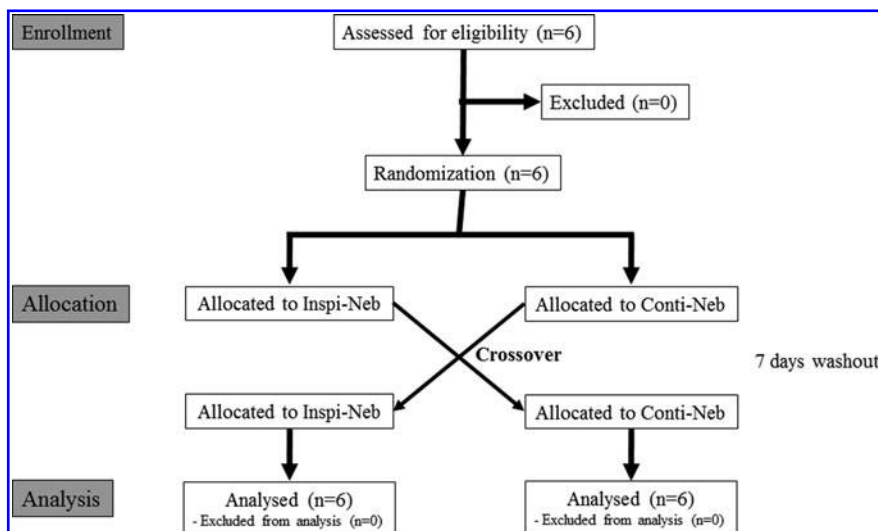


FIG. 2. Flow diagram of the study.

During NIPPV, the subjects were seated comfortably and breathed spontaneously through the facial mask secured with standard headgear and straps. The facial mask was adjusted until the participant felt comfortable and there was no leak from the interface between the face and mask. All volunteers were encouraged to breathe normally through the mouth. Nebulization was started 5 minutes after the bilevel ventilator to allow the subjects to acclimatize to the ventilator and their breathing pattern to stabilize. Nebulization was considered to be finished when no aerosol cloud was visible for a period of 30 seconds. The bilevel ventilator was switched off 1 minute after the end of the nebulization time.

All experiments were performed by three investigators (J.B.M., A.S.A., and E.J.). In this double-blind trial, the enrolled subjects were assigned by the investigator J.B.M. The total daily amount of amikacin excreted in the urine was assessed by the investigator A.S.A. who was blinded to the nebulization mode. The investigator E.J. and subjects were blinded to the nebulization mode used in each session and results obtained.

Measurements

During both nebulization sessions, the respiratory rate, total leaks, tidal volume, minute ventilation, inspiratory flow, and T_i/T_{tot} ratio monitored by the bilevel ventilator were recorded and analyzed with DirectView v1.3 ventilation data management software (Philips Respironics, Murrysville, PA).

Just before the experiments, the volunteers were requested to empty their bladder and to collect the first urine sample. Then, urine samples were collected at each micturition for 24 hours after nebulization. The precise volume and exact time of the micturition were recorded. The concentration of amikacin in each sample was measured using the fluorescence polarization immunoassay method (Abbott Laboratories, Abbott Park, IL).

The primary outcome was the total daily amount of amikacin excreted in the urine (Cu max), reflecting pulmonary drug delivery.^(26–28) This outcome was calculated by summing the amount of amikacin measured at each micturition. The Cu max was expressed in absolute values (mg) or as a percentage of the nominal dose of amikacin (%). Secondary outcomes included the constant of elimination (K_e) and the duration of nebulization. K_e was calculated by fitting the curve of the cumulated amount of amikacin excreted in urine plotted over time. The elimination kinetics of amikacin is dose dependent. As the urine

level increases, the value of K_e increases. K_e can be taken as an indirect measure of depth to which drugs penetrate into the lung.^(27,36) The duration of nebulization, defined as the time from the beginning of nebulization (nebulizer turned on) until the end of aerosol production (no aerosol cloud), was also recorded for each nebulization mode. It was measured by the same investigator using a stopwatch.

Statistics

Results are presented as mean \pm standard deviation with 95% confidence intervals or median with interquartile ranges (IQRs) depending on their distribution. Without any previous clinical studies that have used the same method of analysis, the sample size calculation was based on an estimated minimal clinically relevant difference of 10%.⁽³⁷⁾ To detect such a difference in total daily amount of urinary amikacin excretion at a 5% significance level for a two-sided test with a statistical power of 80%, the sample size needed was five subjects ($n=5$).

Differences between the two nebulization modes were assessed using a paired Student's *t*-test or Wilcoxon signed-rank test in case of non-normality distribution according to Kolmogorov–Smirnov tests. A difference was considered statistically significant when the *p*-value was less than 0.05. Statistical analysis was performed with the commercially available software Stata (Stata/IC 12.1 for Windows; StataCorp LP, Texas).

Results

Patients

Six healthy volunteers were assessed for eligibility and none were excluded. Mean anthropometric parameters and pulmonary function tests of the six healthy volunteers are presented in Table 1. They all had normal lung function (FVC = 102.8% \pm 8.8% predicted; FEV₁ = 99.5% \pm 10.1% predicted).

Respiratory monitoring

No significant differences were found between tidal volume [1351.4 mL (IQR: 1194.8–1436.5) vs. 1324.5 mL (IQR: 1276.3–1534.1) for Inspi-Neb and Conti-Neb, respectively, $p=0.60$], respiratory rate [12.1 breath/minute (IQR: 10.4–14.3) vs. 12.5 (11.6–14.4) breath/minute for Inspi-Neb and Conti-Neb, respectively, $p=0.60$], minute volume [16.2

TABLE 1. ANTHROPOMETRIC AND PULMONARY FUNCTION DATA OF SIX VOLUNTEERS

Subject	Age (years)	BMI (kg/m ²)	FEV ₁ (% predicted)	FVC (% predicted)	FEV ₁ /FVC (% predicted)	PEF (L/min)
1	23	27.2	89	92	87	624
2	47	23.9	113	116	100	826
3	28	25.5	91	99	94	533
4	32	26.3	92	97	85	585
5	24	26.0	105	110	96	652
6	40	24.8	107	103	97	726
Mean	32.3	25.6	99.5	102.8	93.2	657.7
SD	9.5	1.2	10.1	8.8	5.9	104.9

BMI, body-mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV₁/FVC, Tiffeneau index; PEF, peak expiratory flow.

L/min (IQR: 15.2–17.4) vs. 16.7 L/min (IQR: 13.0–20.5) for Inspi-Neb and Conti-Neb, respectively, $p=0.60$], and Ti/Ttot ratio [0.36 (IQR: 0.34–0.41) vs. 0.37 (IQR: 0.36–0.39) for Inspi-Neb and Conti-Neb, respectively, $p=0.91$] measured during each type of nebulization.

Nebulization monitoring

The duration of nebulization was influenced by the nebulization mode. It was significantly longer with Inspi-Neb than with Conti-Neb [median: 46.25 minutes (IQR: 43.15–48.15) vs. 18.35 minutes (IQR: 17.80–22.10) for Inspi-Neb and Conti-Neb, respectively; $p=0.01$].

Drug monitoring

The total daily amount of amikacin excreted in the urine was influenced by the nebulization mode. It was significantly higher with Inspi-Neb than with Conti-Neb [median: 44.72 mg (IQR: 40.50–65.13) vs. 40.07 mg (IQR: 31.00–43.73) for Inspi-Neb and Conti-Neb, respectively; $p=0.02$]. In addition, the elimination rate constant of amikacin was significantly higher with Inspi-Neb than with Conti-Neb [median: 0.137 (IQR: 0.113–0.146) vs. 0.116 (IQR: 0.105–0.130) for Inspi-Neb and Conti-Neb, respectively; $p=0.02$].

Discussion

The purpose of this randomized crossover study was to compare the lung delivery of amikacin with inspiratory synchronized and continuous vibrating mesh nebulization in healthy volunteers undergoing NIPPV with a single-limb circuit bilevel ventilator. We found (1) higher urinary excretion of amikacin, (2) a greater constant of elimination of amikacin, and (3) a longer nebulization time with inspiratory synchronized nebulization (Inspi-Neb) than with continuous nebulization (Conti-Neb).

The higher level of effectiveness of breath-actuated nebulization has already been reported in intubated and mechanically ventilated patients.^(38,39) In a clinical study involving patients undergoing treatment with antibiotics, Miller et al.⁽³⁹⁾ showed that when a breath-actuated jet nebulizer is used, instead of a continuous operating jet nebulizer, the delivered dose increases by more than five times. However, it is difficult to extrapolate these results to subjects on NIPPV using a single-limb circuit bilevel ventilator. Indeed, in our present study, urinary excretion of amikacin with synchronized nebulization was ~1.30 times greater than with continuous nebulization.

This low difference between continuous and synchronized nebulization regarding the previous articles in mechanical ventilation could be explained by several factors related to our experimental aerosol delivery system: (1) The use of a vibrating mesh device normally designed to operate continuously. The intermittent operating of our device associated with the high viscosity of amikacin could have affected its performance (e.g., particle size distribution and residual volume) and led to a decrease in aerosol delivery with Inspi-Neb.^(21,40,41) (2) The delay of 20 milliseconds measured between the beginning of insufflation and actuation of our nebulizer (unpublished data) could have released the drug late in the inspiratory phase of subjects. The time for the nebulized drug to reach the lungs before the onset of

exhalation could have been too short, especially in subjects with low Ti/Ttot.^(12,21,42) Therefore, a higher amount of drug might have been delivered to the oropharynx⁽⁴³⁾ and lost in the circuit (including the face mask),⁽²¹⁾ thereby reducing the deep pulmonary delivery (e.g., alveolar spaces) with Inspi-Neb.^(12,21,42,44)

(3) The delay of 20 milliseconds measured between the end of insufflation and the stop actuation of the nebulizer (unpublished data) could have increased the amount of drug lost during exhalation. This delay could have increased total lost dose, and thus decreased aerosol delivery with Inspi-Neb.^(44,45) (4) The ventilation techniques such as the use of ventilator with single-limb circuit, face mask, and ventilator settings could have promoted a large reservoir effect with Conti-Neb.^(16,46) A large amount of drug nebulized during the expiratory phase could have been stored in the circuit (including the face mask) and delivered during the next inspiratory phase, thereby improving aerosol delivery with Conti-Neb,^(16,21,42,44) and hence its difference in pulmonary drug with Inspi-Neb.

Other than in the study by Galindo-Filho et al.,⁽⁴⁾ the vibrating mesh nebulizer coupled to a bilevel ventilator has never been tested in clinical studies. In a crossover study assessing radioaerosol pulmonary deposition in noninvasive ventilated healthy subjects, the authors showed that the vibrating mesh nebulizer delivered up to twice more radioaerosol particles into the respiratory tract than the jet nebulizer device.

To our knowledge, our study is the first clinical study to investigate the use of inspiratory synchronized vibrating mesh nebulization in subjects undergoing NIPPV with single-limb circuit bilevel ventilators.^(2,3) The present results confirmed the findings of our previous bench study,⁽²¹⁾ where inspiratory synchronized vibrating mesh nebulization, during NIPPV with single-limb circuit bilevel ventilators, significantly enhanced pulmonary delivery compared with continuous vibrating mesh nebulization. The higher urinary excretion with Inspi-Neb (on average 21% more than with Conti-Neb) may be mainly explained by the fact that aerosol loss through the passive exhalation port is minimized during expiratory time (unlike Conti-Neb), because the nebulizer only operates during the total inspiratory time, therefore increasing the dose of medication available to the patient.^(12,13,39,45)

In our previous bench study⁽²¹⁾ that compared both nebulization modes during NIPPV with different respiratory conditions (respiratory rate, resistance, and Ti/Ttot), we showed that the total lost dose (including drug lost through the passive exhalation port and in the circuit) was significantly reduced (up to 35% of the nominal dose), and the respirable dose was significantly increased (up to 32% of the nominal dose) with Inspi-Neb compared with Conti-Neb. Although our current results were quite well predicted by our previous bench study,⁽²¹⁾ it is difficult to match pulmonary drug delivery evaluated, by the total daily urinary amount of drug, with the respirable dose measured *in vitro*.⁽²⁹⁾ The difference between the results of the total daily urinary amount of drug and the respirable dose could be partly explained by two factors.

First, unlike the respirable dose measured at the outlet of the ventilator circuit, pulmonary drug delivery was influenced by the face mask, and by anatomical and mechanical characteristics of the subject's airways.⁽²⁹⁾ Second, the breathing patterns of healthy volunteers likely differed from

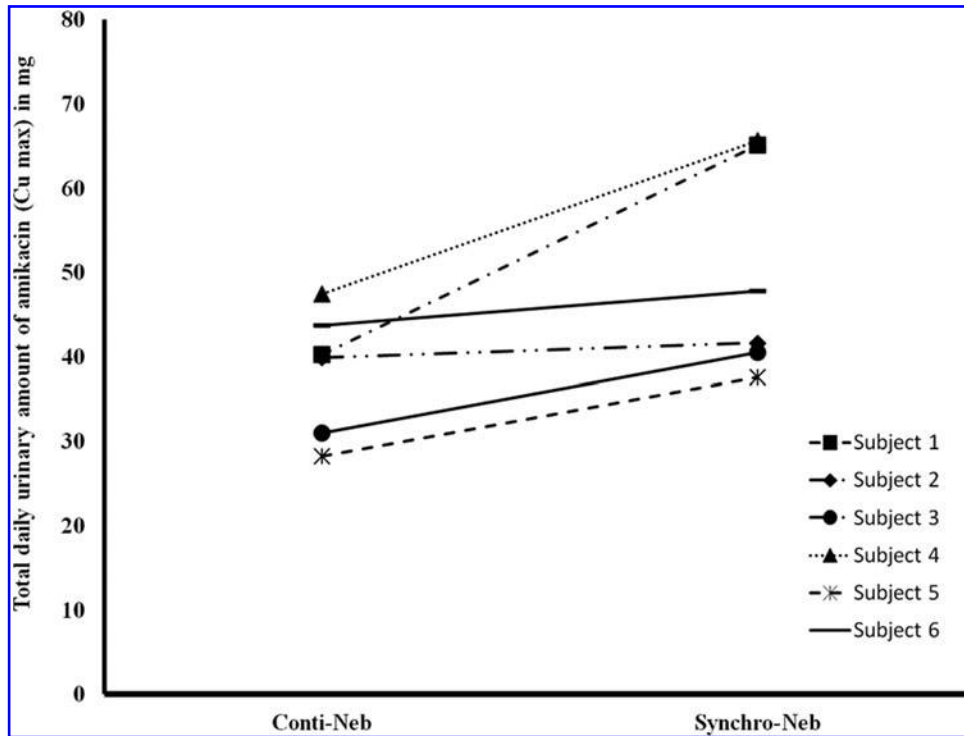


FIG. 3. Individual data of total daily urinary amount of amikacin (CU max) obtained with Conti-Neb and Synchro-Neb showing the difference of interindividual variability.

the respiratory parameters set in our bench model (e.g., tidal volume, respiratory rate, and inspiratory time) and could have influenced the lung dose delivered with Conti-Neb.^(6,14,16,17,24)

The increasing of total daily urinary amount of amikacin showed high intersubject variability (Fig. 3). The high increasing for subjects 1 and 4, and low increasing for subjects 2 and 6 may be explained by two factors. First, the larger minute ventilation and the longer expiratory time measured in subjects 1 and 4, compared with subjects 2 and 6, may have led to an increasing amount of drug lost through the passive exhalation port^(12,14,18,21) and in the circuit.^(16,17,21)

Therefore, the impact of Inspi-Neb, which only operates during the whole inspiratory time, may have been more important, thereby increasing the difference in total daily urinary amount of amikacin. Second, although all subjects were encouraged to breathe through the mouth, we noticed that subjects 2 and 6 were often breathing through the nose during the Inspi-Neb session. Nasal breathing may have affected aerosol deposition in the lungs,⁽⁴⁷⁾ and thus reduced the impact of Inspi-Neb and the difference in total daily urinary amount of amikacin.

The size distribution of aerosol particles is a critical determinant of depth of penetration into the lung.^(11,12,23,29,39,48) We used the constant of elimination as an indirect measure of the depth of penetration of the drug into the lungs.^(27,36) Our results showed that the constant of elimination was significantly higher with Inspi-Neb than with Conti-Neb, suggesting lung deposition of amikacin in more peripheral lung regions (without any other precision on these localizations) when using Inspi-Neb. We hypothesize that this difference might be due to differences in the composition of the aerosol cloud produced at the outlet of the ventilator circuit during nebulization.⁽⁴¹⁾

During Conti-Neb, the aerosol cloud delivered to the lungs resulted in a mixing of the particles produced during the ongoing inspiratory phase with the particles left in the circuit from the preceding expiratory phase.^(12,16) In contrast, during Inspi-Neb, the particles came primarily from the ongoing inspiration phase. In our previous *in vitro* study,⁽²¹⁾ we showed that the volume median diameter (i.e., the particle diameter at which 50% of the volume of the aerosol particles are larger and 50% are smaller) of the particles in the aerosol cloud at the outlet of the ventilator circuit was significantly smaller during Inspi-Neb than during Conti-Neb. Therefore, the size distribution of aerosol particles, produced by Inspi-Neb during NIPPV, could have promoted deeper lung penetration than Conti-Neb. Moreover, the greater lung delivery with Inspi-Neb might also have contributed to the increased rate of elimination.⁽⁴⁹⁾

The use of inspiratory synchronized nebulization mode may significantly increase treatment time in mechanically ventilated patients.^(50,51) In the present study, Inspi-Neb required on average 2.5 times longer time than Conti-Neb to nebulize the same nominal dose of amikacin (500 mg/4 mL), but produced a lung dose $\sim 21\%$ greater. Pulmonary drug delivery rate, expressed as the ratio between the total daily urinary amount of amikacin and the nebulization time, was on average 1.86 times significantly higher with Conti-Neb (2.03 mg/min) than with Inspi-Neb (1.09 mg/min).

This point raises the question whether Inspi-Neb may be useful in clinical situations in which rapid clinical responses with low lung doses are needed (e.g., β_2 -agonist), particularly for the management of noninvasive ventilated patients with acute exacerbations of their condition (e.g., asthma or COPD). Studies in mechanically ventilated patients showed

that a significant bronchodilator response occurs after nebulization of 2.5 mg of albuterol.^(24,52)

In addition, they observed that the delivery of higher doses produced a minimal therapeutic advantage and, moreover, the potential for side effects was increased.^(23,24,53) The use of Inspi-Neb would be more appropriate in clinical situations involving nebulization of expensive or toxic drugs, or when the dose of drug delivered is critical (e.g., antibiotics in ventilated patients with cystic fibrosis (CF)).^(6,50) For the administration of quick relief or rescue medications, such as β_2 -agonists in patients in a phase of exacerbation, the subjects of further research studies should be the development of specific synchronized nebulizers (for use in noninvasive ventilation) with high mass output and short reaction time.

Some limitations should be considered when interpreting the results of this study.

First, we used an experimental aerosol delivery system based on a vibrating mesh nebulizer normally designed to operate continuously. The intermittent operating mode of the nebulizer may have modified its behavior (e.g., vibration frequency of the device) and its performances (e.g., particle size distribution and residual volume).^(21,41) Moreover, a delay of 20 milliseconds has been measured between the onset of insufflation and actuation of the nebulizer, and between the end of insufflation and stop actuation of the nebulizer (unpublished data). The results observed with Inspi-Neb may be different with another synchronization system.

Second, aerosol delivery may be affected by several factors, including the structure and mechanical properties of patients' airways,^(29,54,55) respiratory parameters, and ventilator settings.^(14,17,27) However, since a within-subject design was used to compare nebulization modes, with the same ventilator settings for each mode and no significant differences found in the breathing patterns, the influence of these factors was minimized. Further investigations with patients with different pulmonary diseases (e.g., COPD and cystic fibrosis), physiological parameters, and ventilator settings are needed to extrapolate the present results to other conditions.

Third, we evaluated pulmonary drug delivery in healthy volunteers limiting the ability to demonstrate a differential response to various respiratory patterns and inhaled medications. Information regarding the pharmacological response of patients with pulmonary diseases can, therefore, not reliably be derived from these data. Further clinical studies with patients are warranted to establish whether these results are clinically relevant.

Fourth, we did not use a humidifier in our study because it is an important factor affecting aerosol delivery. The heat and moisture exchanger acts as a physical barrier to aerosol delivery, therefore it should be removed before drug nebulization.⁽²³⁾ Although switching off the heated humidifier is not recommended for routine aerosol therapy (e.g., bronchodilators),^(23,56,57) suspending humidification could be indicated during nebulization of expensive drugs (e.g., antibiotics)^(23,56) because of the hygroscopic effects of humidification.⁽²³⁾ However, the effects of switching off the heated humidifier before administration of aerosol are difficult to predict,⁽⁴⁶⁾ especially in long-term NIPPV patients where it enhances comfort and tolerance.^(58,59) Indeed, it has been shown that after 3 hours of humidifier operation, turning off the heated humidifier for up to 30 minutes before aerosol therapy did not improve drug delivery.⁽⁴⁶⁾ Therefore,

the results of our study may not be extrapolated to NIPPV with a heated humidifier even if it is turning off before administration of aerosol.

Fifth, aerosol delivery may be affected by properties of the drug solution^(40,60) and brand of the vibrating mesh device.⁽¹⁸⁾ Moreover, the reliability of reusable vibrating mesh nebulizers may be decreased with repeated use over time.^(18,61) The results may not be applied to the same nebulizer used with other medications or to other brands of vibrating mesh nebulizers or reusable devices.

Sixth, even if subjects were encouraged to breathe through the mouth with a face mask, it cannot be excluded that amikacin concentration may be influenced by nasal drug deposition. However, amikacin diffusion from the nasal cavities to the blood is affected by a large number of factors, such as the physicochemical properties of nasal mucus (low permeability to cationic drugs, such as aminoglycosides),^(62,63) the nasal epithelium structure (mainly ciliated pseudostratified columnar epithelium hindering nasal drug diffusion),⁽⁶⁴⁾ and the nasal mucociliary clearance rate (high mucociliary clearance rate shortening nasal residential time of drugs and thus limiting diffusion of drug).^(65,66) The results of our study may not be extrapolated to NIPPV using nasal masks.

In conclusion, during NIPPV with a single-limb circuit bilevel ventilator, the use of inspiratory synchronized vibrating mesh nebulization may improve pulmonary drug delivery compared with conventional continuous vibrating mesh nebulization. Therefore, the development and commercial availability of breath-actuated nebulizer systems should be considered for bilevel ventilators to reduce aerosol loss and ensure optimal aerosol delivery, especially for nebulization of expensive or toxic drugs. However, clinical trials in patients with pulmonary diseases are required to determine if these results are clinically relevant.

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Author Disclosure Statement

The authors declare that no competing financial interests exist.

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