Airway resistance, the volume of thoracic gas, and specific airway resistance were determined before and after administration of an isoproterenol-phenylephrine mist in random fashion to 20 patients with obstructive ventilatory disorders from a hand-triggered apparatus either used by the patient or given by the physician, and from a nebulizer automatically activated by patient inspiration. Specific airway resistance changes were the most sensitive guide to broncholytic effects. Maximal change followed exposure to the breath-activated unit, suggesting that its use in similar drug trials may reduce an important source of error in estimates of the efficacy of bronchopulmonary aerosols.

Some limitations of aerosol studies using gas or hand-driven nebulizers were removed by giving test inhalants from mechanical hand devices delivering fixed amounts of drug with each valve depression (Kallós and Kallós-Deffner, 1959; Cohen, 1965). While there are advantages to the technique (Zohman and Williams, 1958; Feinmann and Newell, 1963; Cohen and Hale, 1965), the apparatus is frequently used incorrectly (Saunders, 1965). The introduction of a nebulizer triggered automatically on inspiration (McIlreath and Cohen, 1970) allowed the present examination of the influence of method of administration of pressurized aerosols upon the broncholytic responses in a trial of inhalants.

MATERIALS AND METHODS

Twenty patients were selected because they had a potentially reversible component to their obstructive ventilatory disorders (American Thoracic Society, 1962; Cohen and McIlreath, 1964), and had had previous instruction in and subsequent use of a particular mechanical hand device supplying a fixed dose mixture of isoproterenol with phenylephrine.3 No patient had received pharmacological or mechanical aid to respiration for at least one week before this study.

Airway resistance (Rn) and the related volume of thoracic gas (Vtg) were derived with a whole-body, volume-displacement plethysmograph (Cohen, 1969) and their product ([Ra × Vtg]) was used as the index of specific airway resistance (Lloyd and Wright, 1963).

The automatic inhalation device4 released its mist automatically when triggered by patient inspiratory effort. As the subject began his inhalation through the apparatus, a vane situated in a chamber behind the mouthpiece moved forward, releasing a spring-loaded driver which depressed the valve into the pressurized cartridge, discharging a metered dose of aerosol. The mechanism was reactivated by closing the cover of the device.

The subjects reported at the same time daily. On three successive mornings, after control determinations had been made, each patient received two inhalations of his usual isoproterenol-phenylephrine mist (Duo-Medihaler) either from the hand-triggered device used by himself or from the same apparatus triggered by the physician or from the automatic firing device (Duohaler), the particular order of administration for each subject following Latin-square assignment. The dose of each drug was identical for each valve actuation by both the hand-triggered and automatic inhalation nebulizers, and was 0·16 mg isoproterenol (equivalent to 0·137 mg of isoproterenol base) and 0·24 mg phenylephrine bitartrate (equivalent to 0·126 mg of phenylephrine base). All data were the means of three determinations of Ra and Vtg at each time point.

RESULTS

All 20 patients completed the study. The table lists the mean control and serial post-exposure values and their standard deviations for the three techniques for [Ra × Vtg] in absolute values, and
TABLE

SPECIFIC AIRWAYS RESISTANCE IN 20 PATIENTS

<table>
<thead>
<tr>
<th>Ra × Vtg</th>
<th>Hand Nebulizer Self-administered</th>
<th>Hand Nebulizer Physician-administered</th>
<th>Automatic Firing Nebulizer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 5 min 90 min</td>
<td>Control 5 min 90 min</td>
<td>Control 5 min 90 min</td>
</tr>
<tr>
<td>Mean</td>
<td>29.72 ± 6.80</td>
<td>28.31 ± 7.60</td>
<td>29.37 ± 6.22</td>
</tr>
<tr>
<td>S.D.</td>
<td>24.96 ± 6.61</td>
<td>19.83 ± 5.99</td>
<td>19.13 ± 5.43</td>
</tr>
<tr>
<td>% Change</td>
<td>-16.00 ± -5.24</td>
<td>-3.07 ± -2.99</td>
<td>-34.8 ± -4.98</td>
</tr>
<tr>
<td>Ra × Vtg</td>
<td>C-5 min 5-90 min C-90 min</td>
<td>C-5 min 5-90 min C-90 min</td>
<td>C-5 min 5-90 min C-90 min</td>
</tr>
<tr>
<td>t *</td>
<td>2.25 0.05</td>
<td>3.93 0.001</td>
<td>5.56 0.001</td>
</tr>
<tr>
<td>p *</td>
<td>1.00 0.001</td>
<td>2.76 0.001</td>
<td>3.30 0.001</td>
</tr>
</tbody>
</table>

Comparison of effect based on differences significant at 0.05 level or better.
NSD 3 3
NSD 2 2
NSD 1 1

Ra represents airway resistance, Vtg represents the volume of thoracic gas at which the airway resistance was determined, and Ra × Vtg represents specific airway resistance.
NSD equals no significant difference.
P values 0.05 or better calculated according to Croxton (1953).

as per cent changes from baseline. The response of the index was least after patient self-administration of the aerosol, of greatest magnitude with the automatic-firing nebulizer, and intermediate when the investigator gave the aerosol. Statistically significant change (all P-values 0.01 or better) in specific airway resistance was the most sensitive gauge of a bronchodilator effect for the control-5 minute, 5-90 minute, and control-90 minute periods on test days with the physician-given and automatic-firing aerosols, with the control-90 minute difference the only significant deviation for the patient-administered inhalant trials.

The relative efficacy of the three methods in altering the abnormal control index shows that the baseline figures did not differ for any of these on the various test days. The automatic-firing apparatus induced the greatest changes in specific airway resistance and volume of thoracic gas at both 5 and 90 minutes after exposure, while its effects on Ra were equivalent to those following physician administration of the mist; both the breath-actuated and physician-given methods were statistically superior to the patient-administered method at both post-treatment check points (all P-values 0.05 or better for significance in the comparisons).

DISCUSSION

Lower airway determinants obtained with the whole-body plethysmograph yield more meaningful estimates of bronchial reactivity than the indices of traditional spirometry (Cohen and Hale, 1965; Stein, Tanabe, Rege, and Khan, 1966; Payne, Chester, and Hsi, 1967), a sensitivity further enhanced when the resistance figures are related to associated volumes of thoracic gas (Oppenheimer, Rigato, and Fletcher, 1968; Pelzer and Thomson, 1969; Cohen, 1969). In again confirming the greater utility of the [Ra × Vtg] calculation (compared with simple recording of Ra) in estimating bronchial obstruction, our observations suggest that maximally effective inhalant doses may not be provided by conventional pressurized nebulizers whether given by well-instructed patients (Freedman, Meisner, and Hill, 1968) or by a physician (Ishikawa and Cherniack, 1969). Improvement in airways indices following self-dosage of the isoproterenol with phenylephrine aerosol was of lesser degree than the changes seen when the same mist was given by the physician from the identical apparatus, with the effects of both statistically inferior to those following the use of the breath-actuated device which did not require manual synchronization of mist release with patient inspiration. In this trial, neither of the former methods would have disclosed the maximal bronchodilatation possible, a result best approached by the automatic-firing device trials. Incorporation of this new hand nebulizer in clinical trials of inhalants may diminish one of the many sources of error in the evaluation of aerosols of bronchodilator drugs.

REFERENCES


