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

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ABSTRACT: Positive pressure during expiration by face masks applied to the patient has gained wide acceptance in the treatment of chronic obstructive pulmonary disease, 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 1 L), and mucous 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 dyspnoe. Median values of arterial carbon dioxide tension (Paco2) decreased significantly (0.03 kPa) in the placebo group. Cough intensity and dyspnoe 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 a disabling condition with few effective treatments available. In the group of patients with hypoxia, oxygen therapy has prolonged life expectancy [1] and physical training improves exercise tolerance [2, 3], while no convincing clinical benefit 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 ipratropium bromide 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, presumably by collateral re-inflation [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 airway 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 obstructive 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.

Fig. 1. - A PEEP-mask (positive end-expiratory pressure).

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 treat-
ment with 30 mg prednisolone daily was less than 20%
of pretreatment values.

Patients receiving concomitant medication were con-
idered 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 extremi-
ties and other disabling diseases affecting the musculo-
skeletal 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 the
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 of
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.

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) question-
naires assessing smoking habits, degree of breathless-
ness, cough and sputum production, number of acute
exacerbations and antibiotic and other medical treatment;
3) number of days bedridden and hospitalized. In addi-
tion, visual analogue scales (VAS) assessing dyspnea,
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
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 volume of FEV₁ of about 1 l (range 0.50-1.45) but none had severe arterial hypoxaemia (median Paco₂ 9.10 kPa, range 7.39–11.69 kPa, (table 1)).

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

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.

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 (-2.55–1.54)</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>Active</td>
<td>14</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(n=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=22)</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)**

![Graph of FEV₁](image)

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

No correlation was found between the initial FEV₁ or FVC and the change in FEV₁ or FVC during the study (Spearmans 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 compression during expiration. This is partially counteracted by increasing 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 end-expiratory pressure), our masks secured by the way of a constant flow, a continuous flow-dependent airway resistance [30], thereby ensuring a reproducible and constant effect on the respiratory tract. A constant 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 tension, while pressures above 10 cm might decrease cardiac output and thereby decrease the net tissue oxygen delivery [26]. An additive effect of positive end-expiratory pressure might be an opening of the collateral channels, recruiting nonventilated collapsed alveoli [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 indiscriminate use of PEEP-masks is without any clinical documentation and therefore cannot be recommended in patients with irreversible COPD and mucus hypersecretion.

References


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'hypersécrétion 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 \( \text{Paco}_2 \), de la quantité d'expectoration, ou de la dyspnée. Les valeurs médianes de \( \text{Paco}_2 \) ont diminué de façon significative (0.03 kPa) dans le groupe placebo. L'intensité de la toux ou la dyspnée au cours d'une marche sur escaliers, ont été analysées significativement dans le groupe placebo. L'on n'a trouvé aucune différence entre les groupes en ce qui concerne le nombre de jours d'alitement ou d'hospitalisation, ou le nombre d'exacerbations, ou encore la quantité d'antibiotiques consommés.

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