Influence of different oxygen flow on aerosol delivery from Aerogen Solo with Aerogen Ultra: In-vitro and in-vivo study

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Abstract

Background: Aerogen Ultra (AU), a unique holding chamber designed to be utilized with the Aerogen Solo vibrating mesh nebulizer (AS), was developed to maximize the total dose that subjects can breathe in. It can be used for continuous and intermittent nebulization with the elective supply of additional oxygen. **This work's aim** was to see how well an AS coupled to an AU as a holding chamber with a mouthpiece and valved facemask (VFM) work at diverse oxygen flows from 0 to 6L/min. **Methods**: this was an In-vitro and in-vivo study, First, in the in-vitro part, with 500 mL tidal volume, fifteen breaths every minute, and a ratio of 1:1 between inhalation and exhalation, we were able to imitate adults' natural breathing patterns. Five evaluations were done for the combination of AS and AU adaptor with VFM or mouthpiece and 0, 2, 3, 4, and 6L/min oxygen flow. Secondly, we conducted an in-vivo trial with 12 healthy non-smokers who were > 18 years old and had a typical forced expiratory volume in one second (FEV1) that was ≥ 90% of predicted. The subjects used AS linked to AU with VFM or mouthpiece and 0, 2, 3, 4, and 6L/min oxygen flow to inhale Salbutamol nebulized in 1 mL (5,000 µg) during normal tidal breathing. Urine was taken 30 minutes after dosage as a measure of lung deposition, and urine was collectively gathered over the course of 24 hours as a measure of systemic absorption. **Results:** The salbutamol amount deposited on the inhalation filter and the amounts of excreted salbutamol in the 30 minutes and over 24 hours after the start of the inhalation were improved until oxygen flow of 2 L/min, and 3 L/min with the mouthpiece and VFM, respectively. In comparison to the other oxygen flows, this flow had significantly greater salbutamol and the delivered dose was then steadily declined until at 6L/min of oxygen flow, $p < 0.05$. **Conclusions:** With the AS connected to the AU, mouthpiece, or VFM, the total inhalable doses and the amount of excreted salbutamol within the first 30 minutes and over the course of 24 hours after the start of inhalation were inconsistent at different oxygen flows. Up until oxygen flow reached 2 L/min with the mouthpiece and 3 L/min with the VFM, there were notable improvements; however, beyond that, there was a steady decline to lower values at 6 L/min of oxygen flow.

Keywords: Aerogen Ultra; holding chamber; Aeogen Solo; vibrating mesh nebulizer; total inhalable dose.

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Background

The Aerogen Ultra holding chamber (AU; Aerogen, Galway, Ireland) was formed to help spontaneously breathing subjects use easily Aerogen Solo vibrating mesh nebulizer (AS; Aerogen, Galway, Ireland) with either a mouthpiece or a valved facemask (VFM). [1] According to Aerogen Limited, the AU works as an aerosol tank and permits low oxygen flow (1-6 L/min) supplies. [1] It could be operated on for continuous or intermittent nebulization in pediatric or adult subjects. The AU connects to the AS and a side-mounted mouthpiece or VFM. The passage of the aerosol from the AU to the subject is managed by a valved system. Through the entrance valve on the bottom of the AU, oxygen from the AS is sucked into the chamber. [2] During inhalation, the medicated aerosol is delivered to the subject through the mouthpiece valve. The mouthpiece valve close during exhalation while the AS refills the AU with aerosol, the subject can exhale throughout the mouthpiece exhalation valve. [2]

These characteristics increase nebulizer effectiveness and reduce aerosol loss through condensation and expiration. [1] AS connected to AU with oxygen flowing at 2 L/min delivered more aerosol than a jet nebulizer, according to Ari et al. [2] In this study comparison was done among AS and a jet nebulizer However AS with different interfaces and oxygen flows was supposed to be employed. Furthermore, multiple tests have shown that the AS, due to its better efficacy, releases more aerosol than the jet nebulizer regardless of the setting.[3-13]

According to a prior study, employing the AU with the AS significantly improved delivered aerosol in comparison to T-piece. [1] They went on to add oxygen at a flow of 6 L/min to AU. [14] Supplying oxygen at the supreme suggested flow (6 L/min) caused a significant decrease in aerosol delivery. [14] This wok aim was to in-vitro and in-vivo compare the effect of AS connected to AU with different oxygen flow rates (0 to 6 L/min), and different interfaces (mouthpiece or VFM) on delivered nebulized salbutamol.

Methods

Amount of emitted aerosol

As illustrated in Figure 1, the AS was linked to the AU coupled with mouthpiece and VFM. At variable flows of 0 to 6 L/min, oxygen was delivered through an inlet in the bottom of the AU. The breathing simulator model (5600i, Michigan Instruments, Kentwood, Michigan) was set to mimic a resting breathing pattern as suggested in European Standard EN 13544-16, which is 20 breaths per minute at a tidal volume of 500 mL, 15 breaths/minute, with an inhalation-exhalation ratio of 1:1 (CEN methodology). [15]

As shown in Figure 1, the nebulizer-adapter combination was connected to one side to the breathing simulator, and the other side of an electrostatic filter pad within a filter holder (Pari, Starnberg, Germany) as an inhalation filter. For the VFM interface, The experimental setup had a plate with an opening in the center, and the VFM was attached to it as illustrated in Figure 1. It has been discovered before that there are no appreciable differences between the face anatomical model and this plating technique for determining the inhalable mass from a nebulizer. [16, 17] Each determination was made using a distinct filter. As a result, the entire amount of aerosol left in this filter during inspiration could be accurately estimated. [4, 18] The simulator was turned on 30 seconds before nebulization of 1 mL respirable solution comprising 5000 µg salbutamol (Farcolin Respirator Solution, Pharco Pharmaceuticals, Egypt).

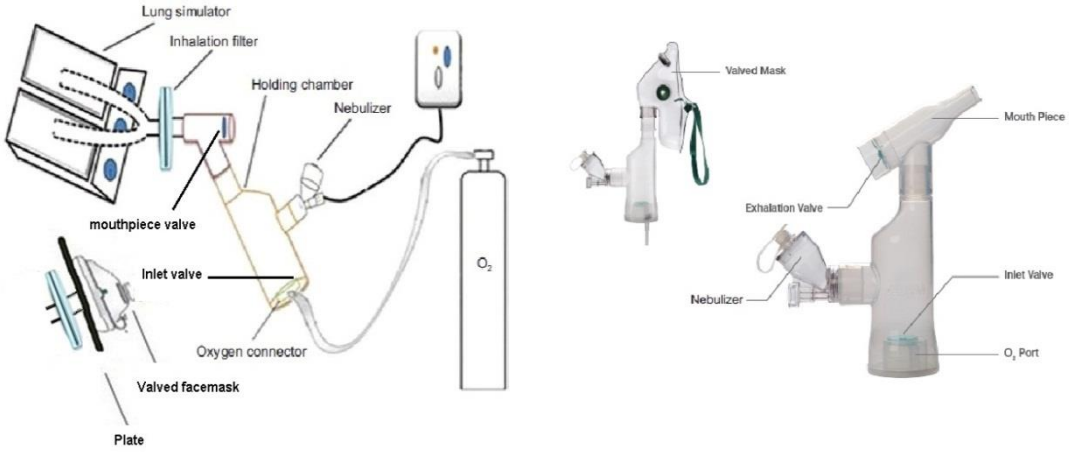

Figure 1: Shows a schematic diagram of the in-vitro experimental setup for determining the amount of aerosol released (the total inhalable aerosol dose).

Five measurements were made for each combination of nebulizer-adaptor-inhalation flow. Nebulization was to dryness. Salbutamol deposited on the filter was recovered by washing and sonication with 20% acetonitrile for 3 minutes. Salbutamol concentration was evaluated using high-performance liquid chromatography (HPLC) with ultraviolet detector.[19]

Lung deposition and systemic bioavailability

To calculate salbutamol's relative systemic bioavailability and lung deposition after inhalation, Hindle and Chrystyn developed urine pharmacokinetic technique. [20] The drug amount excreted within 30 minutes after inhalation was used as a measure of lung deposition, and the excreted drug amount during the following 24 hours was utilized as a measure of systemic absorption. [20] This non-invasive pharmacokinetic approach has been utilized to identify pulmonary drug deposition in individuals with asthma or COPD exacerbations, subjects receiving ventilation, and healthy volunteers. [3-13] Similarly, we compared lung deposition and systemic absorption using the same methods. The updated Helsinki Declaration was followed this investigation. The procedure was approved by regional institutional review boards and an independent ethical committee (REC-H-PhBSU-21003), and each subject provided written informed consent. Twelve healthy volunteers over the age of 18 who were not smokers and had a forced expiratory volume in one second ≥ 90% accepted to inhale a nebulized aerosol of a salbutamol respiratory solution. They received the first instruction on how to use the nebulizers for inhalation. The test volunteers were instructed to gently inhale and exhale while holding the mouthpiece between their lips or wearing the VFM

connected to the AU with oxygen flow 0, 2, 3, 4, 6L/min as shown in Figure 2. Each participant inhaled 1mL of salbutamol respirable solution (5,000µg/mL) in a random manner. HPLC was used to monitor and analyze the drug excretion in 30 minutes and 24 hours after inhalation. The collected urine samples were given an internal standard of bambuterol hydrochloride. Using solid-phase extraction, bambuterol, and salbutamol were removed from the urine sample, and salbutamol concentration was evaluated using HPLC with ultraviolet detection. [19]

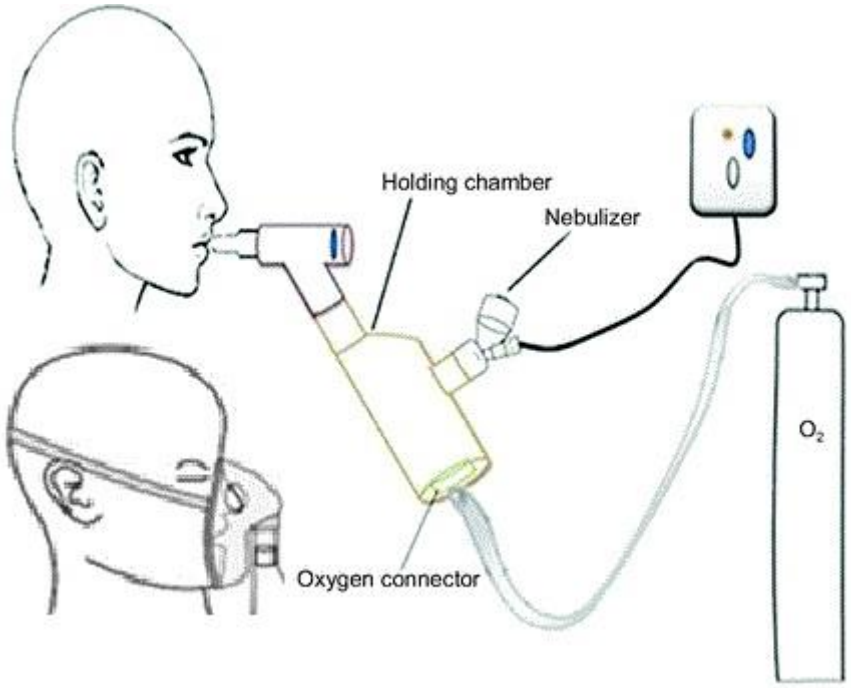

Figure 2: Schematic diagram of in-vivo methodology indicating the position of the nebulizer to volunteer with the oxygen source

Statistical analysis: The mean and standard deviation of all data are displayed. To analyze the impacts of various flows utilizing a mouthpiece and a VFM, a one-way ANOVA analysis of variance with adjustment for the least significant difference was carried out using SPSS V15.0 (SPSS, Chicago, Illinois, USA). To compare the efficacy of the mouthpiece and the VFM a T-test analysis was used.

Results

The amount of salbutamol delivered to the filter pad increased dramatically, reaching 2 L/min of oxygen flows with the mouthpiece and 3 L/min with VFM. Table 1 presents the outcomes of the delivered salbutamol of the AS and AU linked to the mouthpiece and VFM with different oxygen flows (0 to 6 L/min) as mean and standard deviation (mean±SD). When compared to the other oxygen flows, this flow supplied more salbutamol, which was preceded by a gradual decrease. The lowest administered salbutamol dose was delivered at an oxygen flow of 6L/min, as shown in Table 1. Table 1 shows that administered inhalable salbutamol doses with oxygen flows of 0, 1, 2, and 5 L/min did not significantly differ using mouthpiece or VFM (p-values=0.947, 0.944, 0.132, and 0.142, respectively), whereas with oxygen flows of 3, 4, and 6 L/min it significantly differs (p-values = 0.001, 0.003, and <0.001, respectively).

Table 1 also shows the mean±SD of the salbutamol amounts excreted from the 2 nebulizer-adapter combinations with the used different oxygen flows following inhalation. With no oxygen, the amount of salbutamol excreted in 30 minutes and over the next 24 hours was much higher (106.83±23.84 µg, and 962.48±214.80 µg, respectively with the mouthpiece and 962.48±214.80 µg, and 962.48±214.80 µg, respectively with the VFM) than with oxygen flow of 6 L/min (75.94±16.95 µg, and 856.13±191.07 µg, respectively, with the mouthpiece and 98.02±21.88 µg, and 975.26±217.66 µg, respectively with the VFM, $p<0.05$) however with no oxygen results was significantly lower than at oxygen flow of 2 L/min with the mouthpiece (121.31±27.07 µg, and 1092.90±243.91 µg, respectively, $p < 0.05$) and 3 L/min with the VFM (130.63±29.15 µg, and 1299.77±290.08 µg, respectively, $p < 0.05$). Similar to the in-vitro study, a gradual decrease was observed at oxygen flow 4 L/min followed by the lowest delivery at flow 6 L/min.

Table 1: Comparison between delivered dose in micrograms using mouthpiece and facemask

	Mouthpiece			Facemask		
O_2 flow rate	**Delivered dose**	**salbutamol excreted in the first 30 min**	**salbutamol excreted in the over a 24-hour**	**Delivered dose**	**salbutamol excreted in the first 30 min**	**salbutamol excreted in the over a 24-hour**
0	2153.9±495.1	106.8±23.8	962.5±214.8	2136.3±285.5	106.0±23.7	954.6±213.1
1	2184.6±393.4	-	-	2164.7±477.4	-	-
2	2445.7±315.4	121.3±27.1	1092.9±243.9	2230.6±105.0	102.7±22.9	1022.2±228.1
3	2190.1±296.5	100.9±22.5	1003.6±224.0	2836.2±188.6	130.6±29.2	1299.8±290.1
4	2158.6±201.8	99.4±22.2	989.2±220.8	2570.2±76.1	118.4±26.4	1177.8±262.9
5	2076.2±506.8	-	-	2284.2±246.5	-	-
6	1814.5±162.3	75.9±17.0	856.1±191.1	2128.1±243.1	98.0±21.9	975.3±217.7

Discussion

In the current study, flow rates ranging from 0 to 6 L/min are used to compare the performance of an AS coupled to an AU utilizing a mouthpiece and VFM.

The nebulizer and interface utilized for aerosol treatment have a significant influence on how much medication is inhaled.[2] Since the AU was shown to boost the given aerosolized dose, we chose to employ it in place of a T-piece for our experiment. [1] Additionally, the AS is normally placed next to the AU, which lessens the gravitational sedimentation of the medicine nebulized. [1]

With values of 2,197.7 ± 470.7 µg and 1,081.5 ± 333.9 µg, respectively, Sarhan et al. [14] observed that the given dose was substantially larger when utilizing an AS coupled to an AU and mouthpiece without oxygen than at oxygen flow of 6 L/min. Though, there was an extra influence when utilizing different oxygen flows. In our study, comparable results were found when using a VFM and mouthpiece. We found that the oxygen flow had a substantial impact on the given salbutamol dose by raising the provided dose till the flow was 2 L/min when using the mouthpiece and 3 L/min when using the VFM. The supplied salbutamol dose then steadily decreased as the oxygen flow increased until it had reached its lowest point at 6 L/min. The study's in-vivo and in-vitro results revealed the same impact .[21]

Bennett et al. [22] measured the given dose using humidified air rather than oxygen at flows of 0, 2, and 6 L/min using an AS connected to an AU with a mouthpiece and VFM. For both the mouthpiece and the VFM, a flow of 2 L/min created the highest inhalable dose. They did not, however, take measurements at oxygen flows of 1, 3, 4, and 5 L/min. Their outcomes were comparable to ours even without these four oxygen flows.

The maximum inhalable dose of oxygen was produced at the oxygen flow of 4 L/min, according to the results of another study that examined three oxygen flows (2, 4, and 6 L/min). [23] This investigation supports our conclusions even if the detected flow was different from the one we predicted. They suggested a higher oxygen flow than we did, which was the only difference. That could be because they only employed a VFM, for which we discovered the best oxygen flow was 3 L/min [23], and a larger tidal volume (750 mL), which is 250 mL more than the average tidal volume used in most in-vitro investigations (500 mL). [24-35] This implies that the increased tidal flow improved the benefit of oxygen provided as a supplement to the aerosol within the AU.

Higher oxygen flows during the exhale phase could flush the aerosol from the AU. When there is little or no oxygen flow, the aerosol gathers in the AU and is made available to the subjects during inspiration. 130 mL in size, the AU at a flow of 6 L/min (100 mL/seconds). The breathing simulator was programmed with a 1:1 inhalation-exhalation ratio, a breathing rate of 15 breaths per minute, and a tidal volume of 500 mL. As a result, with the 2 seconds expiration, which is equal to 200 mL of oxygen, at a flow rate of 6 L/min, the majority of the preserved aerosol in the AU throughout exhalation could be flushed out before inhalation. Our in-vivo data, which revealed that the optimal aerosol delivery was at an oxygen flow of 2 L/min for the mouthpiece and 3 L/min for the VFM, confirmed this theory by showing that the amount of aerosol gathered in the AU between breaths decreased as oxygen flow increased. Researchers should evaluate the inhaled salbutamol dose from AS coupled with AU across various tidal volumes and flows in light of this discovery to see how the inhalable dose correlates. For VFM the finest aerosol delivery was at 3 L/min with a tidal volume of 500 mL and 4 L/min in the Brady et al study with a tidal volume of 750 mL, showing the influence of tidal volume on aerosol delivered evidently when comparing the results of the two studies.[23]

Additionally, our research revealed that the supplied salbutamol dose with a VFM and oxygen was significantly higher than with a mouthpiece. These outcomes might be clarified by the fact that VFMs, as opposed to mouthpieces, may offer more room for storing aerosol during exhalation. This would result in less aerosol waste from the oxygen flow throughout the exhalation stage of the

respiratory cycle. [36-38] The in-vivo and in-vitro results are comparable but there should be modeling to correlate them to each other so that when looking at the in-vitro data of any study using AS with the AU we could expect the clinical outcomes of it as was previously done in several studies. [12, 39-42]

Conclusion

The total inhalable dose delivery was affected differently by different oxygen flows inside the AU linked to the AS, with mouthpiece, or VFM. There were notable improvements up till oxygen flows of 2 L/min with the mouthpiece and 3 L/min with the VFM, followed by steady declines to lowest values at oxygen flows of 6 L/min.

List of abbreviations

Aerogen Ultra **(AU)**
Aerogen Solo Vibrating mesh nebulizer **(AS)**
Valved Facemask **(VFM)**
High Performance Liquid Chromatography **(HPLC)**

Declarations

a. Ethics approval and consent to participate
(REC-H-PhBSU-21003)

b. Consent for publication
Not applicable

c. Availability of data and materials
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

d. Competing interests
The authors declare that they have no competing interests

e. Funding
There was no external funding for this study itself. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

f. Authors' contributions
(1) Conception and design: MA
(2) Administrative support: All authors.
(3) Provision of study materials: All authors.
(4) Collection and assembly of data: ME.
(5) Data analysis and interpretation: ME.
(6) Manuscript writing: ME
(7) Final approval of manuscript: All authors.
All authors have read and approved the manuscript

f. Acknowledgments
Not applicable

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