Output characterization of the Vyntus™ APS dosimeter according to the current standards

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Introduction

Bronchial challenge testing (BCT) is a method used to assess the presence and degree of airway hyperresponsiveness, which is a hallmark of asthma.[1, 2, 3] The recommended and most commonly used stimulus for this test is methacholine chloride.[4] During the challenge test, the dose of methacholine is gradually increased while monitoring airway hyperresponsiveness by measuring the lung function, usually by the forced expiratory volume in one second (FEV1).[4, 2] Bronchial hyperreactivity is then expressed as the inhaled dose of methacholine that causes a 20% decrease in FEV1. This inhaled dose is the primary endpoint of the BCT labeled as the provocative dose (PD20). From a clinical standpoint, BCT results are usually interpreted as either positive or negative test results.[5] The absence of airway hyperresponsiveness (i.e., a negative test result) is highly sensitive in indicating that asthma is unlikely. On the other hand, the existence of airway hyperresponsiveness (i.e., a positive test result) confirms the presence of asthma.[3] Therefore, the degree of bronchial hyperreactivity detected in the challenge test has important implications for treatment and prognosis.[2, 4, 6]

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Devices for administering the stimulus

To administer the stimulus, either a nebulizer or a dosimeter device can be used.[4] Nebulizers can deliver the stimulus in two ways: continuously or only during inhalation. Continuous nebulizers administer the stimulus throughout the full respiration cycle, even during exhalation [Figure 1A]. Breath-actuated nebulizers (BAN) only release the aerosol during inhalation [Figure 1B]. When using a dosimeter device, the stimulus is administered exclusively during inhalation, as a pulse, for a specific and predetermined time ranging from 0.2 to 1.0 seconds [Figure 1C].

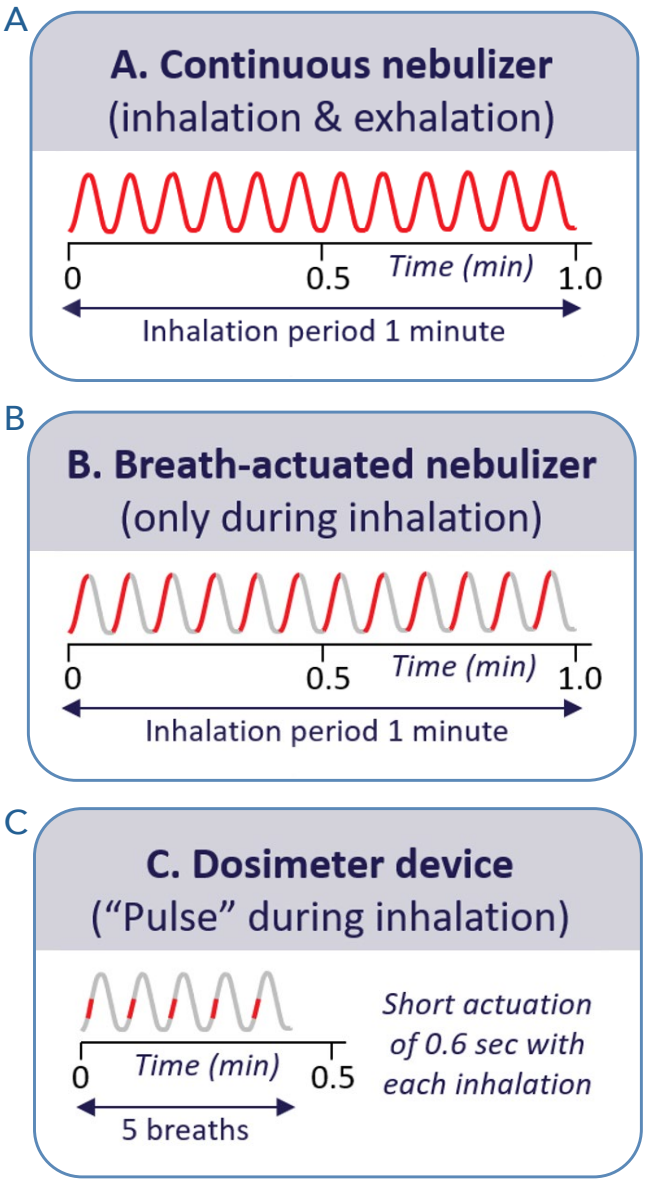


Figure 1. Methods for administering the stimulus during BCT..

The Vyntus™ APS dosimeter offers both "Breath-actuated" [Figure 1B] and "Pulse" [Figure 1C] nebulization modes for administering the stimulus. Its ability to measure the nebulization time during inhalation enables accurate calculation of the administered dose and therefore the PD20, which is essential for accurately measuring the degree of airway hyperresponsiveness.

Recommendations for characterizing the nebulizer performance

Previous 1999 American Thoracic Society (ATS) guidelines, recommended characterizing nebulizers by measuring weight loss over time without a breath simulator, and determining if the nebulizer produces an aerosol with a particle size distribution where the mass median aerodynamic diameter (MMAD) falls between 1.0 and 3.6 µm.[2] The MMAD represents the diameter of aerosol particles at which 50% are larger and 50% are smaller by mass. It was believed that particles within this range were more likely to reach the peripheral airways, with smaller-sized particles evaporating and larger-sized particles depositing in the mouth and throat tissues.[7]

More importantly, the European Respiratory Society (ERS) updated these guidelines in 2017, resulting in significant changes compared to the recommendations put forth by the ATS in 1999.[4] Instead of solely relying on weight loss without a breath simulator, current guidelines recommended to measure the inhaled mass using a breath simulator.[4, 8] This approach involves the collection of aerosols using a filter positioned between the simulator and the patient's outlet on the device. Additionally, instead of MMAD, the guidelines now recommend using the respirable fraction, which represents the mass fraction of inhaled particles with a size of 5 µm or less.[7] Overall, this significantly changed requirement ensures a comprehensive approach to characterize the nebulizer output used during bronchial challenge testing accurately.

Nebulizer performance of the Vyaire dosimeter

Previously, the output of the MasterScreen APS dosimeter, when used with the reusable Philips SideStream Nebulizer, was determined to be approximately 240 mg/min, based on ATS 1999 recommendations.[2] This characterization was conducted in 2002 by Inamed GmbH, where the output was solely based on measuring weight loss for two minutes of continuous nebulization, without using a breath simulator. Following this characterization, a peer-reviewed verification study was conducted. This study showed acceptable agreement between a single-concentration dosimeter protocol using the MasterScreen APS dosimeter and the characterized output of 240 mg/min to a multi-concentration dosimeter protocol recommended by the ATS.[9]

With the introduction of the latest guidelines,[3] a new bench study was carried out by MedSpray in 2022 to assess the output of the Vyntus™ APS dosimeter when used with the disposable Philips Side Stream nebulizer. Given the short actuation times utilized by the Vyntus™ APS dosimeter for both the "Breath-actuated" and "Pulse" nebulization modes, it was decided to assess the

nebulizer's performance, the way the Vyntus™ APS is intended to be used, with actuation times of 0.2, 0.4, and 1.0 seconds, rather than nebulizing continuously for two minutes. This characterization was executed according to the latest ERS guidelines and included measuring the inhaled mass, inhaled volume, and respirable fraction via a breath simulator.[10, 8] The measured inhaled volume and respirable fraction are essential in the determination of the output in mg/min, used by the Vyntus™ APS dosimeter, for setting up BCT protocols and calculating the inhaled dose. The methods and results of this bench study are described in this white paper.

Methods characterization of the Vyntus™ APS dosimeter

Inhaled mass and inhaled volume

To assess the performance of the Vyntus™ APS dosimeter when used with the SideStream nebulizer in terms of inhaled mass and inhaled volume, we performed tests using albuterol formulation with a breath simulator and a filter positioned at the patient's side, as illustrated in Figure 2. We utilized five randomly selected nebulizers of the same model (Philips Respironics SideStream nebulizer, Single use; V-8922608, Phillips Respironics, USA). Each nebulizer underwent five tests while pressurized by the Vyntus™ APS compressor. For each test, the nebulizer was filled with 2 mL of 0.0625% albuterol hemisulfate formulation with the addition of 0.5% fluorescein to allow measurement of inhaled mass by ultraviolet-visible (UV VIS) method.[11] A filter (AirLife™ Single Use; V-892020, Vyaire Medical, USA) was connected to the patient's outlet of the Vyntus™ APS to collect the aerosolized albuterol. We utilized a breath simulator (BRS 1100, Copley Scientific, United Kingdom) to mimic patient inhalation and exhalation profiles, set at inhalation time (Ti)/total time (Ttot) = 0.5; tidal volume (VT) = 750 mL; and breathing frequency (BF) = 15/min. The inhaled mass on the filter was determined via the UV-VIS method. The Vyntus™ APS was controlled using SentrySuite™ 3.20 software installed on a PC and was set to a "Pulse Nebulization" protocol with pulse durations of 0.2, 0.4, and 1.0 seconds. The amount of nebulization for each pulse duration was 30x, 15x, and 10x actuations in a single measurement, respectively.

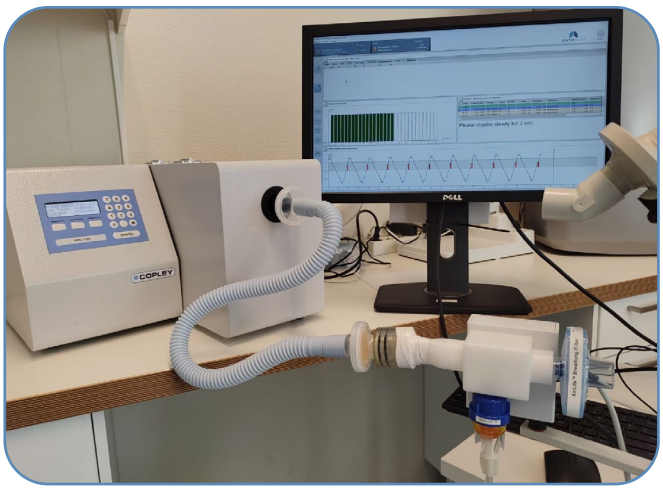


Figure 2. Experimental setup inhaled mass and volume.

Respirable fraction characterization (droplets ≤ 5µm)

The respirable fraction of the SideStream nebulizer when used with the Vyntus™ APS was assessed using a formulation of albuterol hemisulfate (0.0625%), along with the Malvern Spraytec laser diffraction system and a breath simulator. The experimental measurement setup is shown in Figure 3. We utilized the same breath simulator and profiles as those used for measuring the inhaled mass and volume. The Philips SideStream nebulizer was filled with 2 mL of the albuterol formulation. The respirable fraction was determined using laser diffraction[12] for actuation times of 0.2, 0.4, and 1.0 seconds, utilizing a "Pulse" nebulization protocol within the SentrySuite™ 3.20 software.

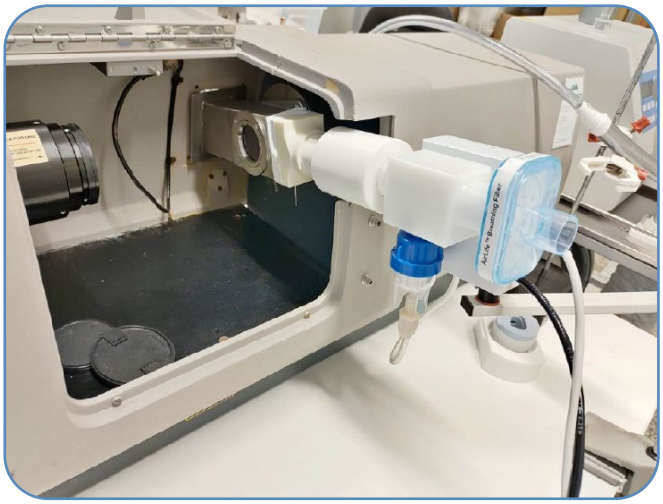


Figure 3. Experimental setup respirable fraction.

Results from the characterization of the Vyntus™ APS dosimeter

Inhaled mass and inhaled volume

Measurement results of inhaled volume and inhaled mass per second are presented in Table 1. The results shown are based on the average outcome for each tested actuation time (i.e., 0.2, 0.4, and 1.0 seconds). The inhaled volume per second (µL/sec) is calculated by dividing the recovered active ingredient in the filter by the total nebulization time. The inhaled mass of albuterol (µg/sec) is determined by dividing the total amount of albuterol in the filter by the total nebulization time.

Actuation time [sec]	Inhaled volume [µL/sec]	Inhaled mass albuterol [µg/sec]
0.2	9.02	5.63
0.4	8.74	5.46
1.0	8.39	5.24

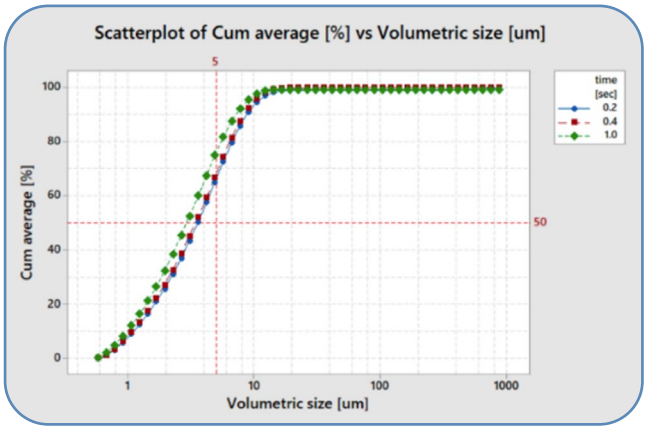
Table 1. Results inhaled volume and inhaled mass per second per actuation time.

Respirable fraction

Graph 1 displays the cumulative fractions versus the volumetric diameter for each actuation time. By examining this graph, we can determine the particle sizes below 5 µm, known as the respirable fraction. Values in Table 2 represent the respirable fractions for each actuation time (i.e., 0.2, 0.4, and 1.0 seconds). These values are obtained from the data presented in Graph 1.

Actuation time [sec]	Respirable Fraction
0.2	0.67
0.4	0.69
1.0	0.75

Table 2. Results respirable fraction per actuation time.



Graph 1. Cumulative fractions versus volumetric diameter.

Output of the Vyntus™ APS dosimeter

The inhaled mass of methacholine can be calculated by extrapolating the inhaled mass of albuterol to the inhaled mass of methacholine at a concentration of 16 mg/ml.[2] Using this process, the inhaled mass of albuterol using an actuation time of 0.2 seconds was measured as 5.63 µg/sec, or 0.00563 mg/sec:

- The nebulizer is filled with 2 ml albuterol formulation with a concentration of 0.625 mg/ml; the total amount of albuterol in the nebulizer is 1.25 mg (2 mL x 0.625 mg/ml)
- The filter collection reveals 0.00563 mg of albuterol over 1.0 second, which corresponds to 0.45% of the mass of albuterol delivered in 1 second ((0.00563 mg/sec / 1.25 mg) x 100)
- Extrapolating this to methacholine at 16 mg/ml for a 2 ml fill, the inhaled mass for methacholine is calculated as 0.144 mg/sec ((16 mg/ml x 2 ml) x 0.0045 per second)

In summary, when actuations of 0.2 seconds are applied and a nebulizer is filled with 16 mg/ml of methacholine, the inhaled mass of methacholine is approximately 0.144 mg per second.

However, for a dosimeter such as the Vyntus™ APS, calculating the inhaled mass of methacholine differs from the calculation as described above. Instead of using the inhaled mass of albuterol, it relies on the inhaled volume. In addition, actuation time during a breath, total number of breaths, and methacholine concentration are needed to calculate the inhaled mass of methacholine. As an example, with actuation times of 0.2 seconds, the characterized inhaled volume was measured as 9.02 µl/sec (see Table 1). When the nebulizer contains a solution with 16 mg/ml of methacholine, and the dosimeter protocol is set to nebulize ten times with an actuation time of 0.2 seconds per breath, the inhaled mass of methacholine can be calculated as follows:

- Total volume nebulized = inhaled volume per second x actuation time x number of breaths
  Total volume nebulized = 9.02 µl/sec x 0.2 sec x 10 = 18.04 µl
- Inhaled Mass methacholine = total volume nebulized x methacholine concentration
  Inhaled Mass methacholine = 18.04 µl x (16 mg/ml / 1000) = 0.288 mg
- Inhaled mass methacholine per second = inhaled mass / total nebulization time
  Inhaled mass methacholine per second = 0.288 mg / 2 seconds = 0.144 mg per sec

In summary: the inhaled mass of methacholine, when actuations of 0.2 seconds are applied, is approximately 0.144 mg per second.

As anticipated and validated by the calculation example above, both calculation methods (inhaled mass versus inhaled volume) result in identical values for the inhaled mass of methacholine. Therefore, the decision was made to use the inhaled volume for calculating the inhaled mass expressed in mg/min when using the Vyntus™ APS dosimeter. For instance, when actuations of 0.2 seconds are used, the characterized inhaled volume is found to be 9.02 µl/sec, which translates to 541 µl/min (9.02µl/sec x 60 sec). Considering a density conversion close to 1 for albuterol, the inhaled mass when applying actuation times of 0.2 seconds is approximately 541 mg/min.

As a final step in the calculation of the output used with the Vyntus™ APS dosimeter for generating BCT protocols, the inhaled mass (determined as described above) is multiplied by the respirable fraction tested at the same actuation time. In our example, using an actuation of 0.2 sec, the output is calculated as 541 mg/min x 0.67 = 363 mg/min. See Table 3 for the calculation of the output in mg/min for each actuation time based on inhaled mass multiplied by the respirable fraction:

Actuation time [sec]	Inhaled Mass [mg/min]	Respirable Fraction	Output [mg/min]
0.2	541	0.67	363
0.4	524	0.69	362
1.0	503	0.75	378
Average	**523**	**0.70**	**368**

Table 3. Calculation of output used with Vyntus™ APS.

Since the output values for the tested actuation times did not show a significant variation, the average of the three values was determined as the output for the Vyntus™ APS dosimeter when used with the disposable Philips SideStream nebulizer. The final determined output for the Vyntus™ APS is 368 mg/min.

Discussion

Compared to the previous characterization results conducted by Inamed in 2002, which involved two-minute continuous nebulization, this study focuses on the specific use of shorter actuation times ranging between 0.2 and 1.0 seconds utilized with the Vyntus™ APS dosimeter. This updated characterization revealed a significant increase in output, with the Vyntus™ APS dosimeter generating 368 mg/min when used with the single-use Phillips SideStream nebulizer. This updated output value is applicable for actuation times ranging between 0.2 to 1.0 seconds and can be used with both "Pulse" and "Breath-actuated" nebulization modes within the SentrySuite™ software.

Although the latest guidelines recommend setting the breath simulator to a Ti/Ttot of 0.4, the simulator used in this study could only achieve 0.5. Despite this limitation, the study proceeded as planned because the Vyntus™ APS dosimeter accurately measures nebulization time in both "Pulse" and "Breath-actuated" modes. By measuring the nebulization time during inhalation, variability in patient breathing patterns can be mitigated, rendering the setting Ti/Ttot of the breath simulator irrelevant to the test results.

Limitations

This study has certain limitations. This is a bench study, and the applicability to use of in vivo is not clear. In addition, we used albuterol hemisulfate instead of methacholine. Both agents are readily soluble in water. We assumed that the Vyntus™ APS dosimeter should be relatively agent-agnostic for a water-soluble pharmacologic agent. However, there may be subtle differences depending on room temperature, pH, and ventilation. albuterol was selected as a less expensive (and safer for the staff) alternative to the use of methacholine.

Conclusions

The inhaled mass, inhaled volume, and respirable fraction of the Vyntus™ APS dosimeter have been assessed following the latest international standards. When using the Vyntus™ APS dosimeter with the single-use Philips SideStream nebulizer, an output of 368 mg/min should be used when setting up bronchial challenge protocols in either "Pulse" or "Breath-actuated" nebulization modes. This 368 mg/min output value is now included in newly integrated factory-locked protocols within SentrySuite™ software 3.30.

References

1. J. Schulze, M. Rosewich, C. Riemer, M. Dressler, M. A. Rose, and S. Zielen, "Methacholine challenge - Comparison of an ATS protocol to a new rapid single concentration technique," Respir. Med., vol. 103, no. 12, pp. 1898–1903, Dec. 2009, doi: 10.1016/j.rmed.2009.06.007.
2. R. O. Crapo et al., "American Thoracic Society guidelines for methacholine and exercise challenge testing -1999," Am. J. Respir. Crit. Care Med., vol. 161, no. 1, pp. 309–329, 2000.
3. R. Louis et al., "European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults," Eur. Respir. J., p. 2101585, 2022, doi: 10.1183/13993003.01585-2021.
4. A. L. Coates et al., "ERS technical standard on bronchial challenge testing: General considerations and performance of methacholine challenge tests," Eur. Respir. J., vol. 49, no. 5, May 2017, doi: 10.1183/13993003.01526-2016.
5. D. W. Cockroft, B. A. Berscheid, and K. Y. Murdock, "Unimodal distribution of bronchial responsiveness to inhaled histamine in a random human population," Chest, vol. 83, no. 5, pp. 751–754, 1983, doi: 10.1378/chest.83.5.751.
6. T. S. Hallstrand et al., "ERS technical standard on bronchial challenge testing: Pathophysiology and methodology of indirect airway challenge testing," Eur. Respir. J., vol. 52, no. 5, pp. 1–18, 2018, doi: 10.1183/13993003.01033-2018.
7. J. S. Brown, T. Gordon, O. Price, and B. Asgharian, "Thoracic and respirable particle definitions for.pdf," Part. Fibre Toxicol., vol. 10, pp. 1–12, 2013, [Online]. Available: http://www.particleandfibretoxicology.com/content/10/1/12.
8. A. Coates et al., "Characterizing nebulizer performance for methacholine challenge tests," Am. J. Respir. Crit. Care Med., vol. 198, no. 8, pp. 988–990, 2018, doi: 10.1164/rccm.201805-0942ED.
9. R. Merget, R. A. Jörres, E. Heinze, M. G. Haufs, D. Taeger, and T. Brüning, "Development of a 1-concentration-4-step dosimeter protocol for methacholine testing," Respir. Med., vol. 103, no. 4, pp. 607–613, 2009, doi: 10.1016/j.rmed.2008.10.010.
10. A. L. Coates et al., "ERS technical standard on bronchial challenge testing: General considerations and performance of methacholine challenge tests," Eur. Respir. J., vol. 49, no. 5, pp. 1–17, 2017, doi: 10.1183/13993003.01526-2016.
11. F. S. Rocha, A. J. Gomes, C. N. Lunardi, S. Kaliaguine, and G. S. Patience, "Experimental methods in chemical engineering: Ultraviolet visible spectroscopy—UV-Vis," Can. J. Chem. Eng., vol. 96, no. 12, pp. 2512–2517, 2018, doi: 10.1002/cjce.23344.
12. S. J. Blott, D. J. Croft, K. Pye, S. E. Saye, and H. E. Wilson, "Particle size analysis by laser diffraction," Geol. Soc. Spec. Publ., vol. 232, pp. 63–73, 2004, doi: 10.1144/GSL.SP.2004.232.01.08.

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