Fine particle output of breath-controlled dry powder inhalers (DPI’s) depends on the patient-generated inspiratory flow curve. And because the driving force for a flow is the pressure difference across the inhaler, there must also be a relationship between the performance of DPI’s and the inspiratory pressure. In this study it is hypothesised that the peak maximal inspiratory pressure (P·MIP), as indicator for inspiratory muscle strength, is a predictor for the peak inspiratory flow (PIF) through a DPI with a particular inhaler specific resistance to airflow.

Six orifice disks, simulating the resistance to airflow of DPI’s, were used as an add-on device on a pneumotachograph. Inspiratory flow volume curves through these resistances to airflow were measured, and related to the recorded P·MIP for the same patient or healthy subject. The study was performed in twenty-five healthy subjects, thirty asthmatics and twenty COPD patients. For each external resistance to airflow, the PIF and flow increase rate are linearly related to the square root of P·MIP.

It is found that both inspiratory muscle strength and the inhaler specific resistance are determinants for the generated inspiratory flow curve through DPI’s. These determinants should be taken into account by prescribing of DPI’s and by the development of new DPI’s.
Inhalation is the preferred route of administration for respiratory drugs in the treatment of asthma and COPD. A lot of research has been done into the effects of particle size and required airflow on the achievement of an optimal pulmonary deposition of respirable particles\(^1,\ 2\). Dry powder inhalers (DPI’s) are breath-controlled inhalers. The inspiratory flow controls the mechanisms for disintegration and delivery of the powdered drug into the inhaled airstream. The design of the DPI results in an inhaler specific resistance to airflow (figure 3.1), which is a parameter that limits the airflow.

A minimally required peak inspiratory flow (PIF) and/or acceleration in inspiratory flow rate (flow increase rate, FIR) is necessary for an optimal drug deposition into the airways\(^1-4\). Many studies have been performed to measure peak inspiratory flow through a DPI\(^5-10\). These studies investigated the flow through a DPI in relation to the disease or in relation to inhaler specific resistance to airflow.

Besides peak inspiratory flow rate, inhaled volume and flow increase rate may be relevant inspiratory flow parameters for the performance of dry powder inhalers\(^1\).

Patient-generated pressure drop across an inhaler is the driving force for a flow rate through the device\(^11\). Knowing the inhaler’s specific resistance to airflow, the flow profile can be computed from the inspiratory pressure curve (equation 3.1). Most studies refer to PIF as determinant for DPI-performance. The PIF, which is the peak pressure difference across a certain DPI, is a function of the patients inspiratory muscle strength, but also depends on the inhaler specific resistance to airflow. A resistance independent patient parameter would be
much more convenient to use for predicting a patient’s inspiratory performance through a certain type of inhaler. Some studies\textsuperscript{9, 12, 13} suggest that the peak maximal inspiratory pressure (P·MIP), which is a well accepted indicator for the inspiratory muscle strength\textsuperscript{(11)}, could be used as independent parameter. The suggestion is based upon the assumption that P·MIP is predictive or the peak pressure difference across a known resistance to airflow.

In this study, the generated inspiratory flow curve through a DPI is investigated in relation to the subject generated P·MIP, and to the inhaler specific resistance to airflow. The study is performed in three groups of subjects, healthy subjects, asthmatics and COPD patients. Minor differences are expected between healthy subjects and asthmatics due to the similar airway structure. However, in COPD patients a decrease in maximal inspiratory pressure is expected due to remodelling of the airway structure and to hyperinflation\textsuperscript{(11)}.

![Graph](image)

Figure 3.1: Relationship between resistance to airflow and the orifice diameter ($O = \text{orifice disk, denoted as } R_x$). Resistance to airflow of commercial available DPI’s are also indicated.

### 3.2 Material and Methods

#### 3.2.1 Methods

Inhaler specific resistance to airflow of DPI’s was simulated by orifice disks with bores of different diameters. Six different exchangeable orifice disks were used, with diameters
ranging from 3 to 8 mm (R₁ - R₈), with an increment of 1 mm. The different orifice disks are denoted as Rₓ, in which x indicates the specific orifice diameter. Spirometry results, without noticeable external resistance to airflow, are denoted with Rₛ. The used orifice disks cover the range of resistances to airflow of commercially available dry powder inhalers (figure 3.1). A large orifice diameter corresponds to a low resistance to airflow. Orifice disks were mounted in a housing on the inspiratory side of an 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 (figure 3.2). Because airflow measurements with the pneumotachograph were influenced by the use of the add-on resistance to airflow device, all recorded flow volume curves were corrected for changes in gas density in the pneumotachograph as described in chapter 7.

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 applied in random order. At least five 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% of each other. 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.

Figure 3.2: Experimental set-up for inhalation through external resistance to airflow.
For the comparison of all recorded curves, the individual inspiratory flow volume curves were normalised to flow against percentage of inhaled volume (%VC\textsubscript{i}).

Peak maximal inspiratory pressure (P·MIP) was measured with the pressure transducer of the pneumotachograph (ML-Masterlab, Jaeger, Würzburg, Germany). 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\textsuperscript{(14)}. At least 8 maximal inspiratory manoeuvres were carried out with a minimum of 30 seconds rest between each measurement. The three highest achieved pressures were used for further analysis. 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 3.1: Demographic and lung function data of the participants**

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n =</td>
<td>25 (15m/10f)</td>
<td>30 (11m/19f)</td>
<td>20 (13m/7f)</td>
</tr>
<tr>
<td>mean ± SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>34 ± 2.6</td>
<td>39 ± 2.7</td>
<td>57 ± 1.2</td>
</tr>
<tr>
<td>Smokers / Ex-smokers / never</td>
<td>2 / 6 / 17</td>
<td>5 / 9 / 16</td>
<td>2 / 14 / 4</td>
</tr>
<tr>
<td>PEF (%pred)</td>
<td>110.5 ± 4.1</td>
<td>94.7 ± 4.1</td>
<td>87.7 ± 6.7</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (%pred)</td>
<td>106.7 ± 2.6</td>
<td>89.5 ± 3.8</td>
<td>77.3 ± 6.0</td>
</tr>
<tr>
<td>PIF\textsubscript{RS} (l/s)</td>
<td>6.58 ± 0.30</td>
<td>5.96 ± 0.29</td>
<td>5.60 ± 0.42</td>
</tr>
<tr>
<td>FIV\textsubscript{1} (l)</td>
<td>4.86 ± 0.18</td>
<td>3.96 ± 0.21</td>
<td>3.87 ± 0.22</td>
</tr>
<tr>
<td>P·MIP\textsubscript{all} (kPa)</td>
<td>11.22 ± 0.72</td>
<td>9.97 ± 0.64</td>
<td>8.48† ± 0.68</td>
</tr>
<tr>
<td>P·MIP\textsubscript{female} (kPa)</td>
<td>9.95 ± 1.27</td>
<td>8.80* ± 0.64</td>
<td>6.21*‡ ± 0.95</td>
</tr>
<tr>
<td>P·MIP\textsubscript{male} (kPa)</td>
<td>12.06 ± 0.82</td>
<td>11.99 ± 1.15</td>
<td>9.70¶ ± 0.73</td>
</tr>
</tbody>
</table>

* p<0.05 compared to P·MIP\textsubscript{male}; † p<0.01 compared to healthy P·MIP\textsubscript{all}; ‡ p<0.05 compared to healthy and asthma P·MIP\textsubscript{female}; ¶ p<0.05 compared to healthy P·MIP\textsubscript{male}.

### 3.2.2 Study subjects

Twenty-five healthy subjects and fifty patients volunteered for the study, which was approved by the medical ethics committee of the University Hospital Groningen. The healthy subjects were without any respiratory symptoms according to the MRC-ECSC questionnaire\textsuperscript{(15)}. Inclusion criteria for patients were a doctor’s diagnosis of asthma (30 patients) or COPD (20 patients). Demographic and lung function data of the participants are presented in table 3.1. No drugs were administered during the test. All measurements of dynamic lung function were
obtained during a single visit to the pulmonary out-patient clinic. Spirometry was performed followed by maximal inspiratory pressure measurements. After a 10-15 minutes recovery, inspiratory flow volume curves through three external resistances to airflow were recorded. Subjects were allowed to practice inhalation through the external resistance to airflow, before the actual measurement.

3.2.3 Analysis

3.2.3.1 Resistance to airflow
Specific resistances to airflow \((R)\), for the different orifice disks and dry powder inhalers, were calculated from the slopes of the linear relationships between the square root of pressure drop \((\Delta p)\) and the volumetric flow \((\Phi)\), according to equation 3.1:\(^{16}\)
\[
\sqrt{\Delta p} = R \cdot \Phi
\] (equation 3.1)

3.2.3.2 Relationship between PIF\(_R\) and P·MIP
Measured peak flow rates through each orifice disk \((\text{PIF}_{R_x})\) have been expressed as function of P·MIP. Assuming that P·MIP is predictive for the peak pressure difference achieved across a resistance to airflow, and that PIF\(_{R_x}\) is considered to be the peak pressure difference across a resistance to airflow, there must be a subject dependent relationship between P·MIP and PIF\(_{R_x}\). Therefore, the relationship between PIF\(_{R_x}\) and P·MIP is expressed by an equation similar to equation 3.1, in which \(\Delta p\) is substituted by P·MIP and \(\Phi\) by PIF\(_{R_x}\).
In the expression between PIF\(_{R_x}\) and P·MIP (equation 3.2), \(\beta_{R_x,1}\) is a function of the reciprocal resistance to airflow and \(\beta_{R_x,0}\) is an intercept from linear regression analysis.
\[
\text{PIF}_{R_x} = \beta_{R_x,1} \cdot \sqrt{\text{P·MIP}} + \beta_{R_x,0}
\] (equation 3.2)

3.2.3.3 Flow increase rate (FIR\(_{20-80\%}\))
Flow increase rate (FIR) is calculated over a representative part of the inspiratory flow curve and is defined as the average flow increase rate from 20% to 80% of PIF\(_{R_x}\) (FIR\(_{20-80\%}\) (l·s\(^{-2}\))).

3.3 Results
The main results of this study are summarised in table 3.2. Results are given for each subgroup of subjects who inhaled through the different resistances to airflow. Given are the number of male and female subjects in the subgroups, with the mean P·MIP (±SEM), PIF (±SEM), and FIR\(_{20-80\%}\) (±SEM) values. Parameters of the linear relationships between PIF\(_{R_x}\) and the square root of P·MIP (equation 3.2) are given with their coefficients of determination \((r^2)\).
Table 3.2: Results for each subgroup in healthy subjects, asthmatics and COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>Healthy m/f</th>
<th>P·MIP ± SEM (kPa)</th>
<th>PIF ± SEM (l·s⁻¹)</th>
<th>FIR_{20-80%} ± SEM (l·s⁻²)</th>
<th>β_{Rx,1} \cdot 10^{-2}</th>
<th>β_{Rx,0} †</th>
<th>r^{2‡}</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₃</td>
<td>9/4</td>
<td>10.91 ± 1.14</td>
<td>0.57 ± 0.01</td>
<td>1.91 ± 0.15</td>
<td>0.26</td>
<td>0.31</td>
<td>0.48</td>
</tr>
<tr>
<td>R₄</td>
<td>6/6</td>
<td>11.55 ± 0.91</td>
<td>1.33 ± 0.02</td>
<td>7.67 ± 0.64</td>
<td>0.73</td>
<td>0.56</td>
<td>0.68</td>
</tr>
<tr>
<td>R₅</td>
<td>8/4</td>
<td>10.42 ± 1.12</td>
<td>1.89 ± 0.04</td>
<td>10.54 ± 1.06</td>
<td>0.78</td>
<td>1.11</td>
<td>0.36</td>
</tr>
<tr>
<td>R₆</td>
<td>7/6</td>
<td>11.95 ± 0.93</td>
<td>3.00 ± 0.05</td>
<td>20.13 ± 1.80</td>
<td>1.71</td>
<td>1.15</td>
<td>0.60</td>
</tr>
<tr>
<td>R₇</td>
<td>6/7</td>
<td>10.38 ± 0.95</td>
<td>3.92 ± 0.06</td>
<td>23.61 ± 1.80</td>
<td>1.51</td>
<td>2.42</td>
<td>0.41</td>
</tr>
<tr>
<td>R₈</td>
<td>9/3</td>
<td>12.12 ± 1.07</td>
<td>4.78 ± 0.11</td>
<td>33.57 ± 3.34</td>
<td>3.36</td>
<td>1.13</td>
<td>0.62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Asthma m/f</th>
<th>P·MIP ± SEM (kPa)</th>
<th>PIF ± SEM (l·s⁻¹)</th>
<th>FIR_{20-80%} ± SEM (l·s⁻²)</th>
<th>β_{Rx,1} \cdot 10^{-2}</th>
<th>β_{Rx,0} †</th>
<th>r^{2‡}</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₃</td>
<td>6/5</td>
<td>10.56 ± 1.07</td>
<td>0.53 ± 0.01</td>
<td>1.71 ± 0.19</td>
<td>0.47</td>
<td>0.05</td>
<td>0.90</td>
</tr>
<tr>
<td>R₄</td>
<td>5/14</td>
<td>9.62 ± 0.80</td>
<td>1.22 ± 0.03</td>
<td>6.26 ± 0.47</td>
<td>1.06</td>
<td>0.19</td>
<td>0.74</td>
</tr>
<tr>
<td>R₅</td>
<td>7/13</td>
<td>11.13 ± 0.79</td>
<td>1.81 ± 0.04</td>
<td>9.84 ± 0.75</td>
<td>1.62</td>
<td>0.13</td>
<td>0.70</td>
</tr>
<tr>
<td>R₆</td>
<td>4/8</td>
<td>8.27 ± 0.67</td>
<td>2.39 ± 0.08</td>
<td>12.54 ± 1.28</td>
<td>3.31</td>
<td>-0.62</td>
<td>0.66</td>
</tr>
<tr>
<td>R₇</td>
<td>8/12</td>
<td>10.67 ± 0.84</td>
<td>3.68 ± 0.09</td>
<td>22.13 ± 1.59</td>
<td>2.85</td>
<td>0.80</td>
<td>0.52</td>
</tr>
<tr>
<td>R₈</td>
<td>3/5</td>
<td>7.88 ± 0.79</td>
<td>3.45 ± 0.15</td>
<td>17.90 ± 2.37</td>
<td>5.27</td>
<td>-1.25</td>
<td>0.73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>COPD m/f</th>
<th>P·MIP ± SEM (kPa)</th>
<th>PIF ± SEM (l·s⁻¹)</th>
<th>FIR_{20-80%} ± SEM (l·s⁻²)</th>
<th>β_{Rx,1} \cdot 10^{-2}</th>
<th>β_{Rx,0} †</th>
<th>r^{2‡}</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₃</td>
<td>6/3</td>
<td>8.88 ± 1.00</td>
<td>0.48 ± 0.02</td>
<td>1.36 ± 0.15</td>
<td>0.47</td>
<td>0.05</td>
<td>0.61</td>
</tr>
<tr>
<td>R₄</td>
<td>7/4</td>
<td>8.15 ± 0.96</td>
<td>1.05 ± 0.04</td>
<td>4.42 ± 0.57</td>
<td>1.21</td>
<td>-0.01</td>
<td>0.84</td>
</tr>
<tr>
<td>R₅</td>
<td>5/5</td>
<td>8.66 ± 1.27</td>
<td>1.63 ± 0.09</td>
<td>7.52 ± 1.26</td>
<td>2.11</td>
<td>-0.32</td>
<td>0.82</td>
</tr>
<tr>
<td>R₆</td>
<td>8/2</td>
<td>8.29 ± 0.59</td>
<td>2.52 ± 0.08</td>
<td>11.61 ± 1.57</td>
<td>1.00</td>
<td>1.48</td>
<td>0.13</td>
</tr>
<tr>
<td>R₇</td>
<td>4/5</td>
<td>8.36 ± 1.28</td>
<td>3.07 ± 0.17</td>
<td>16.64 ± 2.07</td>
<td>3.92</td>
<td>-0.39</td>
<td>0.80</td>
</tr>
<tr>
<td>R₈</td>
<td>9/1</td>
<td>8.82 ± 0.76</td>
<td>3.65 ± 0.14</td>
<td>19.02 ± 2.67</td>
<td>4.90</td>
<td>-0.89</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*: β_{Rx,1} = slope; †: β_{Rx,0} = intercept; and ‡: r^2 = coefficient of determination; for the relationship between PIF_{Rx} and the square root of P·MIP as given in equation 3.2.

3.3.1 Respiratory muscle strength

As expected, the peak maximal inspiratory pressure, as achieved by the study subjects, is related to gender as well as disease. The difference in P·MIP between asthmatics and healthy volunteers is not significant. However, significant (p<0.01) differences are found between P·MIP-values of the COPD patients and the healthy volunteers (table 3.2).
Figure 3.3 shows the mean P·MIP-values (± SEM) as generated by the three subject groups (R₃) and the mean P·MIP-values for the subjects in the subgroups, which inhaled through the resistances to airflow, R₄ and R₇. R₄ is considered to be representative of the high resistance to airflow dry powder inhalers, while R₇ is considered to be representative of the low resistance to airflow dry powder inhalers (figure 3.1). For the R₄ subgroup, the mean P·MIP for the COPD patients is significantly (p<0.05) lower compared to the healthy subjects.

![Figure 3.3: Mean P·MIP-values (± SEM) as generated by each subject group (R₃) and for the subject groups for resistances to airflow R₄ and R₇. ★ = Mean P·MIP-value for COPD patients is significantly (p < 0.01) lower compared to healthy subjects. † = Mean P·MIP-value for COPD subgroup R₄ is significantly (p < 0.05) lower compared to healthy subjects subgroup R₄.]

### 3.3.2 Flow volume curves

Mean normalised inspiratory flow curves through resistances to airflow R₄ and R₇ are given in figure 3.4 for each subject group. Mean PIFᵣ₄-values are indicated with standard error of mean (SEM), both in flow rate and volume.

The external resistance to airflow limits the PIFᵣ₄-values. In healthy subjects PIFᵣ₇ of 3.92 (± 0.02) l·s⁻¹ found for R₇, is reduced to a PIFᵣ₄ of 1.33 (± 0.06) l·s⁻¹ for R₄. PIF-values for asthmatics are approximately 10% lower compared to the healthy subjects. However, PIF-values for the COPD patients are reduced by approximately 20% compared to the healthy
subjects (figure 3.4, table 3.2).
Limitation of flow by the resistance to airflow results in an increase in inhalation time. For the asthmatics, for instance, total inhalation time is increased from 1.49 ± 0.07 seconds for R₈ to 7.85 ± 0.33 seconds for R₃. For healthy subjects and COPD patients this increase in inhalation time is of the same order of magnitude.

![Image of flow curves](image)

**Figure 3.4: Normalised mean inspiratory flow curves through resistance to airflow R₄ and R₇ for healthy subjects (continuous line), asthmatics (dash dot line), and COPD patients (dotted line). Indicated are the PIF_{Rx}-values with SEM, both in flow and volume.**

### 3.3.3 Relationship between PIF_{Rx} and P·MIP

For each orifice disk, linear relationships between PIF_{Rx} and the square root of P·MIP were found according to equation 3.2 (table 3.2). For healthy subjects, asthmatics and COPD patients, these relationships for R₄ and R₇ are given in figure 3.5. Different slopes are found for the three groups. Minor differences in slopes are found for a high resistance to airflow (R₄), but significant (p<0.05) different slopes are found for the three groups at a low resistance to airflow (R₇).
3.3.4 Flow increase rate (FIR\textsubscript{20-80%})

Figure 3.6 shows the almost linear relationship between the flow increase rate (FIR\textsubscript{20-80%}) and the generated PIF\textsubscript{Rx} in the asthmatics and COPD patients. A similar relationship is found for the healthy subjects (not shown), in which the FIR\textsubscript{20-80%} values were 16% higher than found for the patients. For the entire dataset (all subjects and all orifice disks) FIR\textsubscript{20-80%} ranged between 0.49 and 48.1 l·s\textsuperscript{-2}. Within a specific chosen resistance to airflow, high FIR\textsubscript{20-80%}-values are found at high PIF\textsubscript{Rx}-values.

3.4 Discussion

The results (figure 3.5) demonstrate that PIF\textsubscript{Rx} depends on subject-generated P·MIP and on the used external resistance to airflow.

The used resistance to airflow limits the inspiratory flow rate, which results in distinct curves for each resistance to airflow (figure 3.4). In this, it should be noted that total inhalation time has been increased with increased resistance to airflow. For example, the total inhalation time for R\textsubscript{3} has been increased five times compared to R\textsubscript{5}. 
Figure 3.6: Relationship between FIR_{20-80%} and PIF_{Rx} for patients with varying resistances to airflow (R_3 (○); R_4 (▲); R_5 (◇); R_6 (+); R_7 (△); R_8 (●)).

The inspiratory flow rate profiles as function of %VC_{in} for asthmatics do not reach the same levels as those for the healthy subjects. The flow rates achieved by COPD patients are even less than those for asthmatics over the whole duration of inhalation (figure 3.4). For COPD patients also significant (p<0.01) lower P·MIP-values are found, compared to healthy subjects. The reduction, both in P·MIP and PIF_{Rx}, supports the conclusion that generated PIF through a resistance to airflow is related to the subject-generated P·MIP.

For each resistance to airflow, a linear relationship between PIF_{Rx} and the square root of P·MIP as calculated according to equation 3.2 has been obtained (table 3.2). At increasing resistance to airflow the slope is reduced, and a better correlation is found (higher r^2-values). This means that P·MIP-values, achieved by patients, are very important when using a low resistance inhaler. For high resistance inhalers the achieved P·MIP-values are less important to generate sufficient inspiratory flow.

An increased resistance to airflow reduces absolute variation in generated PIF_{Rx}, over a wide range of P·MIP-values. This reduced variation improves reproducibility in DPI performance. Moreover, increased resistance to airflow reduces the velocity of inhaled drugs particles and therefore, reduces oropharyngeal deposition of inhaled drug powder^{17}. Especially for those patients who cannot produce high P·MIP-values, as is the case in COPD and emphysema, the use of high resistance to airflow DPI’s is preferred.
The operation of DPI’s is related to a minimally required PIF$_{Rx}$-value. The relationship between PIF$_{Rx}$ and the square root of P·MIP (figure 3.5) suggests that a minimally required P·MIP is necessary, below which the patient is unable to generate sufficient PIF$_{Rx}$ for an optimal use of a DPI. At this point the inspiratory motor function is too low to generate the required inspiratory flow. All subjects tested, even in the COPD patients, were able to generate sufficient P·MIP-values for an optimal use of the DPI’s. This may be due to the fact that only very mild COPD patients participated in this study (table 3.1). Therefore, complementary measurements with more severe COPD patients, with strongly reduced PMIP, must be performed (chapter 4).

The relationship between PIF$_{Rx}$ and the square root of P·MIP (figure 3.5) is based on equation 3.1, in which P·MIP is considered to be a predictive for the pressure drop ($\Delta p$). P·MIP is measured at a very high resistance to airflow. The actual pressure drop over the applied resistances to airflow, simulating DPI’s, is only a fraction of P·MIP. Only for a high resistance to airflow ($R_4$) the pressure drop over the orifice approaches the P·MIP-value. Therefore, generated PIF$_{Rx}$ through a high resistance to airflow is closely related to the inspiratory muscle strength parameter P·MIP. Pressure drop over a low resistance to airflow ($R_7$) is only a small fraction of P·MIP. In this case, generated PIF$_{Rx}$ is more related to maximal contraction velocity of the inspiratory muscles.$^{(18, 19)}$

Characterisation of the inspiratory flow curve with flow increase rate (FIR) is used in several studies for evaluation of particular DPI performance.$^{(2-4)}$. In each of the studies FIR is differently defined. In our opinion these methods of FIR-calculation have some disadvantages. Everard et al.$^{(3)}$ defined FIR ($s^{-1}$) as flow after a certain amount of inhaled volume (150 ml). This value is dimensionally not representative. Burnell et al.$^{(4)}$ defined FIR ($l\cdot min^{-1}\cdot s^{-1}$) as flow acceleration during dose emission. But time of dose-emission is not comparable for different DPI’s. De Boer et al.$^{(2)}$ defined FIR ($l\cdot s^{-2}$) as flow increase rate from 30 to 40 $l\cdot min^{-1}$. This definition is only applicable for a particular inhaler. In our study, for each resistance to airflow, FIR ($l\cdot s^{-2}$) is defined as the flow increase rate from 20% to 80% of the peak inspiratory flow (FIR$_{20-80\%}$). During this part of the inspiratory flow curve a representative FIR is measured in a wide range of resistances to airflow. As shown in figure 3.6, FIR$_{20-80\%}$ relates to the PIF$_{Rx}$. It was already shown in figure 3.5 that PIF$_{Rx}$ depends on the square root of P·MIP. Therefore, it can be concluded that the generated FIR$_{20-80\%}$ is also a pressure driven parameter, and depends linearly on the square root of P·MIP.

An increased resistance to airflow reduces variation in generated PIF$_{Rx}$, but also limits the FIR$_{20-80\%}$ (figure 3.6). Therefore, for those DPI’s in which a certain FIR$_{20-80\%}$ is required for optimal fine particle output, the increase in resistance to airflow in the DPI design is limited. These findings should be taken into account by prescribing DPI’s as well as by the development of new DPI’s.
3.5 Conclusion

Peak maximal inspiratory pressure (P-MIP), as indicator of the inspiratory muscle strength, has a predictive value for the driving force for inhalation. At increased resistance to airflow the effect of the inter-individual variation in P-MIP on the generated inspiratory flow is reduced. Varying the resistance to airflow enables one to control the inspiratory flow through a PDI. Increased resistance to airflow will reduce variance in PIFRx, which improves the reproducibility in the performance of the DPI. Due to this aspect, the use of high resistance to airflow DPI’s is preferred. The generated P-MIP and PIFRx-values in the investigated group of asthmatics and COPD patients were sufficient for an optimal use of DPI’s.

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3.7 References


