Received: 12 March 2019 | Accepted: 5 July 2019

DOI: 10.1002/ppul.24467

ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

PEDIATRIC PULMONOLOGY WILEY

# Home videos of cystic fibrosis patients using tobramycin inhalation powder: Relation of flow and cough

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**Funding information**
Unconditional research grant Novartis Pharma B.V., Anhem, The Netherlands, agreement number, Grant/Award Number: 3249/14

## Abstract

**Background:** Many cystic fibrosis (CF) patients chronically infected with *Pseudomonas aeruginosa* are on maintenance tobramycin inhalation therapy. Cough is reported as a side effect of tobramycin inhalation powder (TIP) in 48% of the patients. Objectives of this study were to investigate the association between the inspiratory flow of TIP and cough and to study the inhalation technique. We hypothesized that cough is related to a fast inhalation.

**Materials and Methods:** In this prospective observational study, CF patients ≥ 6 years old on TIP maintenance therapy from four Dutch CF centers were visited twice at home. Video recordings were obtained and peak inspiratory flow (PIF) was recorded while patients inhaled TIP. Between the two home visits, the patients made three additional videos. CF questionnaire-revised, spirometry data, and computed tomography scan were collected. Two observers scored the videos for PIF, cough, and mistakes in inhalation technique. The associations between PIF and cough were analyzed using a logistic mixed-effects model accounting for $FEV_1$% predicted and capsule number.

**Results:** Twenty patients were included, median age 22 (18–28) years. No significant associations were found between PIF and cough. The risk of cough was highest after inhalation of the first capsule when compared to the second, third, and fourth capsule ($P \leq .015$). Fourteen patients (70%) coughed at least once during TIP inhalation. A breath-hold of less than 5 seconds after inhalation and no deep expiration before inhalation were the most commonly observed mistakes.

**Conclusion:** PIF is not related to cough in CF patients using TIP.

KEYWORDS
cough, cystic fibrosis, dry powder inhaler, inhalation, tobramycin

## 1 | INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder characterized by severe chronic lung disease. The mucus of CF patients is thickened, resulting in impaired clearance of pathogens.[1] Patients with CF suffer from chronic infections and increased inflammatory response in the lungs. This causes irreversible lung damage, resulting in a reduced quality of life, and a shortened life span.[1] *Pseudomonas aeruginosa* is the most predominant pathogen that causes progressive lung disease.[2] The overall prevalence of chronic infection with *P. aeruginosa* in 2016 was around 30% in Europe and the United States of America.[3,4]

Suppressive inhalation antibiotic therapy is a standard treatment for patients with chronic *P. aeruginosa* infection: The guidelines of the United States of America recommend long-term use of tobramycin inhalation solution (TIS) as the first-line choice, and the more recent European guidelines add that TIS and tobramycin inhalation powder (TIP) is equally effective. Alternatively, options are aztreonam lysine (both guidelines) and colistin (European guidelines).[5-7] Nebulization therapy comes with some disadvantages: it is time-consuming, nebulizers are in general not easy to carry around, need disinfection after each use, and require periodic technical maintenance.[8] To overcome these disadvantages, TIP was developed. TIP is administered with the T-326 inhaler (Tobi Podhaler™; Novartis Pharma AG, Basel, Switzerland). A full dose of TIP contains four capsules of 50 mg each (28 mg tobramycin + 22 mg excipients). It is advised to inhale each capsule at least twice. Like TIS, TIP is administered twice daily. The administration time of TIP is one-third of that of TIS, the T-326 inhaler is pocket-size, and does not require extensive post-use cleaning or technical maintenance.[9,10] Importantly, TIP has shown to be noninferior compared to TIS in terms of reducing exacerbations and *P. aeruginosa* colony-forming units. In addition, higher treatment satisfaction was reported for TIP compared to TIS.[9] However, a disadvantage of TIP is the occurrence of cough immediately after inhalation. In the pivotal noninferiority study comparing TIS and TIP, the cough was reported in 48% of patients using TIP (n = 308) compared to 31% using TIS (n = 209).[9] The authors did not mention specific instructions given to patients with regard to an inspiratory flow. TIP particles might induce a cough reaction for various reasons: First of all, TIP particles are dry where TIS particles are wet. Second, TIP particles might hit the throat wall with greater impact, due to the relatively faster inhalation of TIP compared to TIS. The T-326 inhaler has a low-to-medium resistance (approximately 0.08 [cm $H_2O$]$^{½}$/[L/min]), fast inspiratory flows between 40 up to 115 L/min were observed in a laboratory setting when inhaling TIP.[11] On the contrary, TIS is inhaled with tidal volume breathing. Third, tobramycin sputum concentrations were found to be double after inhalation of TIP compared to that of TIS.[9] This might be a result of higher upper airway deposition. Importantly, according to an in vitro study by Haynes et al,[11] the total lung dose of TIP is independent of inspiratory flow.

It is unknown which inspiratory flows are generated by patients for routine use of TIP in the home setting. Furthermore, we do not know what the prevalence of cough is in the home setting, nor whether correct inhalation techniques are being used.

The primary objective of our study was to record TIP inhalations by CF patients on video in the home setting and to study the association between inspiratory flow and cough. We hypothesized that a faster inhalation maneuver by patients would increase the risk of cough. Secondary objectives were (a) to assess the percentage of patients that coughed after inhaling TIP, and (b) to study mistakes in the inhalation technique of TIP inhalations. In a multicentre, prospective observational study, we assessed inhalation maneuvers and the relation with cough for TIP in the home setting.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

Patients were recruited from four CF centers in the Netherlands: Erasmus Medical Center in Rotterdam, Haga Hospital in The Hague, University Medical Center Utrecht and Academic Medical Center in Amsterdam.

Inclusion criteria:

1. Proven diagnosis with CF.
2. Minimum age of 6 years.
3. Maintenance treatment with TIP for at least 1 month.

Exclusion criteria:

1. Respiratory exacerbation requiring intravenous treatment with antibiotics at the time of inclusion or during the study period.
2. Any medical condition that increases the risk of cough according to the treating physician, not directly related to CF lung disease (ie, otitis media).
3. Unable to understand and execute instructions.

Informed consent was obtained from both parents if the patient was younger than 12 years, from the patient and both parents if the patient's age was between 12 to 18 years, and only from the patient if the patient was 18 years and older. This study was approved by the Institutional Review Board of the Erasmus Medical Center (MEC-2015-329).

### 2.2 | Study design

The study design is shown in Figure 1. The study consisted of five study moments: two home visits by an investigator (JM) and three video recordings by the patient between the home visits.

During the first home visit (visit 1), the patient inhaled a full dose of TIP without any instructions, while being recorded on video by the investigator (video S1). Inspiratory flow patterns of the first inhalation of the third capsule were measured with an inspiratory profile recorder (IPR). When inhaling the third capsule, we assumed the patient was used to the situation, and the fourth capsule could be used if measurements failed. Furthermore, the patient received instructions to record himself/herself on video on three separate

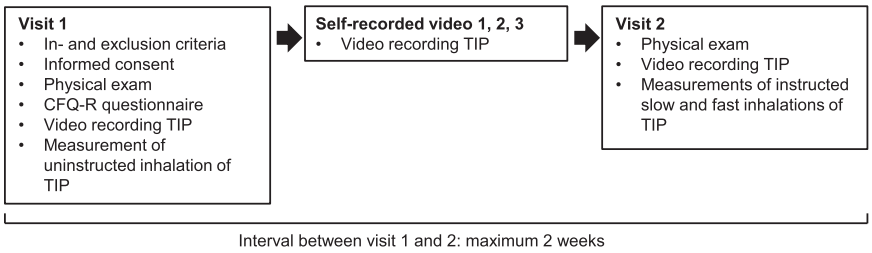


**FIGURE 1** Study design. Patients were visited twice by an investigator. On three separate days in between, the patients were asked to record their inhalations on video. CFQ-R, cystic fibrosis questionnaire-revised; TIP, tobramycin inhalation powder

days while inhaling a full dose of four TIP capsules (self-recorded video 1, 2, and 3). The investigator and patient together looked for a suitable place to record, and a video-camera including a tripod was left behind with the patient.

During the second home visit (visit 2), the patient also inhaled a full dose of TIP while being recorded on video by the investigator. However, the patient was randomized and instructed to either inhale the first capsule slowly and the second capsule fast, or vice versa. The inspiratory flows of the first two capsules were recorded with the IPR, and if the recordings failed, the third and fourth capsule were recorded with the same instructions. Otherwise, the third and fourth capsule were inhaled as usual and not recorded with the IPR. In case the investigator noticed any mistakes in the inhalation technique, this was recorded and discussed with the patient after completion of all study proceedings.

Importantly, except for the instructed fast and slow inhalation of visit 2, the patients were asked to inhale TIP the way they would normally do.

Patient demographics (age, sex, duration of treatment) were collected at visit 1. Chest computed tomography (CT) scans were collected when available and made within 24 months before inclusion. Structural changes on CT scans were analyzed using the PRAGMA-CF scoring method.[12] The highest forced expiratory volume in 1 second ($FEV_1$) measured within 12 months before inclusion and the forced vital capacity (FVC) were collected. Both values were expressed as a percentage of predicted values.[13]

## 2.3 | Inhalation measurements

The IPR measured the dynamic pressure drop at the mouthpiece of the inhaler during inhalation and converted the data to inspiratory flow in L/min.[11] The peak inspiratory flow (PIF) was used to analyze the association between inspiratory flow and cough, to which we refer as "recorded PIF." Furthermore, inhaled volume and flow acceleration were extracted from these recorded measurements.

## 2.4 | Standardization of video scoring

The estimated PIF was independently assessed by two observers (JM and MA). The observers were trained as follows: First, reference videos were made of a slow (40 L/min or less), medium (40-85 L/min), and fast (85 L/min or higher) inhalation, referring to the PIF. Next, a practice batch of videos was made for which 20 volunteers performed one inhalation with an empty TIP capsule. The volunteers were at random instructed to inhale slow, medium or fast. The two observers, blinded for these instructions, scored the estimated PIF of this practice batch. The agreement between the observers on the estimated PIF of this practice batch was 80%. To standardize the assessment of inhalation technique, both observers scored 10 videos made for a previous study by Bos et al,[14] in which patients inhaled using various nebulizers. Although the inhalation maneuvers of nebulizers and TIP differ, some of the technique items "lips sealed around the mouthpiece," "upright position during inhalation", and "a horizontal position of the inhaler" could be practised.

All videos were renamed and randomized, and scored by both observers. Because the T-326 inhaler has a distinctive rattle depending on inspiratory flow, scoring was performed using a high-quality active noise-canceling headset.

Nonmatching scores for estimated PIFs and cough were discussed during a consensus meeting to come upon a final score. Nonmatching scores for inhalation technique were not discussed during the consensus meeting since these were no main outcome parameters. For these latter scores, the mean of both observers was calculated.

## 2.5 | Checklist video recordings

Every inhalation was scored using a checklist that contained the following items:

1. Estimated PIFs: slow, medium, or fast.
2. Occurrence and moment of cough (during inhalation, breath-hold, exhalation or afterward).
3. Inhalation technique. These items were derived from the manufacturers' instructions: deep exhalation before inhalation, exhalation outside of the inhaler, lips sealed around the mouthpiece, upright position during inhalation, a horizontal position of the inhaler, and breath-hold ≥5 seconds after inhalation.

## 2.6 | Statistical analysis

Descriptive data are expressed as median with interquartile ranges (IQR), as numbers and as percentages (%).

To analyse the association between cough and PIF, a McNemar test was planned to compute the difference between the risk of cough after a slow inhalation (assuming $p_{cough}$ = lowest reported cough rate, 0.10)[15] and a fast inhalation (assuming $p_{cough}$ = highest reported cough rate, 0.48)[9] resulting in a sample size of 30 patients. However, in total only 20

patients were included and the performed instructed inhalations (slow and fast) did not meet the study definitions (slow PIF < 35 L/min, fast PIF > 85 L/min) for which reasons the McNemar was not appropriate. Instead, two analyses were performed using logistic mixed-effects models, to correct for other variables while investigating the association of PIF and cough, accounting for multiple measurements per patient: analysis 1 was performed to study the association between all recorded PIFs and cough, and analysis 2 to study the association between the all estimated PIFs and cough. For this latter analysis, estimated PIFs were collected of visit 1, and self-recorded videos 1, 2, and 3. The estimated PIFs of visit 2 were excluded, because they included instructed inhalations which could bias results.

For both analyses, only the first inhalation of each capsule was included, as some capsules (25%) were only inhaled once. We accounted for $FEV_1$% predicted as we assumed that lung function would be a confounding factor. In analysis 2, we added the capsule number to our model, as this showed to be a confounder.

Additionally, with mixed-effects model analyses the relation between inhaled volume (accounting for $FEV_1$% predicted and height) and cough, and between flow acceleration (accounting for $FEV_{1\%}$ predicted) and cough were assessed.

To determine the prevalence of cough after the inhalation of TIP, we assumed each capsule of TIP would be empty after two inhalations.[16] Therefore, only data of the first, and if present, the second inhalation per capsule are presented. Also for this analysis, visit 2 videos were excluded as they contained instructed inhalations which could bias the results.

Mistakes made in the inhalation technique are presented as mean percentages of both observers. All inhalations were included and overall technique scores were calculated as follows: for each checklist item on inhalation technique, one point was assigned per item when executed correctly, and scores of both observers were added. The mean technique score was expressed as a percentage of the maximum score. The differences in inhalation technique between the videos with and without the presence of the investigator were calculated with the Wilcoxon signed-rank test.

To assess the interobserver and intraobserver agreement of the checklist items Cohen's kappa was calculated. The interobserver agreement was calculated for all inhalations. The intraobserver agreement was calculated after each observer rescored 20 randomly selected videos. We interpret Cohen's kappa values as follows: poor (<0), slight (0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (>0.81).[17]

Statistical analyses were performed using SPSS version 24.0 and R version 3.4.3. The significance level was defined as $P < .05$.

## 3 | RESULTS

### 3.1 | Study population

We approached 55 eligible patients, of whom 20 patients were included. Characteristics of the study patients are summarized in Table 1. Sixteen adults (80%) and four children (20%) were included, of whom 13 (65%) were male. Seventeen patients (85%) used TIP month-on month-off, three patients (15%) used TIP continuously, and the median duration of treatment at the time of participation was 19 months. Details of the PRAGMA-CF scores and CFQ-R scores are presented in Tables S1 and S2.

**TABLE 1** Patient characteristics

| Characteristic | Values | Outcome |
|---|---|---|
| Age (y) | Median (IQR) | 22 (18–28) |
| Male sex | n (%) | 13 (65) |
| Use of TIP (mo) | Median (IQR) | 19 (11–53) |
| PRAGMA-CF CT analyses | | |
| Total disease score (%) (n = 12) | Median (IQR) | 9 (7–17)[a] |
| Trapped air score (%) (n = 11) | Median (IQR) | 17 (1–30)[a] |
| Spirometry | | |
| $FEV_{1\%}$ predicted | Median (IQR) | 82 (62–100) |
| FVC % predicted | Median (IQR) | 98 (83–106) |

Abbreviations: CT, computed tomography; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; TIP, tobramycin inhalation powder.
[a]Expressed as a percentage of the total lung volume. In total 20 patients were included.

### 3.2 | Association between recorded PIF and cough

Recorded PIFs of an uninstructed, instructed fast, and instructed slow inhalation were obtained from 19 patients, resulting in 57 measurements. Data of one patient were lost in the data transfer process. Figure 2 shows a scatter plot of the recorded PIFs in L/min in relation to the outcome

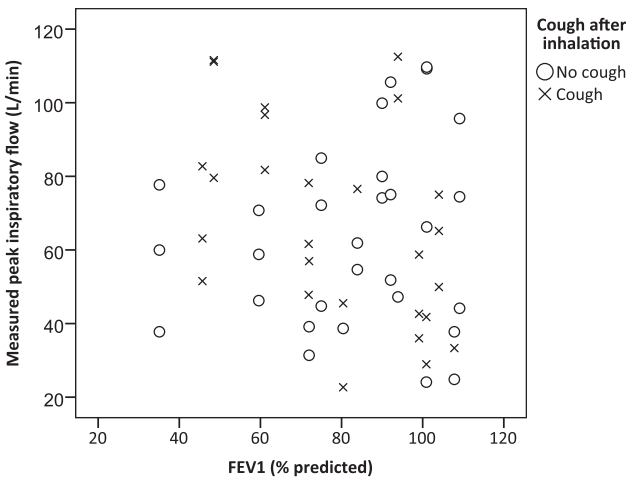


**FIGURE 2** Scatter plot of recorded peak inspiratory flows (PIF). This scatter plot shows the recorded PIF in relation to cough and the forced expiratory volume in one second ($FEV_1$) % predicted. The *x*-axis shows the $FEV_1$% predicted and the *y*-axis shows the PIF in liter per minute. The circles represent the inhalations without cough and the crosses represent the inhalations with cough. Three inhalations per patient were obtained, of 19 patients (data missing of one patient); resulting in 57 measurements. $FEV_1$, forced expiratory volume in one second

**TABLE 2** Output mixed model analyses for association between cough and recorded and estimated peak inspiratory flow

| Recorded PIF (n = 57) | Effect (log odds) | Standard error (log odds) | *P* |
|---|---|---|---|
| Baseline | −0.38 | 5.20 | |
| PIF (L/min) | 0.02 | 0.04 | .182 |
| $FEV_1$ (% predicted) | −0.01 | 0.06 | .616 |
| **Estimated PIF (n = 319)** | **Effect (log odds)** | **Standard error (log odds)** | ***P*** |
| Baseline[a] | 2.24 | 3.08 | |
| PIF | | | |
| Medium | −0.96 | 1.15 | .080 |
| Fast | −1.12 | 1.39 | .094 |
| $FEV_1$ (% predicted) | −0.02 | 0.04 | .149 |
| Capsule number | | | |
| Second capsule | −0.88 | 0.53 | <.001* |
| Third capsule | −0.56 | 0.50 | .015* |
| Fourth capsule | −1.17 | 0.58 | <.001* |

*Note:* This table shows the output of the mixed model analysis to study the association between cough and recorded and estimated PIF. $FEV_1$ % predicted was added to both models as possible confounder. In the analysis of the estimated PIF, the capsule number was also added as this was a significant confounder.
Abbreviation: $FEV_1$, forced expiratory volume in one second.
[a]A slow inhalation of the first capsule and $FEV_1$ % predicted of 0 is baseline.
*$P < 0.05$.

cough and to $FEV_{1\%}$ predicted, in which no association could be detected. In line with the interpretation of the scatter plot, the mixed-effects model analysis showed no association between the recorded PIF and cough ($P = .182$) (Table 2). The additional analyses showed that inhaled volume and flow acceleration were also not associated with cough ($P = .506$ and.138) (Table S3).

## 3.3 | Association between estimated PIF and cough

We obtained 319 estimated PIFs. For one patient the inhalation of one capsule was missing on one of the self-recorded videos. Initially, the mixed-effects model analysis was performed without accounting for capsule number, and then it seemed that a fast PIF significantly reduced the risk of cough ($P = .039$). However, we identified capsule number as a significant confounder and therefore added this to our model. We found no significant association between the estimated PIF and cough ($P$ medium inhalation = .080 and $P$ fast inhalation = .094) (Table 2). However, the risk of cough is significantly lower for the second, third, and fourth capsule compared to the first capsule ($P < .001$, $P = .015$, and $P < .001$, respectively).

## 3.4 | Prevalence of cough

A total of 319-first and 240-second inhalations of the capsules were analyzed on the visit 1 and self-recorded videos. The prevalence of cough per estimated PIF of the first inhalation was 22% (slow), 28% (medium), and 29% (fast). The first inhalation of the first capsule resulted in cough in 42% of the inhalations, compared to 22%, 26%, and 16% for the second, third, and fourth capsule. Forty-eight % of the inhalations were performed with a medium PIF, 28% with a slow PIF, and 25% with a fast PIF. Fourteen patients (70%) coughed at least once. The patients coughed during inhalation in 27% of the cases, during breath-hold in 17%, during exhalation in 32%, and after exhalation in 24% of the cases.

Of 319 inhaled capsules, 25% of the capsules were inhaled only once, 54% were inhaled twice, 13% were inhaled three times, and 9% of the capsules were inhaled four up to seven times.

## 3.5 | Inhalation technique

The inhalation technique varied widely among patients. The median (IQR) total score for all patients on the inhalation technique was 75 (71–92). Table S4 shows the median (IQR) scores on inhalation technique per patient. One patient was excluded from this analysis because of the low quality of the self-recorded videos.

The mean prevalence of both observers for each mistake in the inhalation technique of all 828 inhalations is shown in Figure 3. Most commonly made mistakes were a breath-hold after inhalation less than 5 seconds (54% and 52% of the inhalations according to observer 1 and 2, respectively), followed by an inhalation that was not preceded by a complete exhalation (54% and 22%). The presence of an investigator was not of influence on the inhalation technique ($P = .133$).

## 3.6 | Interobserver and intraobserver agreement

Table S5 shows Cohen's kappa for the interobserver and intraobserver agreement. The interobserver agreement was fair (0.29-0.36) for the items deep exhalation, exhalation outside the inhaler, upright

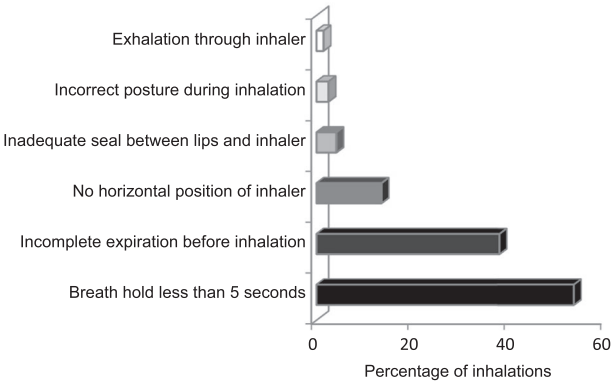


**FIGURE 3** Bar chart of mistakes of inhalation technique. This bar chart presents the mean prevalence of the two observers of mistakes made in the inhalation technique while inhaling tobramycin inhalation powder. All inhalations captured on video were used for this analysis (n = 828).

position of the patient, and horizontal position of the inhaler. The interobserver score on estimated PIF was moderate (0.48), however, disagreement on PIF was solved during consensus meetings. One observer scored systematically more mistakes than the other observer. The intraobserver was for moderate for three items of one observer, while the remaining scores were substantial or almost perfect.

## 4 | DISCUSSION

With this multicentre observational study, we assessed whether cough after inhalation of TIP is associated with the inspiratory flow. The inspiratory flow was assessed using objective measurements of the PIF and was estimated using video registrations.

We did not find a significant relation between recorded nor estimated PIF and cough, even though cough occurred frequently. Our estimated PIF analysis initially showed that a fast inhalation reduced the risk of cough. However, the order of capsules was a significant confounder, and when accounting for the order of the capsules, the correlation between estimated PIF and cough disappeared. The first capsule resulted in more cough than the second, third, and fourth ($P \leq .015$). It is well possible that patients inhale the first capsule more slowly than the consecutive capsules in their attempt to reduce cough. Then, once they have managed the first inhalations, they are more confident and start inhaling faster, which results in counterintuitive associations of more cough for the slower inhalations.

With a post hoc analysis of the IPR data, we did not find an association between inhaled volume and cough or the acceleration of flow and cough.

Around two-thirds of patients coughed at least once after inhaling TIP. The reported prevalence of cough for TIP in the literature is in general lower and varies between 10% and 48%.[9,15] An explanation for our higher numbers is that we used video registrations while in the referred studies only adverse event registrations from emergency care visits (which indicates very severe cough), or self-reporting surveys were used. Self-reporting surveys are known to suffer from recall bias. Hence, we think our numbers are likely to be more realistic.

The video recordings of TIP inhalations provided a unique opportunity to assess the inhalation technique of the patients. Two relevant mistakes in inhalation technique were most frequently observed: half of the inhalations showed a breath-hold of fewer than 5 seconds, and two-fifths of patients did not perform a deep exhalation before inhalation. Of note is that when cough occurred, patients were often unable to hold their breath for at least 5 seconds. Both these mistakes are likely to reduce the efficiency of drug deposition in the small airways. Importantly, proper instruction of the patient and repeated (video) evaluation of inhalation technique offers a great opportunity to reduce the prevalence of mistakes empowering patients to get the most out of their inhalation treatment.

A strength of our study is the large number of supervised and unsupervised video registrations in the home setting. We believe to have obtained a realistic impression of the use of TIP that is reflecting daily life practice. Another strength was the thorough observation of all videos by two observers, providing detailed information on both (estimated) inspiratory flow and inhalation technique.

A limitation of the study is the relatively small sample size. The planned statistical test (McNemar) was not performed and instead, we used the more complex mixed-effects model. An important advantage of this analysis is the chance to correct for multiple measurements within patients and to add confounders. Due to a large number of observations and the lack of association in both the raw data plot and both mixed-effects models we believe that the lack of association between inspiratory flow and cough in our study population indicates that the occurrence of cough might be explained by other factors than inspiratory flow. A possible explanation that was not studied, is adherence to treatment. A hypothesis is that the patient who is more compliant gets used to TIP, and as a result, suffers less from cough. Another factor that might be related to cough is respiratory effort during inhalation, which has been measured in CF patients using electromyogram.[18]

Another limitation of the study is that observer 1 was somewhat stricter in scoring inhalation technique than observer 2. However, the intraobserver agreement was good for most scored items which is an important condition for a robust statistical analysis. For future similar studies, the interobserver variability can be further improved by using training material specifically developed for dry powder inhalers.

Instead of estimating the PIF, the flow analysis could have been optimized by using the IPR in all observations. Alternatively, automated sound analysis has been described in other studies to successfully perform flow analysis.[19] However, the primary aim of this current study was to observe inhalation in a real-life situation, even without the presence of an investigator. The methods described above would have interfered with this aim. Therefore, although we realize that it is at the expense of precision, we choose not to add more advantaged analysis methods.

The final remark on the technique scores is that all steps were weighted equally. Consequently, inhalations of patients with similar overall technique scores might not be equally effective.

## 5 | CONCLUSION

In summary, cough immediately after inhalation of the first capsule is a common side effect of TIP. Less cough occurs after inhalation of the consecutive capsules. Cough was not related to inspiratory flow. Furthermore, we found that inhalation techniques are often suboptimal, and therefore periodical counseling is highly recommended to optimize the treatment effect of TIP.

## ACKNOWLEDGMENTS

We would like to thank the patients and their families for participating in this study, HM Janssens for input in concept of study, BG Bannink for technical support, and the CF research staff of participating centers: AL Geel, M Geerdink, I Heeres, NE Kok, P Mau Assam, S Michels, RDB Meijer, W Olde, M Smink. For this investigator-initiated study we received an unconditional grant from Novartis Pharma B.V., Arnhem, the Netherlands; agreement number 3249/14.

## CONFLICT OF INTERESTS

JM, MA, EW, EA, ME, HA, CM, and HH declare no conflicts of interest. HT reports grants from Roche, Novartis, CFF, Vertex, Gilead, and Chiesi outside the submitted work, has a patent on the PRAGMA-CF scoring system issued and is heading the Erasmus MC-Sophia Children's Hospital core laboratory LungAnalysis.

## AUTHOR CONTRIBUTIONS

JM study design, data collection, analysis and first manuscript draft; EW study design; MA analysis and first manuscript draft; EA statistical analysis; ME, CM, HA, HH local principal investigators, HT principal investigator, concept of study, grant application, study design and manuscript draft; all authors revised and approved the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Meerburg JJ, Albasri M, van der Wiel EC, et al. Home videos of cystic fibrosis patients using tobramycin inhalation powder: relation of flow and cough. *Pediatric Pulmonology*. 2019;1-7. https://doi.org/10.1002/ppul.24467