PEEP-masks in patients with severe obstructive disease: a negative report

H.R. Christensen, K. Simonsen, P. Lange, P. Clementsen, J.P. Kampmann, K. Viskum, J. Heideby, U. Koch

ABSTRACT: Positive pressure during expiration by face masks applied by the patient has gained wide acceptance in the treatment of chronic bronchitis, but the efficacy is still unproven. The effect of 6 months of treatment with PEEP-masks (positive end-expiratory pressure) was therefore studied in 47 patients with severe irreversible obstructive pulmonary disease (forced expiratory volume in one second (FEV₁) about 10%, and massive hypersecretion. Patients were double-blindly randomized at least 65 ml daily treatment with PEEP-masks with either 10 or 0 cm water pressure. After 6 months of treatment, no statistical difference was found between the two groups in change of median values (month 6 - month 0) of FEV₁, forced vital capacity (FVC), arterial oxygen tension (PaO₂), amount of sputum or dyspnoea. Median values of arterial carbon dioxide tension (PaCO₂) decreased significantly (0.03 kPa) in the placebo group. Cough intensity and dyspnoea during walking on staircases improved significantly in the placebo group. No difference among groups was found in number of days bedridden, hospitalized, number of exacerbations or antibiotic consumption. We conclude, that the use of PEEP-masks in these patients is without clinical documentation and cannot be recommended.


Severe chronic obstructive pulmonary disease (COPD) is an disabling condition with few effective treatments available. In the group of patients with hypoxemia, oxygen therapy by prolonged life expectancy [1] and physical training improves exercise tolerance [2, 3], while no convincing clinical benefits have been proven by using ventilatory muscle training [2, 4], chest physiotherapy [5] or breathing reconditioning [5-8]. Treatment with mucolytics, steroids, beta₂-agonists, methylxanthines and inhaled bronchodilators is commonly used, in spite of irreversibility in pulmonary function tests, and results from various clinical trials have been conflicting [2, 9-11].

Positive expiratory pressure improves the distribution of ventilation by re-expanding collapsed lung tissue, primarily by collateral reinflation [12] and thereby increases functional residual capacity in states of acute lung injury [13]. This principle has been extensively used in the treatment of adult respiratory distress syndrome (ARDS), neonatal respiratory distress syndrome (NRDS), in the prevention and treatment of post-operative atelectasis and in cystic fibrosis. While the efficacy of positive expiratory pressure has been convincingly demonstrated in the treatment of ARDS and NRDS [14-16], its value in the treatment of atelectasis and cystic fibrosis seems less clear [13, 17-22].

Positive airway pressure in COPD has been investigated thoroughly in two large studies [1, 23]. In the IPPB-trial (intermittent positive pressure breathing) [23], treatment with nebulized beta₂-agonists alone was compared with the effect of nebulized beta₂-agonists combined with intermittent positive pressure breathing in 1,000 patients with variable degrees of reversible airway obstruction. During a three year follow-up, no significant differences were observed between the two groups with respect to morbidity, mortality, lung function and quality of life.

In the study of KLEIN et al. [1], IPPB was compared with oxygen therapy in 44 hypoxaemic patients with severe irreversible COPD. After four years of treatment the survival rate in the oxygen group was twice that observed in the IPPB group (p=0.06). Positive airway pressure during expiration with flow independent resistance (PEEP: positive end-expiratory pressure), has gained wide acceptance in the treatment of patients with COPD and chronic copious and viscid sputum. No controlled trials have, however, been performed in these patients. We therefore undertook the
present randomized study to evaluate a possible effect of PEEP-masks (Fig. 1) compared with placebo masks in patients with severe irreversible COPD and chronic mucus hypersecretion during a period of 6 months.

Methods

Subjects

The study population was recruited from patients attending the outpatient chest-clinic of Bispebjerg Hospital, Copenhagen. All patients suffered from severe COPD with forced expiratory volume in the first second (FEV₁) less than 40% of predicted values and FEV₁/FVC (forced vital capacity) less than 0.7. The increase in FEV₁ and FVC after inhalation of 200 µg albuterol and 40 µg ipratropium bromide and after one week of oral treatment with 30 mg prednisolone daily was less than 20% of pretreatment values.

Patients receiving concomitant medication were considered valid, if consumption remained unchanged throughout the study. All patients complied with the definition of chronic bronchitis given by the British Medical Research Council [24].

Subjects with pulmonary malignancy, pulmonary fibrosis, heart failure, arterial hypertension, chest malformations, arterial insufficiency in the lower extremities and other disabling diseases affecting the musculoskeletal system were excluded. No patient received beta-blocking agents.

Design of the study

The patients were randomized double-blindly to 6 months of treatment with face masks with an expiratory resistance of either 10 cm or 0 cm water pressure (placebo-masks). Even though the valves were adjusted to these resistances, the addition of the valve system resulted in an increase of 1.5 cm water pressure in placebo-masks [25]. The resistances were controlled by a manometer before and after the trial and no changes were observed. A resistance of 10 cm water pressure was chosen because of an anticipated optimal ratio between the increase in arterial oxygenation and decrease in cardiac output [26]. Another reason was the inability of most patients to cope with a resistance greater than 10 cm on water for more than a few minutes. All masks appeared identical, with no possibility of change in the resistance during the study.

In the beginning of the trial, all patients were instructed by trained chest-physiotherapists in the usage of the masks and were told to apply it for at least 15 min 3 times a day. At two later visits these instructions were repeated and the patient's technique was evaluated as acceptable and consistent throughout the study. Compliance was checked by thorough questioning at each visit.

Before randomization and at monthly visits the following parameters were evaluated: 1) FEV₁ and FVC before and after bronchodilator inhalation with 200 µg albuterol and 40 µg ipratropium bromide; 2) questionnaires assessing smoking habits, degree of breathlessness, cough and sputum production, number of acute exacerbations and antibiotic and other medical treatment; 3) number of days bedridden and hospitalized. In addition, visual analogue scales (VAS) assessing dyspnoea, cough, amount and viscosity of sputum and exercise capacity were completed by the patients at each visit. Blood gas tensions of oxygen and carbon dioxide were measured before and after 3 and 6 months of treatment. At the final visit, the patients were asked to assess the global effect of the treatment.

All the patients were evaluated by the same physician and chest-physiotherapist throughout the study. The study was performed according to the Helsinki II declaration and approved by the Ethical Committee of Copenhagen.

Data analyses

The data were evaluated by the Mann-Whitney test, Fisher's exact test and the Chi-squared test since normal distribution of all values could not be demonstrated. A p level of 0.05 was considered as significant.

Results

Sixty patients were randomized to the study, 30 in each group. Forty seven of the patients completed the study, 25 patients in the PEEP-mask group, 22 in the placebo-mask group. Thirteen patients withdrew from the study due to causes not related to the trial. Patient characteristics at the time of inclusion are presented in table 1. There was no statistically significant difference between the two groups in terms of the variables shown, indicating that the randomization was successful. Forty five (96%) patients had smoked tobacco regularly, on
average for 40 yrs. Thirty one (66%) were still smoking at the time of inclusion. The number of smokers and non-smokers was equal in the two groups.

All the patients had severe airway obstruction with a median value of FEV₁ of about 1 l (range 0.50-1.45) but none had severe arterial hypoxaemia (median Pao₂ 9.10 kPa, range 7.39-11.69 kPa, (table 1).

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Table 1. - Base-line characteristics of 47 patients studied (values given as medians, ranges in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>PEEP-masks (10 cm water)</th>
<th>Placebo-masks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Male/Female</td>
<td>14/11</td>
<td>7/15</td>
</tr>
<tr>
<td>Age yrs</td>
<td>62 (43-71)</td>
<td>65 (54-75)</td>
</tr>
<tr>
<td>FEV₁ l</td>
<td>1.03 (0.50-1.45)</td>
<td>0.90 (0.55-1.35)</td>
</tr>
<tr>
<td>FVC l</td>
<td>1.95 (1.35-3.85)</td>
<td>1.80 (0.80-3.90)</td>
</tr>
<tr>
<td>Pao₂ kPa</td>
<td>9.10 (7.65-11.00)</td>
<td>9.10 (7.39-11.69)</td>
</tr>
<tr>
<td>Paco₂ kPa</td>
<td>5.66 (4.34-8.62)</td>
<td>5.65 (4.14-7.02)</td>
</tr>
</tbody>
</table>

No significant difference between the two groups by Mann-Whitney and (male/female) Fisher's exact test. FEV₁: forced expiratory volume in one second, FVC: forced vital capacity; Pao₂; arterial oxygen tension; Paco₂; arterial carbon dioxide tension; PEEP; positive end-expiratory pressure.

During the study, one of the current smokers in the PEEP-mask group and two in the placebo-mask group stopped smoking.

The results of the pulmonary function tests and blood gas analyses are shown in table 2. When comparing the changes in the investigated parameters between the last and initial visit, no statistically significant differences with respect to FEV₁, FVC and Pao₂ were found between groups. No changes were observed within each of the two groups after 6 months of treatment compared with initial values. The change of Paco₂ in the active group was significantly different from that in the placebo group, as Paco₂ increased by 0.05 kPa in the active group compared with a decline of 0.03 kPa in the placebo group.

The results of VAS are shown in table 3. Only with respect to dyspnoea while walking on a staircase, and to the degree of cough, was a statistically significant difference found between the two groups. The greatest improvement was seen in the placebo-group. Amount and viscosity of sputum were unchanged. On the VAS scales (function scale) the patients could indicate the maximal level of physical activity limited by dyspnoea. This scale also showed no difference between groups. No significant difference (Chi-squared) was found from the questionnaire assessing cough, dyspnoea and mucus hypersecretion graded as being unchanged, worse or better. Consumption of medicine was unchanged during the 6 months trial period. In number of days bedridden, hospitalized, number of exacerbations and antibiotic consumption.

Table 2. - Changes (month 6 - month 0) in FEV₁, FVC and arterial gas tensions between PEEP and placebo groups (values given as medians, ranges in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>PEEP-masks</th>
<th>Placebo-masks</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ l</td>
<td>0.00 (-0.50-0.35)</td>
<td>0.00 (-0.35-0.35)</td>
<td>NS</td>
</tr>
<tr>
<td>FVC l</td>
<td>0.05 (-0.80-0.60)</td>
<td>0.00 (-0.48-0.55)</td>
<td>NS</td>
</tr>
<tr>
<td>Pao₂ kPa</td>
<td>0.12 (-2.55-1.64)</td>
<td>-0.05 (-1.59-2.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Paco₂ kPa</td>
<td>0.05 (-0.40-3.30)</td>
<td>-0.03 (-2.02-0.62)</td>
<td>*</td>
</tr>
</tbody>
</table>

*: 0.01<p<0.02 (Mann-Whitney). For abbreviations see legend to table 1.

Table 3. - Changes (month 6 - month 0) in visual analogue scales (mm) (values given as medians, ranges in parentheses). Negative values in this table indicates an improvement

<table>
<thead>
<tr>
<th></th>
<th>PEEP-masks</th>
<th>Placebo-masks</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea walking on staircase</td>
<td>-1 (-69-53)</td>
<td>-6 (-63-50)</td>
<td>*</td>
</tr>
<tr>
<td>Dyspnoea walking on ground level</td>
<td>3 (-56-53)</td>
<td>-3 (-63-60)</td>
<td>NS</td>
</tr>
<tr>
<td>Cough</td>
<td>-11 (-69-75)</td>
<td>-21 (-46-35)</td>
<td>**</td>
</tr>
<tr>
<td>Amount of sputum</td>
<td>-8 (-51-49)</td>
<td>1 (-47-57)</td>
<td>NS</td>
</tr>
<tr>
<td>Viscosity of sputum</td>
<td>-1 (-80-70)</td>
<td>-7 (-67-79)</td>
<td>NS</td>
</tr>
<tr>
<td>20 cm function scale</td>
<td>4 (-88-115)</td>
<td>-1 (-88-83)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*: 0.01<p<0.02; **: p<0.01 (Mann-Whitney test). PEEP: positive end-expiratory pressure.
consumption no differences between the two groups were observed.

The final assessment of the global effect of whether the treatment influenced the condition to the better, to the worse or was without change at all is shown in table 4. No significant difference was found between the groups.

Table 4. - Global self-assessment of 6 months treatment with PEEP or placebo-masks

<table>
<thead>
<tr>
<th></th>
<th>Better</th>
<th>Worse</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>n=21*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>14</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>n=22*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi-square = 3.39, nonsignificant; *: Data are missing from 1 and -3 patients, respectively; PEEP: positive end-expiratory pressure.

Only two complained about the usage of the mask. Although both had difficulties in breathing through the system, they completed the study. One had a placebo-mask and one an active. Besides this, no adverse events were recorded.

Although we had data from the monthly visits, we decided to make the statistical analysis between the first and last visit in order to avoid repeated statistical testing. To illustrate changes during time for the measured variables, a series of plots like the one seen in figure 2 were made. The changes in FEV₁ are representative for all our variables. From these plots no indication of major differences were found between the groups at any time during the trial.

FEV₁ (median and range)

![Fig. 2. - Forced expiratory volume in one second (FEV₁) in both PEEP and placebo-mask groups during the 6 months treatment. Values given as medians and ranges. PEEP: positive end-expiratory pressure.](image)

No correlation was found between the initial FEV₁ or FVC and the change in FEV₁ or FVC during the study (Spearmanns correlation R about 0.2).

Discussion

In patients with chronic airflow obstruction and loss of elastic recoil, the equal pressure point is moved towards the alveoli increasing the areas of airways exposed to dynamic recoil during expiration. This is partially counteracted by breathing at large lung volumes, increasing airway conductance and preventing airway collapse. The usual habit of "pursed lips" by these patients might move the equal pressure point more orally and thereby prevent premature closing of smaller airways.

During the last ten years positive expiratory pressure imitating "pursed lips", has been increasingly used in many forms of respiratory diseases such as ARDS, NRDS, cystic fibrosis and COPD. The clinical benefit in COPD has, however, never been documented in properly conducted clinical trials. The present study of 6 months of treatment with PEEP-masks in patients with moderate to severe COPD with mucus hypersecretion compared with placebo-masks, did not show any effects on FEV₁, FVC or PaO₂. PaCO₂ decreased significantly but was clinically unimportant in the placebo-group (0.03 kPa). It is not the investigators impression that the reason for the negative results was bad compliance, as the patients were asked at each visit about the usage of the mask and the technique was controlled several times.

VAS scales have been extensively used in the subjective clinical evaluation of pain [27, 28], sedation, dyspnoea [29] and as a part in the assessment of quality of life. A positive correlation has been found between questionnaires and VAS concerning dyspnoea [29]. The statistical evaluation, however, is difficult due to the lack of a general accepted unit of measurement and a pronounced inter- and intra-individual variation in perception of different sensorial modalities. The obvious problem of interpreting VAS, the lack of "a golden standard", makes it difficult to correlate these complaints of the patient to objective physiological measurements.

With this in mind, we found a minor improvement in both groups compared with pretreatment values for almost all measured variables on the VAS scales, the greatest improvement being in the placebo-group, but between groups it only reached significance for dyspnoea while walking on a staircase and the degree of cough. Clinically important parameters such as frequency of acute exacerbations, days of being bedridden, hospitalization episodes and days of antibiotic treatment did not differ between the groups during the study.

The statistical analysis is based on the data from the first and the last clinical visit, since we felt that treatment of this disease should show an efficacy on a long-term basis and this procedure also prevented repeated statistical testing. From the plots illustrating changes during time, we found no indication that major differences existed at any time-point during the trial. Therefore, the risk that a statistical analysis of data from other visits would have given a different result is minimal.

Our results are in agreement with other trials evaluating various forms of positive pressure breathing in patients with COPD [1, 23]. Our study, however, is the first using the simple device of a PEEP-mask for patients.
with irreversible COPD and mucus hypersecretion, for
which other therapeutic possibilities are limited.

In contrast to the generally used PEP-mask (positive
expiratory pressure), our masks secured by the way of a
continuous flow-dependent airway resistance [30], thereby ensuring a
reproducible and constant effect on the respiratory tract.

A positive pressure of 10 cm water was chosen in the
present study, as increasing pressure up to this value
improves arterial oxygenation at a given inspired oxygen
amend, while pressures above 10 cm water decrease
cardiac output and thereby decrease the net tissue oxygen
delivery [26]. An additive effect of positive
expiratory pressure might be an opening of the collateral
arteries, recruiting nonventilated collapsed
areas [12]. Furthermore, 10 cm water pressure seemed
to be close to the maximal resistance tolerated by our
patients and a further increase might have decreased
compliance considerably.

By using Gaussian distribution statistics, based on the
results of FEV, and FVC, the magnitude of a type 2 error
was calculated to 5% for a risk of overlooking a difference
of 100 ml or more, 1% of overlooking a difference
of 200 ml or more, values hardly clinically relevant.

Our conclusion is, therefore, that the widely indiscrimi­
nate use of PEEP-masks is without any clinical
documentation and therefore cannot be recommended
in patients with irreversible COPD and mucus
hypersecretion.

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RÉSUMÉ: La pression positive appliquée au cours de l’expiration par des masques faciaux a été largement utilisée dans le traitement de la bronchite chronique, mais son efficacité n’est toujours pas démontrée. Les effets de traitements de six mois au moyen de masques à PEEP (positive end expiratory pressure) ont été étudiés chez 47 patients atteints d’une maladie pulmonaire obstructive irréversible sévère (VEMS d’environ 1 litre) et d’hypersécration de mucus. Les patients ont été randomisés en double aveugle vers un traitement quotidien d’au moins 45 minutes au moyen de masques PEEP avec soit 10, soit 0 cm de pression d’eau. Après six mois de traitement, l’on n’a trouvé aucune différence statistiquement significative entre les deux groupes en ce qui concerne les valeurs médianes du VEMS (mois 6 - mois 0), de la capacité vitale forcée, de la Pao2, de la quantité d’expectoration, ou de la dyspnée. Les valeurs médianes de Pao2 ont diminué de façon significative (0.03 kPa) dans le groupe placebo. L’intensité de la dyspnée au cours d’une marche sur escaliers, a été analysée significativement dans le groupe placebo. L’on n’a trouvé aucune différence entre les groupes en ce qui concerne le nombre de jours d’alimentation ou d’hospitalisation, ou le nombre d’exacerbations, ou encore la quantité d’antibiotiques consommée.

Nous concluons que l'utilisation de masques PEEP chez ces patients n'est pas assez documentée cliniquement et ne peut pas être recommandée.