Determination of Static Pulmonary Volumes after Bronchodilator Therapy*

Marc H. Lavietes, M.D., and Debra W. Taylor, B.A., Pu.T.

Increased (more positive) end-expiratory and decreased (more negative) end-inspiratory values for intrapleural pressure (Ppl) invariably accompany acute bronchoconstriction. We hypothesize that both the increase in vital capacity (VC) and the decrease in residual volume (RV) observed after dilation of the central airways in patients with reversible obstruction of the airways result, in part, from a restoration of normal Ppl during unforced exhalation. To test this hypothesis, we examined the end-expiratory Ppl during breathing at rest in ten emphysematous and eight asthmatic subjects before and after inhalation of isoproterenol. The VC increased by 0.38 L after therapy, and the specific airway resistance and the RV decreased by 6.8 cm H2O·sec and 0.63 L, respectively. Total lung capacity was unchanged. The response of the VC to administration of isoproterenol is an important sequel to dilation of the large airways. Bronchioles close at a critical Ppl during exhalation. Because Ppl normalizes with administration of isoproterenol, this closure may be delayed to a lower pulmonary volume even if improvement in the function of peripheral airways does not occur.

Both an increase in the resting vital capacity (VC) and a decrease in residual volume (RV) are recognized as immediate consequences of bronchodilatation in patients with reversible obstruction of the airways; however, the mechanism of this response has not been elucidated. Increased (less negative) values for intrapleural pressure (Ppl) during exhalation, often becoming positive relative to the atmosphere, is frequently observed in patients with bronchoconstriction. We hypothesize that this increase in Ppl observed during slow forced exhalation at low pulmonary volumes is a requisite for elevation of RV. Normalization of Ppl occurring immediately after bronchodilatation may account for the rapid improvement often noted in RV and VC.

Functional studies after induction of asthma by either inhalation of antigen or exercise provide insight into the mechanisms which alter static pulmonary volumes during bronchoconstriction. To maintain adequate alveolar ventilation during induced bronchospasm, tested subjects must respond by increasing the respiratory muscular force generated during tidal breathing. Increased (more positive) end-expiratory and decreased (more negative) end-inspiratory values for Ppl result. Positive expiratory Ppl decreases the diameter of the airway at low pulmonary volumes and thus may explain the increased RV observed with acute obstruction of the airways.

Previous studies have demonstrated changes in pulmonary volume and resistance to airflow with bronchodilatation. This study documents the changes in pleural mechanics accompanying inhalation of isoproterenol. We have measured changes in both Ppl at the end of expiration and static pulmonary volumes after therapy. To examine the possibility that increased pulmonary recoil may account for the more negative Ppl or diminished static volumes observed after bronchodilation, we have also measured static pulmonary compliance (Cst) and maximum elastic recoil in our subjects.

MATERIALS AND METHODS

Patients

Eighteen subjects participated in this study. All gave informed consent. We studied ten emphysematous patients who shared the following typical clinical characteristics: dyspnea on exertion; thin body habitus; roentgenographic evidence of large, hyperlucent pulmonary fields; flat diaphragm; and a vertical, small cardiac shadow. All had a recoil pressure at total lung capacity (TLC) that was less negative than —15 cm H2O. Cough and production of sputum were minimal in all but two of these patients. We also studied eight asthmatic patients with periodic episodes of dyspnea and wheezing relieved by bronchodilator therapy. These patients became asymptomatic and had normal pulmonary function after long-term therapy. Patients with heart failure, polycythemia, or hypercapnia were excluded.

Procedures

Spirometric tests were performed on a 9-L spirometer (Collins). The VC was measured during a slow inspiratory maneuver from RV. Airway resistance (Raw) and functional residual capacity (FRC) were measured in a plethysmograph (Collins) by the method of DuBois et al. The Raw was expressed as specific airway resistance (SRaw), the product of FRC times Raw. The SRaw is both sensitive to

*From the Pulmonary Division, College Hospital, College of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark. Manuscript received August 28; revision accepted February 13. Reprint requests: Dr. Lavietes, College of Medicine and Dentistry of New Jersey, Newark 07103
changes in Raw and independent of pulmonary volume (Marc H. Lavietes, M.D., unpublished data).

Esophageal pressure (Pes) was recorded from a balloon positioned in the middle portion of the esophagus, as detailed by Milic-Emili et al. The balloon’s position and volume (0.5 ml) were held constant throughout the study. Pressures were recorded with a transducer (Statham) and a recorder (Electronics for Medicine DR-8). The Pes at the end of expiration is the mean pressure measured at the end of expiration, prior to the next tidal breath.

Maximum elastic recoil was recorded as the Pes at TLC. The Cst was measured by a stop-flow technique during exhalation from TLC. Occlusion of the airway for one second was performed with a manual valve. The Cst was computed from many points of data over the range of tidal volumes taken from three identical maneuvers of exhalation.

**Bronchodilatation**

Studies were done before and after inhalation of 400 μg of isoproterenol. To maximize bronchodilatation, isoproterenol in a Freon propellant was administered by one of us (D.W.T.) in small repeated doses during the middle portion of a slow inspiratory maneuver for VC. A dose of 160 μg of isoproterenol was inhaled twice (immediately following control studies and again ten minutes later). Studies of pulmonary recoil were then repeated. To eliminate possible reflex bronchoconstriction after maneuvers for VC as described in asthmatic patients, a final 80 μg of isoproterenol was administered prior to the postbronchodilator measurement of Raw.

**Calculations**

Predicted values are those of Goldman and Becklake. Statistical analyses included regression analysis and paired Student’s t-test.

Change in all measurements made before and after bronchodilatation was recorded as the postisoproterenol value minus the control value. Changes in SRaw and end-expiratory Ppl were expressed in absolute units (cm H₂O·sec and cm H₂O, respectively). In contrast, to normalize for differences in predicted values, changes in static pulmonary volumes were expressed as a percentage of the control value.

**RESULTS**

Mean static pulmonary volumes for all subjects appear in Table 1. Although VC, FRC, and RV improve with inhalation of isoproterenol, TLC is unchanged. Spirometric determinations from those 14 subjects who demonstrated bronchodilation by plethysmographic studies appear in Table 2. Although VC and the forced expiratory volume in one second (FEV₁) increase, the ratio of FEV₁/VC

| Table 1—Static Pulmonary Volumes before and after Bronchodilator Therapy |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Data | No. of Subjects | Value before Therapy, L | Value after Therapy, L | Paired difference, L | t-test | P |
| TLC | 17 | 6.84 ± 1.38 | 6.60 ± 1.43 | 1.255 | >0.2 |
| VC | 17 | 2.26 ± 0.74 | 2.64 ± 0.80 | 2.958 | <0.01 |
| FRC | 18 | 5.28 ± 1.39 | 4.78 ± 1.34 | 2.384 | <0.05 |
| RV | 17 | 4.58 ± 1.40 | 3.95 ± 1.38 | 3.133 | <0.01 |

*Mean ± SD.

**Table 2—Spirometric Data before and after Bronchodilator Therapy in 14 Subjects**

<table>
<thead>
<tr>
<th>Data</th>
<th>Control</th>
<th>Value after Isoproterenol</th>
<th>Paired t-test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, L</td>
<td>2.24 ± 0.76</td>
<td>2.70 ± 0.76</td>
<td>3.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.11 ± 0.51</td>
<td>1.44 ± 0.55</td>
<td>4.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁/VC, percent</td>
<td>49 ± 11</td>
<td>53 ± 13</td>
<td>2.05</td>
<td>&lt;0.10</td>
</tr>
</tbody>
</table>

*Data from 14 subjects whose SRaw decreased after inhalation of isoproterenol.

**Mean ± SD.**

(percentage) is unchanged.

Before inhalation of isoproterenol in the 18 patients studied, the mean initial values (± SD) for SRaw and end-expiratory Ppl were 22.2 ± 11.5 cm H₂O·sec and 1.5 ± 4.9 cm H₂O, respectively. After the inhalation of isoproterenol, the change in SRaw was −6.8 ± 8.1 cm H₂O·sec, and the change in end-expiratory Ppl was −3.6 ± 6.4 cm H₂O. End-expiratory Ppl decreased (ie, became more negative) following therapy in 12 of the 18 patients studied.

Data from all subjects demonstrate the following relationship between bronchodilatation, expressed as diminished SRaw, and normalization of end-expiratory Ppl (Pplee): ΔPplee = 0.54 ΔSRaw (r = 0.68; P = 0.01). Further regression analysis indicates that normalization of SRaw has a greater effect upon change in RV after therapy with isoproterenol than does the decrease of end-expiratory Ppl. The change in RV does not correlate with the change in end-expiratory Ppl (r = 0.49; P < 0.1) but does correlate with the change in SRaw (r = 0.58; P < 0.05). Multiple regression analysis indicates that the change in SRaw explains 20 percent of the variance in the change in RV not explained by the change in end-expiratory Ppl (ΔPplee): ΔRV = 94.3 + 0.3 ΔPplee + 1.0 ΔSRaw (r = 0.59; P < 0.05).

Finally, we examined the possibility that changes in either end-expiratory Ppl or RV were related to pulmonary recoil. The more positive end-expiratory Ppl observed prior to bronchodilation (when compared to that end-expiratory Ppl after therapy) may result from force generated by respiratory muscles upon the lung during expiration against obstructed airways. On the other hand, the more negative end-expiratory Ppl after therapy with isoproterenol might reflect the diminished pulmonary compliance often observed after bronchodilation. To distinguish between these two possibilities, Cst was measured in four asthmatic subjects before and after bronchodilation. Figure 1 illustrates data from one patient; Table 3 presents all values. Although SRaw and end-expiratory Ppl decreased with therapy in all four subjects, Cst did not change.
Measurements of maximum elastic recoil pressure at TLC recorded after bronchodilator therapy in 11 patients indicate that changes observed in RV after inhalation of isoproterenol were independent of pulmonary recoil. This pressure, which ranged from $-8.4 \text{ cm H}_2\text{O}$ to $-25 \text{ cm H}_2\text{O}$, did not correlate with the change in RV, expressed as a percentage of control ($r = 0.42; n = 11$).

**DISCUSSION**

This study demonstrates that both the increased VC and reduced RV observed after bronchodilation in patients with reversible obstruction of the airways result, in part, from a reduction (that is, a change to a more negative value) of Ppl during unforced exhalation at low pulmonary volumes. Multiple regression analysis indicates that these events all result from dilatation of central airways.

**End-Expiratory Ppl**

The positive end-expiratory Ppl often recorded in the middle portion of the esophagus of patients with severe bronchospasm during quiet breathing results, in part, from force created by the expiratory musculature during exhalation through obstructed airways. Normal subjects achieve exhalation during breathing at rest by passive deflation resulting from pulmonary elastic recoil. The Ppl is thus negative throughout the respiratory cycle. Patients with bronchoconstriction, in contrast, exhale actively. In these patients, Ppl during exhalation may reach or exceed that positive pressure required to achieve maximal expiratory flow. Bronchodilation may restore passive exhalation and thus eliminate positive expiratory Ppl during tidal breathing.

To a minor degree, interdependence among acinar units distal to parallel air conduits with unequal time constants may account for the more positive end-expiratory Ppl during bronchoconstriction. Thus, Zidulka et al. showed that ligation of one segmental bronchus in situ in the dog results in a more negative Ppl adjacent to the obstructed bronchopulmonary segment during inspiration than that measured by the esophageal balloon in regions distant from the obstruction; however, during expiration, Pes exceeded (appeared slightly more positive than) Ppl measured by a catheter adjacent to the obstruction.

**Residual Volume**

During the slow expiratory maneuver for VC, patients with bronchospasm reach RV when Ppl exceed small airway pressure, and expiratory flow ceases. Closure of terminal bronchioles has been demonstrated at low pulmonary volumes.
While reversible pathologic changes in terminal bronchioles during the acute asthmatic attack may account for an increased RV, the positive Ppl developed during exhalation through obstructed central airways contributes to this change in static volume as well. We used the Ppl measured at the end of exhalation as a representative sample of Ppl at all low pulmonary volumes. Since end-expiratory Ppl becomes more positive at FRC with bronchoconstriction, it is likely that Ppl during unforced exhalation below FRC is also elevated. With bronchodilatation, end-expiratory Ppl decreases (becomes more negative). The Ppl most likely decreases at volumes below FRC as well. Therefore, following administration of isoproterenol, the pressure required to close the bronchioles is achieved at a lower pulmonary volume. The RV may decrease before pathologic changes in the bronchioles resolve.

In asthmatic patients, inspissated mucus, edema, and increased tone of the smooth muscles in medium and small airways attenuate the expiratory driving pressure from alveolus to airway. Both the increase of end-expiratory Ppl and the decrease (more negative) of end-inspiratory Ppl have been recognized as important adjustments for maintenance of adequate alveolar ventilation during bronchoconstriction. This study suggests that the normalization of values for Ppl at low pulmonary volumes following bronchodilatation may facilitate emptying of acinar units in regions of severe obstruction of the small airways during the maneuver for VC.

Other Static Pulmonary Volumes

Diminution of TLC after bronchodilatation did not occur consistently in this study. Since RV consistently decreases in the short-term response to inhalation of isoproterenol, while TLC does not, VC increases. This is of practical importance because VC is easily measured on a spirometer.

Although the FRC decreased after inhalation of isoproterenol in this study, this change was not as marked as the decrease in RV. This result might have been anticipated, because FRC is determined, to a large degree, by pulmonary compliance. With acute obstruction of the central airways, pulmonary compliance increases. Although pulmonary compliance normalizes after bronchodilatation, this process is not immediate. Our subjects completed testing of pulmonary function 45 minutes after inhalation of isoproterenol, which may have been insufficient time for normalization of pulmonary compliance.

ACKNOWLEDGMENT: We thank Mrs. Jean Norwood for secretarial assistance and Gerard M. Turino, M.D., and Lee B. Beichman, M.D., for advice and criticism.

REFERENCES