Inhalation Through Dry Powder Inhalers in Chronic Obstructive Lung Disease Patients with Reduced Peak Maximal Inspiratory Pressure

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Abstract

Dry powder inhalers (DPI’s) are breath-controlled inhalers, for which a minimally required peak inspiratory flow (PIF) and/or acceleration in inspiratory flow rate (flow increase rate, FIR) is necessary for an optimal disintegration and pulmonary deposition of respirable drug particles into the airways. The peak maximal inspiratory pressure (P·MIP), is an indicator of the inspiratory muscle strength, and may predict the driving force for inhalation. In the treatment of chronic obstructive lung disease (COLD) patients, with strongly reduced inspiratory muscle strength, the use of DPI’s is questionable, because it is believed that these patients are not able to generate sufficient inspiratory flow for the operation of DPI’s. In this study the possibility to generate inspiratory flow through a resistance to airflow, simulating inhalation through DPI’s, was investigated in a group of 17 COLD patients with reduced P·MIP. The results demonstrate that the PIF depends on the respiratory muscle strength and on the used external resistance to airflow. The generated P·MIP and PIF-values in the investigated group of COLD patients were sufficient for an adequate use of low as well as high resistance to airflow DPI’s.
Inhalation is the preferred route of administration for respiratory drugs in the treatment of pulmonary disease. In this chapter, asthmatics and patients with chronic obstructive pulmonary disease (COPD) are not distinguished, but are indicated as patients with chronic obstructive lung disease (COLD). In the treatment of COLD patients with strongly reduced inspiratory muscle strength, the use of dry powder inhalers (DPI’s) is questionable, because it is believed that these patients are not able to generate sufficient inspiratory flow rate for the operation of DPI’s. Dry powder inhalers are breath-controlled inhalers, in which the inspiratory flow controls the mechanism for delivery and disintegration of the powdered drug into the inhaled airstream. Therefore, a minimally required peak inspiratory flow (PIF) and/or acceleration in inspiratory flow rate (flow increase rate, FIR) is necessary for an optimal disintegration and optimal pulmonary deposition of respirable drug particles into the airways\(^{(1-4)}\). Many studies have been performed to measure PIF through a DPI\(^{(5-10)}\). These studies investigated the inspiratory flow rate through DPI’s in relation to the disease and in relation to inhaler specific resistance to airflow.

As inhalation through a DPI is in fact inhalation through an external resistance to airflow, the effect of inhalation through DPI’s on the inspiratory flow curve can be simulated by inhalation through simple orifices having the same resistances to airflow as these DPI’s. The design of the DPI results in an inhaler specific resistance to airflow (figure 4.1). Specific resistance to airflow \((R_x)\), for the different orifice disks and DPI’s, is calculated as the slope in...
the linear relationship between the square root of pressure drop (∆p) against the volumetric flow (Φ), according to the simplified equation for an orifice type of flow constriction, equation 4.1:\(^{11}\):
\[
\sqrt{\Delta p} = R \cdot \Phi
\] (equation 4.1)

Generation of airflow through breath-controlled DPI’s depends on the patient-generated inspiratory pressure, which is the driving force for an inspiratory flow rate\(^{12}\) (chapter 3). The peak maximal inspiratory pressure (P·MIP) is an indicator for the inspiratory muscle strength\(^{12}\). Most studies only refer to PIF as determinant for DPI-performance. Some studies suggest that the maximal inspiratory pressure is a predictive value for the PIF through a resistance to airflow\(^{9, 13, 14}\), which is also concluded from chapter 3.

![Figure 4.1: Relationship between resistance to airflow and the orifice disk diameter. Resistances to airflow in commercially available dry powder inhalers are indicated.](image)

In this study, generated inspiratory flow through a dry powder inhaler is investigated in relation to the subject's generated P·MIP, and to the inhaler specific resistance to airflow. The relationship between PIF\(_{Rx}\) and P·MIP is expressed by an equation similar to equation 4.1, in which ∆p is substituted by P·MIP and Φ by PIF\(_{Rx}\). In the expression for the relationship between PIF\(_{Rx}\) and P·MIP (equation 4.2), \(\beta_{Rx,1}\) is a function of the reciprocal resistance to airflow and \(\beta_{Rx,0}\) is an intercept from linear regression.
Besides the PIF, the acceleration in airflow at the start of the inspiration, the flow increase rate (FIR), determines the performance of the inhaler importantly (chapter 6). Flow increase rate is calculated over a representative part of the curve and is defined as the average FIR from 20% to 80% of PIF$_{Rx}$ ($\text{FIR}_{20\text{-}80\%}$ (l·s$^{-2}$)).

The present study is performed in COLD patients with reduced P·MIP. The decrease in P·MIP in these patients is due to remodelling of the airways and to hyperinflation$^{(12)}$. An important inclusion criterion was a P·MIP of less than 6 kPa, which is about half the generated P·MIP in healthy subjects (chapter 3).

The hypothesises in this study is that the P·MIP, for patients with reduced P·MIP's, predicts the PIF through a DPI with a particular inhaler specific resistance to airflow.

### 4.2 Material and Methods

#### 4.2.1 Study design

Subjects in the age of 20 to 80 years were recruited from the outpatient clinic of the University Hospital in Groningen and from the pulmonary rehabilitation centre Beatrixoord, in Haren. Inclusion criterion for the patients was a reduced P·MIP, of less than 6 kPa for patients with known obstructive airway disease. No drugs were administered during the test. All measurements of dynamic lung function were obtained during a single visit to the pulmonary function lab. Spirometry was performed, followed by P·MIP measurements. After a 10-15 minutes recovery, inspiratory flow volume curves were recorded through three external resistances to airflow. Subjects were allowed to practice inhalation through the external resistance to airflow before the actual measurement. The medical ethics committee approved this study and all subjects gave their written informed consent.

#### 4.2.2 Study subjects

Seventeen patients were selected, with various causes of airway obstruction and with a large range of airway obstruction (table 4.1). The research population exists of 6 subjects with asthma, 5 subjects with signs of emphysema, 5 subjects with chronic obstructive bronchitis, and 1 subject with chronic obstructive bronchitis and bronchiectasis. All subjects had stable disease. Three subjects were current smokers, eleven subjects were ex-smokers and three subjects never smoked.
4.2.3 Methods

4.2.3.1 Respiratory muscle strength

Peak maximal inspiratory pressure was measured with the pressure transducer of the pneumotachograph (ML-Masterlab, Jaeger, Würzburg, Germany), according to the procedures of Black and Hyatt\(^{(15)}\). All subjects were seated, wore a noseclip and carried out their maximal inspiratory manoeuvres from residual volume (RV). They performed their efforts against a closed shutter through an oval flanged mouthpiece with a leak of 2.1 mm diameter and 33.8 mm length to prevent the use of the buccinator muscles\(^{(15)}\). At least 5 maximal inspiratory manoeuvres were carried out with a minimum of 30 seconds rest between each measurement. The three highest achieved peak pressures of the fast maximal inhalation were used for further analysis\(^{(15)}\). Each effort was displayed on a monitor, and the subjects were coached to improve their efforts. During all measurements no noticeable extra leakage occurred. The three highest pressures recorded were within a range of 5% of each other.

<table>
<thead>
<tr>
<th>Table 4.1: Demographic and lung function data of the participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 17 (12 female / 5 male)</td>
</tr>
<tr>
<td>Median ( range )</td>
</tr>
<tr>
<td>Age (yrs) 59.0 ( 25 – 78 )</td>
</tr>
<tr>
<td>PEF (l·s(^{-1})) 3.98 ( 1.86 – 7.53 )</td>
</tr>
<tr>
<td>PEF (%pred) 52.2 ( 23.4 – 93.4 )</td>
</tr>
<tr>
<td>FEV(_1) (%pred) 47.3 ( 16.9 – 93.3 )</td>
</tr>
<tr>
<td>FEV(_1)/ICV (%) 48.7 ( 25.0 – 77.0 )</td>
</tr>
<tr>
<td>FIV(_1) (l) 2.27 ( 1.38 – 3.74 )</td>
</tr>
<tr>
<td>FIV(_1)/ICV (%) 86.7 ( 65.8 – 100.0 )</td>
</tr>
<tr>
<td>PIF(_{RS}) (l·s(^{-1})) 4.04 ( 2.82 – 5.08 )</td>
</tr>
<tr>
<td>RV%TLC (%pred) 136.4 ( 84.2 – 197.3 )</td>
</tr>
<tr>
<td>P·MIP(_{all}) (kPa) 5.20 ( 2.31 – 5.95 )</td>
</tr>
<tr>
<td>P·MIP(_{female}) (kPa) 5.18 ( 3.03 – 5.95 )</td>
</tr>
<tr>
<td>P·MIP(_{male}) (kPa) 5.22 ( 2.31 – 5.81 )</td>
</tr>
</tbody>
</table>

4.2.3.2 Flow through an external resistance to airflow

Inhaler specific resistance to airflow of DPI’s was simulated by means of orifices with bores of different diameters. Five different exchangeable orifice disks were used, with diameters ranging from 3 to 7 mm (R\(_3\) – R\(_7\)), with an increment of 1 mm. The different orifice disks are denoted as R\(_x\), in which \(x\) indicates the orifice diameter. When no external resistance was applied (unloaded) the results obtained are denoted as R\(_S\). The used orifice disks cover the
range of resistances to airflow of commercially available DPI’s (figure 4.1). A large orifice diameter corresponds with a low resistance to airflow. Orifice disks were mounted on a housing on the inspiratory side of a Y-valve. Inspiratory flow volume curves as generated by the subjects were recorded with the Y-valve connected upstream to a pneumotachograph (Jaeger, Würzburg, Germany) as an add-on device. Because airflow measurements with the pneumotachograph were influenced by the use of the add-on resistance to airflow device (chapter 7), all recorded flow volume curves were corrected from recorded flow to the real flow by correction for the pressure drop.

For each subject, inspiratory flow volume curves through only three out of the six available external resistances to airflow were recorded. The orifice disks were used in random order. At least three inspiratory flow volume curves were measured with the inhalation-instruction to inhale forcefully and deeply during a maximal inhalation. During the measurements all subjects were seated, wore a nose clip and carried out their maximal inspiratory manoeuvres from residual volume (RV) up to total lung capacity (TLC). From a series of five measurements through one orifice disk the three highest flow values were taken if their variation was within a range of 10%. If the last measurement was the highest of all three, additional measurements were performed. Each effort was displayed on a monitor, and the subjects were coached to improve their effort.

For the comparison of all recorded curves, the individual inspiratory flow volume curves were normalised to flow versus percentage of inhaled volume (%VCin).

4.3 Results

<table>
<thead>
<tr>
<th>Median (minimum – maximum)</th>
<th>P-MIP (kPa)</th>
<th>PIF (l·s⁻¹)</th>
<th>FIR₂₀–₈₀% (l·s⁻²)</th>
<th>βₖᵢ,₁ *</th>
<th>βₖᵢ₀ †</th>
<th>r² ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>f/m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R₃</td>
<td>6/3</td>
<td>5.74 (2.31 – 5.89)</td>
<td>0.42 (0.30 – 0.58)</td>
<td>0.82 (0.37 – 1.67)</td>
<td>0.14</td>
<td>0.32</td>
</tr>
<tr>
<td>R₄</td>
<td>7/4</td>
<td>5.04 (2.31 – 5.98)</td>
<td>0.83 (0.37 – 1.11)</td>
<td>2.41 (1.37 – 4.23)</td>
<td>1.22</td>
<td>-0.03</td>
</tr>
<tr>
<td>R₅</td>
<td>11/2</td>
<td>5.58 (3.03 – 5.95)</td>
<td>1.22 (0.78 – 1.67)</td>
<td>4.76 (2.48 – 10.83)</td>
<td>1.88</td>
<td>-0.16</td>
</tr>
<tr>
<td>R₆</td>
<td>4/3</td>
<td>5.18 (2.31 – 5.81)</td>
<td>1.99 (1.09 – 2.57)</td>
<td>10.39 (2.77 – 20.26)</td>
<td>3.28</td>
<td>-0.44</td>
</tr>
<tr>
<td>R₇</td>
<td>6/3</td>
<td>5.04 (3.03 – 5.95)</td>
<td>2.26 (1.11 – 2.80)</td>
<td>10.65 (6.21 – 15.09)</td>
<td>3.34</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

*: βₖᵢ,₁ = slope; †: βₖᵢ₀ = intercept; and ‡: r² = coefficient of determination; for the relationship between PIFₖᵢ and the square root of P-MIP as given in equation 4.2.

The results of this study are summarised in table 4.2. The results are given for each subgroup of subjects who inhaled through the different resistances to airflow. Presented are the
compositions of the subgroups, with the median (minimum – maximum) values for P·MIP, PIF, and FIRQ20-80%. Also the parameters of the linear relationship between PIFRx and the square root of P·MIP (equation 4.2) are presented with their coefficient of determination (r²).

4.3.1 Flow volume curves

Normalised mean inspiratory flow volume curves through resistances to airflow R₃ to R₇ and the unloaded normalised (Rₛ) inspiratory flow volume curve are given in figure 4.2. Mean PIFRx-values are indicated with standard deviation, both in flow rate and volume.

![Flow volume curves](image)

_Figure 4.2: Normalised mean inspiratory flow curves through resistance to airflow R₃ to R₇ and the unloaded inspiratory flow curve (Rₛ) for COLD patients with reduced P·MIP. Indicated (●) are the PIFRx-values with standard deviation, both in flow and volume._

The external resistance to airflow is a limitation for the PIFRx-values. The median (minimum - maximum) unloaded PIFRx of 3.83 (2.28 - 5.29) l·s⁻¹ is reduced to PIFR₇ of 2.26 (1.11 - 2.80) l·s⁻¹ for R₇ and decreases further to a PIFR₃ of 0.42 (0.30 - 0.58) l·s⁻¹ for R₃. Limitation of flow rate by the resistance to airflow results in an increase in inhalation time. The median total inhalation time has increased from 1.20 (0.56 - 2.57) seconds for the unloaded inhalation to 1.60 (1.02 - 3.18) seconds for R₇ and even increased to an inhalation time of 7.47 (4.52 - 13.31) seconds for R₃.
4.3.2 Relationship between PIF<sub>Rx</sub> and P·MIP

Figure 4.3 shows the linear relationships between PIF<sub>Rx</sub> and the square root of P·MIP, as found for the resistances to airflow R₃ to R₇ according to equation 4.2. Detailed results for the resistance to airflow subgroups are presented in table 4.2.

![Figure 4.3: Relationship between PIF<sub>Rx</sub> and the square root of P·MIP for resistance to airflow R₃ to R₇. Trendlines are given for each resistance to airflow. Corresponding P·MIP (kPa) values are given between brackets.](image)

4.3.3 Flow increase rate (FIR<sub>20-80%</sub>)

Figure 4.4 shows the relationship between the flow increase rate (FIR<sub>20-80%</sub>) and the generated PIF<sub>Rx</sub> in COLD patients with reduced P·MIP. As for PIF<sub>Rx</sub>, generated FIR<sub>20-80%</sub> depends on the used resistance to airflow. FIR<sub>20-80%</sub>-values between 0.37 and 15.09 l·s<sup>-2</sup> are found, for the investigated range of resistances to airflow, R₃ to R₇. Median (minimum – maximum) FIR<sub>20-80%</sub> for the unloaded inspiratory flow curve is 22.96 (8.52 – 42.77) l·s<sup>-2</sup>. Within a specific chosen resistance to airflow, high FIR<sub>20-80%</sub>-values corresponds with high PIF<sub>Rx</sub>-values.
Figure 4.4: Relationship between $FIR_{20-80\%}$ and $PIF_{Rx}$ for COLD patients with reduced P·MIP at varying resistances to airflow ($R_3$ (◦); $R_4$ (▲); $R_5$ (○); $R_6$ (+); $R_7$ (△)).

4.3.4 Results of COLD patients with reduced P·MIP compared to healthy subjects, and mild to moderate COLD patients

Results of the COLD patients with significantly reduced P·MIP from this study, are compared with the results of healthy subjects, and mild to moderate COLD patients as described in chapter 3. The values for the COLD patients, as defined in chapter 3, are the combined results of the asthmatics and mild to moderate COPD patients. In chapter 3, it was concluded that the generated normalised mean inspiratory flow curve depends on the P·MIP, and therefore on the disease state of the subjects. Figure 4.5 shows a comparison of the normalised inspiratory flow curve through resistance to airflow $R_4$, as generated by healthy subjects, COLD patients, as described in chapter 3, and the COLD patients with reduced P·MIP presented in this chapter. In table 4.3 the P·MIP, PIF and $VC_{in}$ values of COLD patients and COLD patients with reduced P·MIP are expressed as percentage of the values found for healthy subjects. The proposed relationship between $PIF_{Rx}$ and P·MIP is presented in figure 4.6 as percentage of the mean PIF and P·MIP values of the healthy subjects as described in chapter 3. Individual relative values of PIF and P·MIP for the COLD patients with reduced P·MIP are presented as percentage of the mean PIF and P·MIP values of the healthy subjects. The relative PIF-values are the mean relative values through the three used resistances to airflow for each individual.
Table 4.3: Respiratory variables P·MIP, PIF and VC\textsubscript{in} of COLD patients (chapter 3) and COLD patients with reduced P·MIP compared with values for healthy subjects. Values are expressed as percentage of healthy subjects.

<table>
<thead>
<tr>
<th>% Healthy*</th>
<th>P·MIP</th>
<th>PIF</th>
<th>VC\textsubscript{in}</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLD patients*</td>
<td>78.2 %</td>
<td>86.3 %</td>
<td>71.1 %</td>
</tr>
<tr>
<td>COLD patients with reduced P·MIP</td>
<td>42.6 %</td>
<td>64.0 %</td>
<td>37.8 %</td>
</tr>
</tbody>
</table>

*Date from chapter 3

Figure 4.5: Comparison of normalised inspiratory flow curve through resistance to airflow R\textsubscript{4}, as generated by healthy subjects (continuous line), and COLD patients (dotted line) (data from chapter 3), and COLD patients with P·MIP < 6 kPa (bold continuous line).

4.4 Discussion

In this study the possibility to generate inspiratory flow through a resistance to airflow was investigated in a group of COLD patients with reduced P·MIP, simulating inhalation through DPI's. The results demonstrate that the PIF\textsubscript{Rx} depends on P·MIP, and thus on the respiratory muscle strength (figure 4.3), and on the used external resistance to airflow (figure 4.2). The used resistance to airflow limits the inspiratory flow rate, which results in distinct curves
for each resistance to airflow (figure 4.2). PIF_{Rx} values are reached at smaller inhaled volume for high resistance to airflow (R_3), compared to low resistance to airflow (R_7 or R_5). The standard deviation in PIF_{Rx} for high resistance to airflow is smaller compared to the standard deviation in PIF_{Rx} for low resistance to airflow. This means that the reached PIF_{Rx} is less variable when an individual inhales maximally against a high resistance to airflow.

We studied a selected group of patients based on a P·MIP of less than 6 kPa, which is about half the mean P·MIP as generated by healthy subjects (chapter 3). This selection resulted in a P·MIP between 4 kPa and 6 kPa (figure 4.3). Only two patients had a P·MIP below 4 kPa. In spite of those facts, a linear relationship between PIF_{Rx} and the square root of P·MIP was found for each resistance to airflow. In fact, the relationship may be even more meaningful for COLD patients with reduced P·MIP, than for healthy subjects because the $\beta_{Rx,0}$ -values are closer to zero. The coefficients of determination ($r^2$) for the relationships for R_4 and R_6 were the highest. The coefficient of determination for R_3 is very low, due to the very small slope in the relationship. As a result of the inclusion criterion, the mean P·MIP was only 42% of that found in the healthy subjects (chapter 3), but the generated PIF_{Rx} was still 64% (table 4.3).

![Figure 4.6: Relationship between percentage PIF and percentage P·MIP. The continuous line is the theoretical relationship between PIF and the square root of P·MIP, based on equation 4.2. Indicated are: (●) the relative PIF and P·MIP of the individual COLD patients with reduced P·MIP as percentage of the mean for healthy subject (chapter 3), (△, with dashed dot dropline), mean percentage PIF and P·MIP of all COLD patients with reduced P·MIP, and (◇) COLD patients (chapter 3).]
The shape of the first part of the inspiratory flow curve till PIF can be characterised by means of the flow increase rate, FIR\textsubscript{20-80\%}. The values of FIR\textsubscript{20-80\%} are linearly related to PIF through a resistance to airflow. Because the PIF through a high resistance to airflow is less variable than through a low resistance to airflow, a trumpet shaped relationship is found. An increased resistance to airflow reduces not only the absolute variation in generated PIF\textsubscript{Rx}, but also the variation in FIR\textsubscript{20-80\%}.

Results of COLD patients with reduced P·MIP compared to healthy subjects, asthmatics and mild to moderate COPD patients, demonstrate that a strongly reduced P·MIP results in a serious decrease in inspiratory flow rate. The generated PIF is related to the square root of the P·MIP. Therefore, the reduction of P·MIP in the COLD patients, to 42\% of the P·MIP of healthy subjects, results for the COLD patients in a 64\% of the PIF\textsubscript{Rx} of healthy subjects. This means that, even though these COLD patients have a serious reduction in P·MIP, they are still able to generate significant inspiratory flow rate, even through a high resistance to airflow. Figure 4.6 demonstrates the theoretical relationship between PIF and P·MIP. In the comparison of the COLD patients with reduced P·MIP against the healthy subjects, the mean score of the healthy subjects is defined as 100\%. Projection of the individual as well as the mean relative scores on PIF and P·MIP of the COLD patients with reduced P·MIP, shows that they are projected around the square root relationship between PIF\textsubscript{Rx} and P·MIP, according to equation 4.2 and figure 4.3.

This study shows that the inspiratory performance of healthy subjects may predict the inhalation through a resistance to airflow by patients. However, a restriction is that the P·MIP of the reference group and the target group has to be known.

The operation of dry powder inhalers is related to a minimally required inspiratory flow rate through the inhaler. The relationship between PIF\textsubscript{Rx} and the square root of P·MIP (figure 4.3) suggests that a minimally required P·MIP is necessary. Below that point the patient is not able to generate sufficient PIF\textsubscript{Rx} for an optimal use of a DPI, because the inspiratory motor function is too low to generate the required inspiratory flow rate. The results of this study indicate that the investigated group of COLD patients are able to generate a significant inspiratory flow through a resistance to airflow, even if their inspiratory muscle strength, represented by P·MIP, is strongly reduced. Therefore, the use of DPI’s in COLD patients with reduced P·MIP is not limited because of reduced deposition into the airways. However, it is recognised that those patients are not able to inhale as strongly as healthy subjects or asthmatics, but they are able to generate sufficient inspiratory flow for an acceptable operation of DPI’s.

4.5 Conclusion

The peak maximal inspiratory pressure (P·MIP), as an indicator of the inspiratory muscle strength, is a predictive value for the driving force for inhalation. Inspiratory flow results
obtained in healthy volunteers can be used to predict PIFRX as generated by COLD patients with reduced P·MIP. The generated P·MIP and PIFRX-values in the investigated group of COLD patients are sufficient for adequate use of low as well as high resistance to airflow dry powder inhalers. However, these patients might not reach the most optimal inspiratory flow for the highest disintegration and deposition of the drug particles. Increased resistance to airflow will reduce variance in generated PIFRX over a wide range of P·MIP, which improves the reproducibility in the performance of the DPI. Therefore, the use of high resistance to airflow DPI’s is preferred, even for COLD patients with reduced P·MIP.

### 4.6 Acknowledgements

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### 4.7 References


