Chapter 5

Daily use of a Dry Powder Inhaler Increases Peak Maximal Inspiratory Pressure

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Abstract

Generated peak inspiratory flow rate through a dry powder inhaler (DPI) depends on the subject-generated peak maximal inspiratory pressure (P·MIP). Inhalation through a high resistance DPI can be considered as low intensity inspiratory muscle training (IMT), which can increase P·MIP against time. In this study, the influence of daily use of a DPI on the P·MIP was investigated. P·MIP and peak inspiratory flow rate through a resistance to airflow (PIFₐᵣᵣ) were monitored in a group of 16 healthy volunteers, during an eight-week period. Eight volunteers (intervention group) followed a simulated inhalation therapy, while the other eight subjects were controls. The simulated inhalation therapy consisted of five forceful and deep inhalations, performed twice daily, through a dummy DPI. In the intervention group, P·MIP had increased by 16% after four weeks to 24% after eight weeks of simulated inhalation therapy. The increase in P·MIP also resulted in an increase in PIFₐᵣᵣ of 4% after four weeks to 8% after eight weeks. In the control group, MIP and PIFₐᵣᵣ remained unchanged. In conclusion, the simulated inhalation therapy with a high resistance to airflow DPI resulted in an increase of P·MIP and PIFₐᵣᵣ.
5.1 Introduction

Inspiratory flow through a breath-controlled dry powder inhaler (DPI) is the result of an inspiratory pressure generated by the respiratory muscles. Inspiratory flow rate will increase with increased inspiratory muscle strength (chapter 3 and chapter 4). Moreover, the performance of breath-controlled DPI’s depends on the peak inspiratory flow rate through the inhaler device (chapter 6). Therefore, an increased inspiratory muscle strength increases the fine particle output from the DPI. This will have a positive clinical effect. Peak maximal inspiratory pressure (P·MIP) is a parameter for inspiratory muscle strength(1). The respiratory muscles are striated skeletal muscles, and can be trained like other striated muscles, in order to increase their strength and endurance. This was demonstrated in healthy volunteers(2, 3) as well as in patients(4-7). Training with high force contractions increases maximal force, whereas training with high velocity (low force contractions) increases maximal shortening velocity(8, 9).

Current methods to increase respiratory muscle strength are resistive breathing and threshold-load breathing. Inspiratory muscle training (IMT) is a type of training in which the patient inhales against resistive loads or pressure threshold-loads, while the expiration is unloaded(5, 6). The currently available DPI’s have different resistances to airflow. Inhalation through these DPI’s can be simulated by inhalation through orifices with corresponding resistance to airflow. In this respect IMT resembles daily use of a DPI. Therefore, the question was raised how much increase in respiratory muscle strength can be obtained by the sole use of a dummy DPI (training device) (figure 5.1) without active drug. And how much increase in peak inspiratory flow through a resistance to airflow (PIF<sub>R</sub>), simulating a DPI, can be obtained.
5.2 Material and Methods

5.2.1 Study subjects

Sixteen healthy subjects (8 female / 8 male) volunteered for the study, which was approved by the medical ethics committee of the University Hospital Groningen. The healthy subjects were without respiratory symptoms according to the MRC-ECSC questionnaire\(^{(10)}\). Subjects were matched by gender for the intervention group (4 female / 4 male) and the control group (4 female / 4 male). Median age for the intervention group was 24 years (range 20-37), and median age for the control group was 26 years (range 22-34). Lung function data for intervention group and control group are given in table 5.1.

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Control group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>PEF (%pred)</td>
<td>101.3 ± 5.9</td>
<td>94.2 ± 4.6</td>
</tr>
<tr>
<td>FEV(_1) (%pred)</td>
<td>103.2 ± 5.2</td>
<td>95.8 ± 2.8</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>4.67 ± 0.23</td>
<td>4.91 ± 0.33</td>
</tr>
<tr>
<td>P·MIP(_{baseline}) (kPa)</td>
<td>12.0 ± 0.4</td>
<td>13.7 ± 0.7</td>
</tr>
<tr>
<td>P·MIP(_{t=8\ weeks}) (kPa)</td>
<td>14.9 ± 0.9</td>
<td>13.9 ± 0.7</td>
</tr>
</tbody>
</table>

5.2.2 Study design

During an eight-week period, peak maximal inspiratory pressure (P·MIP) and peak inspiratory flow through the used resistance to airflow (PIF\(_R\)) were monitored. For all subjects, baseline measurements of P·MIP and PIF\(_R\) were performed at time point \(t_0\). Eight healthy subjects in the intervention group followed a simulated inhalation therapy. No drugs
were administered during the simulated inhalation therapy. Each week, P·MIP was measured for the intervention group. PIFR was measured four (t4) and eight (t8) weeks after the start of the simulated inhalation therapy. Five (t5) and ten (t10) weeks after finishing the simulated inhalation therapy, P·MIP was measured again. The eight healthy subjects in the control group did not follow any simulated inhalation therapy. In the control group, P·MIP and PIFR were measured at time point t4 and t8.

5.2.3 Methods

5.2.3.1 Simulated inhalation therapy

In accordance with the commonly used inhalation-instruction for DPI’s, the simulated inhalation therapy consisted of five forceful and deep inhalations, taken twice daily. The first series was performed in the morning and the second series was performed in the afternoon. Each inhalation was carried out with maximal performance with at least 10-15 seconds rest between each inhalation. The training-device consisted of an oval flanged hard plastic mouthpiece (Jaeger, type 892103, Germany), covered by a rubber stopper with a metal pipe of 3.5-mm internal diameter (figure 5.1). The resistance to airflow of the training-device was 140 Pa0.5·s·l -1 , which is relatively high. This resistance to airflow is in between the resistance to airflow of DPI’s and the training loads in commonly used IMT methods.

5.2.3.2 Respiratory muscle strength

Peak maximal inspiratory pressure (P·MIP) is a parameter for inspiratory muscle strength. P·MIP was measured with a differential pressure gauge (HBM, Germany, type PD1 (range 100 kPa)). The three highest achievable pressures were used for further analysis. All subjects 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. At least eight maximal inspiratory manoeuvres were carried out with at least 20-30 seconds rest between each effort. Each effort was displayed on a monitor, and the subjects were coached to better their efforts. All measurements were carried out in such a way that no extra leakage occurred. The three highest pressures recorded were within a range of 5% of each other, and later attempts did not yield higher results.

5.2.3.3 Flow measurements

Inhalation characteristics were measured during inhalation through an orifice disk, with a cylindrical bore of 4 mm in diameter. The resistance to airflow of the orifice disk was 74.9
Pa$^{0.5}$·s·l$^{-1}$, which is comparable with a high resistance to airflow DPI. The external inspiratory resistance to airflow consisted of an Y-valve (Jaeger, Germany) with, on the inlet site, a housing for the exchangeable orifice disk. Pressure drop over the resistance to airflow was measured with a differential pressure gauge connected to the Y-valve. The three highest achievable curves were processed into flow curves and used for further analysis. All subjects wore a noseclip and carried out their maximal inspiratory manoeuvres from residual volume (RV) to total lung capacity (TLC). Each effort was displayed on a monitor, and the subjects were coached to improve their efforts. All measurements were carried out in such a way that no extra leakage occurred. The three highest flows recorded were within a range of 5% of each other, and later attempts did not yield higher results.

5.2.4 Analysis

Changes in P·MIP or PIF$_R$ are expressed as percent of baseline results (time point $t_0$). Mean changes in P·MIP and PIF$_R$ were calculated for the intervention group and the control group. Significance in differences in P·MIP and PIF$_R$ between intervention group and control group was calculated using the Student t-test ($p<0.05$), for time points $t_4$ and $t_8$.

Linear relationship between PIF$_R$ and the square root of P·MIP was calculated based on the general relationship between flow through an orifice disk and the pressure drop across an orifice disk (chapter 3).

5.3 Results

5.3.1 Change in respiratory muscle strength

Daily use of the dummy DPI (training-device), in a simulated inhalation therapy, results in an increase in P·MIP for the intervention group (figure 5.2). Compared to the baseline results, P·MIP was increased by 16% and 24%, respectively, at four and eight weeks after starting the simulated inhalation therapy. The increase in P·MIP was significant ($p<0.05$) compared to the control group. The highest P·MIP-value of 22.1 kPa was measured in a male subject at $t_7$, which was an increase of 63.4%. The individual increase in P·MIP could be categorised in three groups. After eighth weeks of simulated inhalation therapy, two male subjects had an increase of approximately 54%. The majority of the subjects, 2 male and 3 female, had an increase of approximately 18% and one female subject did hardly benefit from the simulated inhalation therapy. Five and ten weeks after finishing the simulated inhalation therapy, P·MIP had slightly decreased but remained still 23% and 22% above the baseline, respectively (figure 5.2). In the control group, P·MIP remained unchanged.
Figure 5.2: Percentage change of $P\cdot MIP$ in time. ($\bullet$ = intervention group, $\circ$ = intervention group after the simulated therapy period, $\Delta$ = control group, presented are the means ± SEM. $\ast$ = significant increase ($p<0.05$) compared to control group).

5.3.2 Change in inspiratory flow rate through an external resistance to airflow

Peak inspiratory flow rate through the external resistance to airflow ($PIF_R$) was measured four and eight weeks after starting the simulated inhalation therapy. In the intervention group, an increase in $PIF_R$ was found of 4.2% and 7.9%, respectively, compared to the baseline results (figure 5.3). After eight weeks this increase in $PIF_R$ was significant ($p<0.05$) compared to the control group. In the control group, $PIF_R$ remained unchanged.

5.3.3 Relationship between $PIF_R$ and $P\cdot MIP$

For the intervention group, a linear relationship between $PIF_R$ and the square root of $P\cdot MIP$ was calculated (figure 5.4). In figure 5.4, each subject is represented by a symbol. Open symbols are female subjects and solid symbols are male subjects.
Figure 5.3: Percentage change of PIFR, after four and eight weeks of simulated inhalation therapy. Presented are the means ± SEM for the control group (open bars) and the intervention group (solid bars). * = significant increase (p<0.05) compared to control group.

Figure 5.4: Relationship between peak inspiratory flow rate and square root of P·MIP. Each symbol represents one subject. Open symbols are female, solid symbols are male.
5.4 Discussion

This study shows that daily use of a high resistance DPI in a simulated inhalation therapy results in a significant increase in P·MIP, and therefore, an increase in PIF$_R$. Previous studies\(^{11-15}\) reported the occurrence of a learning effect during the measurement of P·MIP. The learning effect is mainly an improvement in inspiratory co-ordination. This effect was also found in this study, each time a series of P·MIP measurements was performed. However, after 6 to 8 manoeuvres a maximal value of P·MIP was achieved in all series measured, which was in line with the previous studies\(^{11-15}\). A series of at least eight P·MIP manoeuvres were performed, in both groups of participants, to avoid the learning effect. In the control group, P·MIP remained unchanged. Therefore, the increase in P·MIP in the intervention group is not the result of a learning effect.

Training load and time in the simulated inhalation therapy was relatively low (five forceful and deep inhalations, taken twice daily) compared to commonly used IMT programs for COPD patients (continuous training for 30 minutes a day\(^{5,6}\)). However, a training effect was expected, based on the effects of low intensity training with other striated skeletal muscles as the arm or leg muscles\(^{16}\).

The increase in P·MIP with 24% resulted in an increase in PIF$_R$ of 7.9%. The found increase in PIF$_R$ is in the same order of magnitude as can be expected based on the linear relationship between PIF$_R$ and the square root of P·MIP. The calculated relationship between PIF$_R$ and the square root of P·MIP (figure 5.4) are comparable to those found in an earlier study in a large group of healthy subjects, asthmatics and COPD patients (chapter 3). This relationship shows the dependence of the generated PIF$_R$ through a resistance to airflow on the P·MIP. In addition, the individual effect of the increased P·MIP on the inhalation performance is shown.

The present study was performed in healthy subjects. Results might be similar in asthmatics without any DPI experience. Whether the same results would be obtained in moderate to severe COPD patients is questionable, because physiological changes in lung structure are involved.

In conclusion, the daily use of a high resistance to airflow DPI has a similar effect as low intensity IMT. It results in a significant increase in P·MIP and therefore, in an increase in PIF$_R$.

The used resistance to airflow in the dummy DPI (training-device) was relatively high compared to marketed DPI's. Therefore, comparable research with different training resistances to airflow is needed, before a direct translation to commonly used DPI's can be made.

The results of this study might have consequences for clinical trial studies with DPI's. The results show that the training effect in healthy subjects and powder inhaler naive asthmatics is likely to result in an increase in PIF$_R$. During a clinical trial, a better inhalation performance increases the deposition of inhaled drugs in the airways. This might result in an increase of the
clinical effect of the administrated drugs. Therefore, it is recommended to monitor the peak inspiratory flow rates through the inhaler device frequently during these studies in order to check whether the inspiratory manoeuvre of the patient is constant.

5.5 Acknowledgements

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5.6 References
