Comparison of terbutaline, isotonic saline, ambient air and non-treatment in patients with reversible chronic airway obstruction

O. May, N.C.G. Hansen

ABSTRACT: The increase in forced expiratory volume in one second (FEV₁) seen in asthmatics after inhalation of isotonic saline was studied in a blind, cross-over investigation of 24 consecutive out-patients presenting with reversible chronic airway obstruction. Forced expiratory manoeuvres allowing the measurement of FEV₁ and forced vital capacity (FVC) were performed at six time intervals during a period of one hour according to the following regimes: inhalation of terbutaline by means of a Pari-inhalier Boy for 10 min; inhalation of isotonic saline under the same conditions; inhalation of ambient air under the same conditions (placebo with noisy nebulizer); inhalation of air without the nebulizer (non-treatment) in order to determine whether the impact of treatment by a nebulizer influences the measured lung function. A statistically significant increase in FEV₁ was observed after each of the four regimes. The increase was large following terbutaline inhalation. After the other three regimes, it was significantly smaller and of about the same magnitude in each case. The increase in FEV₁ after the non-treatment regime was unexpected and could possibly be due to the repeated dynamic spirometry. The increase in FEV₁ after isotonic saline and ambient air (noisy nebulizer) did not differ from the increase after the non-treatment regime. We conclude that neither isotonic saline nor the impact of treatment with a noisy nebulizer have a measurable effect on lung function.

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Isotonic saline is frequently employed as a placebo in studies of bronchodilating aerosols [1]. The inhalation of isotonic saline aerosol has given statistically significant increases in forced expiratory volume in one second (FEV₁) in asthmatics [2], the cause of this is unknown. A possible explanation might be that the inhaled saline normalizes the osmotic pressure in the bronchial mucosa, which may be abnormal in asthmatics [3]. Another suggested explanation is the psychological impact of receiving treatment from a noisy machine [2].

The object of this study was to investigate the effect of inhalation of isotonic saline in patients with chronic bronchitis and chronic reversible airway obstruction and to compare it with inhalation of ambient air via a noisy nebulizer and with non-treatment. In order to demonstrate the reversibility of the bronchial obstruction, a regime of terbutaline aerosol was included.

Patients and methods

The investigation included 24 consecutive outpatients presenting at a lung clinic during the period 1st April, 1984 to 1st May, 1985. The FEV₁ of all the patients was <70% of the predicted normal value [4], their FEV₁ increase was at least 20% following the inhalation of terbutaline 5 mg, and they all complied with the criteria for simple chronic bronchitis [5]. The patients were all in a stable phase of the disease. Patients treated with steroids or who had been under treatment with a nebulizer at home were not included. The investigation was approved by the local ethical committee and all patients gave informed consent.

The patients were randomized according to the Latin-square-method for treatment on four consecutive days with four different regimes:

1) Terbutaline. The patient inhaled nebulized terbutaline 2.5 mg·ml⁻¹, 2 ml via a Pari-inhaler Boy. The treatment was given double-blind and the patient considered the treatment to be a nebulized bronchodilator.

2) Isotonic saline. The patient inhaled nebulized isotonic saline, 2 ml via a Pari-inhaler Boy. The treatment was given double-blind and the patient considered the treatment to be a nebulized bronchodilator.

3) Ambient air (placebo). The patient inhaled ambient air for 10 min via a Pari-inhaler Boy. The nebulizer produced its normal noise during each
inspiration as under regimes 1 and 2. The nebulizer was connected to a manometer on a gas-bottle, which contained atmospheric air. The flowmeter was adjusted to give 5 l·min⁻¹. There was no actual connection between the gas bottle and the inspiratory line. This regime could not be carried out double-blind, but it was our impression that the patients thought that they were receiving treatment with a gaseous bronchodilator.

4. Non-treatment. The patient respired through a mouthpiece taken from a Pari-inhalier Boy for 10 min. All the patients were informed that on this day they would not be subjected to treatment, but that the regime was carried out in order to obtain a basis for comparison of the three types of treatment. Thus, the difference between regimes 3 and 4 was that in the latter the patients were aware that they were not receiving treatment and the noisy nebulizer had been turned off. The regime was open, but the nurse in charge of the spirometry did not know whether or not the patient was receiving treatment.

In all four regimes the patients were asked to inspire somewhat more deeply than normal and, if possible, to hold their breath for a moment before expiration. All the regimes were of approximately 10 min duration. All the patients had agreed not to use theophylline or sustained release terbutaline tablets for a period of 48 h prior to the investigation, or to use a beta-stimulator in the usual tablet formulation for 12 h, or sprays for 4 h beforehand. Before the investigation, the patients were informed in writing that on two days they would be treated by means of a nebulized bronchodilator and on one day by means of a gaseous bronchodilator.

In order to minimize the dispersion of the results, the various regimes were carried out at the same time of day. The same physician and nurse were employed for all tests on individual patients.

The spirometry was carried out by a nurse in a separate room. In order to ensure that the investigation was blind with respect to the nurse, both the patient and the nurse were instructed not to discuss the regime employed that day. The spirometry was carried out using a Vitalograph spirometer with a P.F.T. Printer. Each measurement consisted of a number of forced expiratory manoeuvres from maximal inspiration, sufficient to produce three technically satisfactory curves; the two largest had to be almost identical [6]. The largest values of forced vital capacity (FVC) and FEV₁ were employed for the calculations. Spirometry was performed prior to, as well as 0, 5, 15, 30, 45 and 60 min after, each regime. The basic data of the patients is shown in table 1. All the patients completed the investigation.

**Statistical methods**

The analysis showed no periodic or carry-over effect, and for this reason paired tests were employed whenever possible. The t-test for two related samples was used. The Bartlett test demonstrated variance inhomogeneity following comparison of the four regimes, and therefore the Friedman test for K-related samples was used. The difference was considered statistically significant with a value of p < 0.05. Spirometry was carried out six times after each regime; therefore under the null-hypothesis of no real change in lung volumes, a binomial situation is present. At least two positive test results (p < 0.05) are required in this situation in order to repudiate the null-hypothesis, if a maximum risk of 5% for a type-I error is to be accepted.

**Results**

No significant difference was found between the initial values on the four study days.

After inhalation of terbutaline, all measurements of FEV₁ and FVC increased significantly as compared to the initial values (table 2). This increase was observed at each measurement, and was statistically of greater significance than the increase after the other three regimes in respect of both variables (p ≤ 0.002).

After inhalation of isotonic saline, ambient air and the non-treatment regime, FEV₁ increased significantly as compared to the initial values (fig. 1). There was no statistically significant difference between the three regimes.

FVC increased, although only just significantly, after isotonic saline, but not after ambient air and non-treatment (fig. 2). No statistically significant difference was found between the three regimes.

**Discussion**

As expected, FEV₁ and FVC increased significantly after the inhalation of terbutaline, and the increase was greater than that following isotonic saline, ambient air and the non-treatment regime. A significant increase in FEV₁ after inhalation of isotonic saline was also found in this study. However, this increase did not differ significantly from the increase after the ambient air regime. This indicated that a specific effect of isotonic saline is highly improbable.

FEV₁ increased significantly in relation to the initial value after the ambient air regime; this was not significantly different from the non-treatment regime.

**Table 1. - Anthropometric and lung function data for the 24 patients (3 females and 21 males) studied. The predicted volumes are obtained from [4]**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0</td>
<td>7.9</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>1.16</td>
<td>0.46</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>43.5</td>
<td>16.3</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.39</td>
<td>0.7</td>
</tr>
<tr>
<td>FVC %pred</td>
<td>65.3</td>
<td>14.9</td>
</tr>
</tbody>
</table>
COMPARISON OF TREATMENT IN AIRWAY OBSTRUCTION

Table 2. - P-values from paired t-test of the forced lung volumes after the four regimens, as compared to initial values.

<table>
<thead>
<tr>
<th></th>
<th>0 min</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbutaline</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isotonic saline</td>
<td>0.18</td>
<td>0.11</td>
<td>0.033</td>
<td>0.011</td>
<td>0.019</td>
<td>0.001</td>
</tr>
<tr>
<td>Ambient air</td>
<td>0.27</td>
<td>0.026</td>
<td>0.090</td>
<td>0.020</td>
<td>0.002</td>
<td>0.005</td>
</tr>
<tr>
<td>Non-treatment</td>
<td>0.13</td>
<td>0.012</td>
<td>0.001</td>
<td>0.029</td>
<td>0.026</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>FVC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbutaline</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isotonic saline</td>
<td>0.45</td>
<td>0.10</td>
<td>0.24</td>
<td>0.02</td>
<td>0.039</td>
<td>0.010</td>
</tr>
<tr>
<td>Ambient air</td>
<td>0.23</td>
<td>0.76</td>
<td>0.47</td>
<td>0.33</td>
<td>0.052</td>
<td>0.056</td>
</tr>
<tr>
<td>Non-treatment</td>
<td>0.44</td>
<td>0.42</td>
<td>0.28</td>
<td>0.51</td>
<td>0.48</td>
<td>0.045</td>
</tr>
</tbody>
</table>

This therefore suggested that the placebo effect, which we understood to result from treatment with a noisy machine, does not in itself affect the forced lung volumes.

The increase in FEV₁ after the non-treatment regime is not easily explained. Three forced expiratory manoeuvres (FEM) were performed at each lung function test. A dynamic compression occurs with FEM which might clear secretions from the central airways [7]. The flow resistance is reduced when the secretions in the central airways are cleared by means of physiotherapy [8]. All of our patients suffered from chronic bronchitis and coughing and expectoration were often observed during the lung function measurements. The increase in FEV₁ may therefore be seen as an expression of an increased flow due to reduction in the quantity of secretion in the central airways. If this explanation is correct, the increase in
FEV<sub>1</sub> after regimes 2, 3 and 4 must be induced by the measurements themselves.

It is conceivable that the increase seen in FEV<sub>1</sub> was due to airway dilatation following lung inflation (ADF LI). However, ADF LI appears immediately after a deep inspiration and is not increased by multiple deep inspirations [9], therefore the contribution of ADF LI to the measured FEV<sub>1</sub> was already present in the baseline data as each lung function consisted of three FEM and the best reading was chosen. Thus, ADF LI cannot explain the observed increase in FEV<sub>1</sub>.

Another possible explanation of the increase in FEV<sub>1</sub> is the effect of learning. The following facts do not support this hypothesis. Firstly, FEV<sub>1</sub> still increased significantly from zero to five min after the regime (non-treatment: p = 0.032; ambient air: p < 0.001; isotonic saline: p < 0.001). At this time interval the patient had already produced six technically satisfactory curves within the last 15 min. Secondly, the effect of learning would be expected to have its greatest influence on the first day in a series of four, but no statistical significance was found when the increase in FEV<sub>1</sub> was tested against the numerical order of the days in the sequence (p > 0.6).

Finally, an increase due to diurnal variation could be considered. It seems improbable that a significant increase in FEV<sub>1</sub> during 10 min in the middle of the day and again during the next 5 min could be explained by diurnal variation alone.

Scott and König [10] studied asthmatics with normal lung function and found no effect of inhalation of isotonic saline on repeated dynamic spirometry, but when FEV<sub>1</sub> was reduced due to histamine challenge there was a systematic increase in FEV<sub>1</sub>, measured during the second FEM as compared to the first. Their findings are thus in accordance with our results.

Conclusions

Inhalation of isotonic saline does not in itself have any broncholytic effect and must still be considered to be a well-suited inactive reference in studies of broncholytic aerosols.

The psychological effect obtained from believing that an airways dilatating treatment has been given via a Pari-inhaler Boy does not affect the forced lung volumes.

The increase in FEV<sub>1</sub> after non-treatment, ambient air and inhalation of isotonic saline could possibly be due to the repeated forced expiratory manoeuvres.

The increase in FEV<sub>1</sub> after the non-treatment regime was somewhat unexpected, and further studies are necessary in order to confirm that this effect is due to repeated dynamic spirometry.

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References


RÉSUMÉ: L'augmentation du VEMS, observée chez les asthmatiques après inhalation de solution saline isotonique, a été étudiée dans une investigation aveugle avec permutation croisée, chez 24 patients consécutifs se présentant en consultation avec une obstruction chronique réversible des voies aériennes. Les manœuvres expiratoires forçée, permettant la mesure du VEMS et de la capacité vitale forçée, ont été exécutées à six reprises pendant une période d'une heure après les traitements suivants pour déterminer si l'impact du traitement par le nébuliseur influe les valeurs fonctionnelles: inhalation de terbutaline au moyen d'un nébuliseur Pari Boy pendant 10 minutes; inhalation de solution saline isotonique dans les mêmes conditions; inhalation d'air ambiant dans les mêmes conditions (placebo avec nébuliseur bruyant); inhalation d'air sans nébuliseur (absence de traitement). Chacun des traitements a entraîné une augmentation statistiquement significative de VEMS. L'augmentation a été marquée après terbutaline. Après les trois autres types de traitement, elle s'avère significativement plus faible, et environ du même ordre de grandeur. L'augmentation du VEMS après le régime sans traitement est inattendue et pourrait trouver une explication dans l'exécution répétée de spirométries dynamiques. L'augmentation de VEMS après solution saline isotonique et inhalation d'air ambiant au travers d'un nébuliseur bruyant n'est pas statistiquement différente de l'augmentation après le régime sans traitement. On conclut donc que ni la solution saline isotonique, ni l'impact du traitement avec un nébuliseur bruyant, n'ont pour eux-mêmes un effet mesurable sur la fonction pulmonaire.