# EXAMINING USER BREATHING PATTERNS DURING NEBULIZATION WITH A GUIDED INHALATION MANEUVER

Carolina Dantas, Pascal Foerner, Ulf Krueger
Pulmotree Medical GmbH – Munich, Germany

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## Introduction:

- Pulmonary drug delivery is influenced by several factors such as the aerosol characteristics, the airway structure, and the breathing maneuvre, which ultimately leads to a wide variability in particle deposition. Studies have shown that **if the inhalation maneuvre is controlled, variability can be reduced** [1–3].
- Pulmotree Medical GmbH developed the **Kolibri mesh nebulizer** platform with a feedback technology that encourages users to inhale at a specific targeted flow rate and duration. By guiding the inhalation maneuvre during nebulization, a specific lung region could be targeted for aerosol deposition, according to the therapeutic purpose.

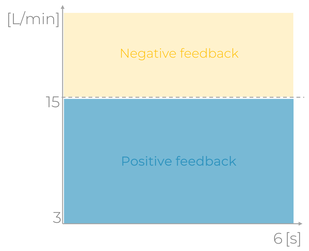
The goal of this study was to validate the Kolibri mesh nebulizer´s feedback technology and its ability to guide the inhalation maneuvre of untrained first-time users. The analysis and comparison of the inhalation flow rate, volume and duration were performed individually and within the group.

## Methods:

- Kolibri is a breath triggered mesh nebulizer developed to be tailored and optimized to each specific drug-device combination. When aiming for an efficient lung periphery aerosol deposition, slow and deep inhalations are encouraged.
- For this study, the following **settings** were defined:

Inhalation technology:

- Ideal inhalation flow rate defined as 15L/min
- Nebulization only occurred if inhalation flow rate was 3 - 18L/min
- Max. of 6 seconds of inhalation is recorded




Haptic feedback:

- a negative vibration feedback when inspiratory flow rate is too high (>15L/min)
- a positive vibration feedback when inspiratory flow rate is correct (≤15L/min)

- Performed in a laboratory setting according to a defined test protocol: each subject should inhale spontaneously (at his/her own breathing rate) 1 mL of saline with the Kolibri nebulizer. Inhalation flow rate (L/min) and duration (seconds) were recorded.
- Initial inclusion of 9 volunteers (5 male; 4 female), with a mean age of 44 years old. One subject was later excluded from the overall analysis, leaving data on **8 subjects**. Subject 4 had an asthma diagnosis, but an individual analysis was performed.

## Results and Discussion:

The results showed that the **Kolibri's feedback technology was able to successfully guide the user's inhalation maneuvre**.

### Intra-individual analysis

- Each participant had every inhalation recorded, which allowed to observe the **intra-individual variability** of the inhalation flow rate and duration during the inhalation of 1 mL of saline. Most individuals (6 of 8) maintained the mean inhalation flow rate below the threshold of 15 L/min with a coefficient of variation between 6–25% (Table 1).
- As an example, Figure 1 shows the graphic representation of the intra individual variability of the inhalation flow rate of subject 6: every inhalation flow was below the threshold and easily sustained for six seconds.

| Subject | Mean inhalation flow rate L/min (min; max) | SD | Coef. Variation of the test |
|---|---|---|---|
| 1 | 11,2 (3,0; 15,2) | 2,4 | 21% |
| 2 | 10,4 (3,3; 16,5) | 0,6 | 6% |
| 3 | 11,6 (3,1; 18,2) | 1,8 | 16% |
| 5 | 18,1 (3,2; 34,6) | 7,1 | 39% |
| 6 | 11,6 (3,2; 15,9) | 1,5 | 13% |
| 7 | 10,1 (3,0; 21,7) | 2,5 | 25% |
| 8 | 11,3 (3,2; 18,7) | 1,7 | 16% |
| 9 | 19,0 (3,2; 35,7) | 7,3 | 38% |

Table 1. Participants inhalation data (n = 8 ± StDev.)

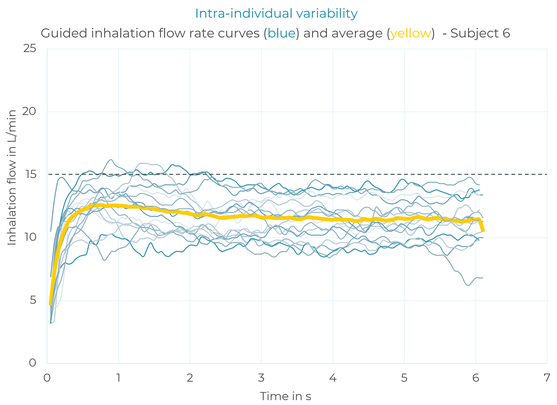



Figure 1. Example of the intra-individual analysis of inhaled flow rate variability of subject 6 over time. Each blue line corresponds to one inhalation maneuvre and the yellow line corresponds to the average inhalation flow rate of the test.

### Key experience: higher variability due to a learning curve

- Participants 5 and 9 showed a **learning curve process**, which explains the higher mean inhalation flow (18 and 19 L/min) and higher coefficients of variation (38% and 39%) observed in Table 1. These results show the ability of the technology to rapidly guide the users through a learning process, but also highlight the need of future adjustments on the vibration feedback of the Kolibri.

The detailed analysis of Figure 2 reveals:

- The first 10 inhalations were performed with higher flow rates (> 15L/min)
- Then, the users perceived the feedback system correctly and adjusted the breathing maneuvre (yellow arrow)
- Until the end of the session the users were able to maintain inhalations at a lower flow rate (<15L/min)

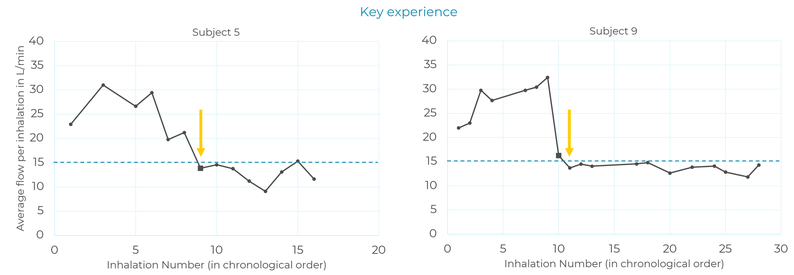



Figure 2. Learning curve: average inhalation flow rate per inhalation (in chronological order) during the test of subjects 5 and 9; yellow arrow signalling the change of feedback and turning point of the learning curve.

### Inter-individual analysis

- The **inter-individual analysis** (Figure 3) shows that the mean inhalation flow rate of the eight participants was consistent and maintained around 10.1 and 11.6 L/min and sustained for 6 seconds of duration.

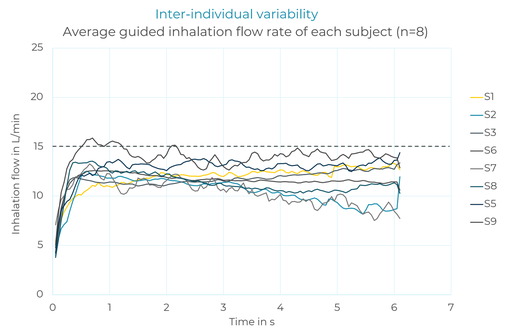



Figure 3. Inter-individual variability of the average inhalation flow rate of each subject (n = 8); the initial inhalations from subjects 5 and 9 were excluded, and here are represented the inhalations after the learning point described in figure 2.

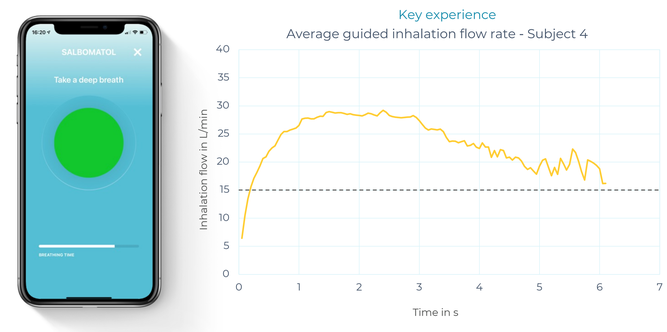



Figure 4. Average inhalation flow rate of the later excluded subject 4. The smartphone app illustrates a potentially useful digital feedback system for patients who require further support.

### Key experience: some patients can benefit from additional feedback functionalities

- **Subject 4**, a 60-year-old female, was later **excluded** from the study due to an asthma diagnosis and the occasional use of a dry powder inhaler for relief medication.
- Figure 4 illustrates her test: she consistently inhaled at very high flow rates (> 25 L/min), exceeding the desired limits, and frequently had to prematurely end the inhalation maneuver due to a reactive cough.
- This case highlights the **challenges associated with real patient use** of nebulizers and emphasizes the **potential benefits of incorporating other supportive tools**, such as smartphone apps featuring visualization feedback, in inhaled therapy platforms.

## Conclusions :

- **Haptic feedback technology can successfully guide the inhalation maneuvre during nebulization**, leading to a reduction in both intra- and inter-individual variability of breathing patterns.
- Despite the study setting and small sample size, it is highlighted the importance of **early validation tests** to optimize the feedback systems of the devices to different use cases.
- Illustrates the **potential value of other feedback tools for specific users** to achieve a correct and optimal inhalation technique as, for example, visual and digital feedback in smartphone apps.
- In the future new valuable patient-side parameters generated during nebulization, that when integrated into lung deposition models, can unlock new pathways for inhaled drug development.

References: 1) Brand P, Friemel I, Meyer T, Schulz H, Heyder J, Haeubetainger K: Total deposition of therapeutic particles during spontaneous and controlled inhalation. *Journal of Pharmaceutical Sciences* 2000, 89: 724–731. 2) Brand P, Meyer T, Haeussermann S, Schulte M, Scheuch G, Bernhard T, Sommerauer B, Weber N, Griese M: Optimum peripheral drug deposition in patients with cystic fibrosis. *Journal of Aerosol Medicine* 2005, 18: 45–74. 3) Scheuch G, Kohlhaeufl MJ, Brand P, Siekmeier R: Clinical perspectives on pulmonary systemic and macromolecular delivery. *Advanced Drug Delivery Reviews* 2006, 58: 996–1008.