Tidal volume amplitude affects the degree of induced bronchoconstriction in dogs

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Tidal volume amplitude affects the degree of induced bronchoconstriction in dogs. J. Appl. Physiol. 87(5): 1674–1677, 1999.—When isolated constricted airway smooth muscle is oscillated, muscle tone decreases. We investigated whether changing tidal volume (VT) would affect induced bronchoconstriction in an in vivo canine model. Open-chest dogs were intubated with a double-lumen endotracheal tube, which isolated each main bronchus, and mechanically ventilated with a dual-cylinder ventilator. Bronchial pressure (Pbr) and flow were measured separately in each lung. Resistance and elastance were calculated by fitting the changes in Pbr, flow, and volume to the equation of motion. After baseline measurements at the same VT (150 ml), the two lungs were ventilated with different VT (50 vs. 250 ml) at a constant positive end-expiratory pressure. A continuous infusion of methacholine was begun, and measurements were repeated. The two lungs were then ventilated with the same VT (250 ml), and measurements were again repeated. A similar protocol was performed in a second group of dogs in which mean Pbr was kept constant. Bronchoconstriction was more severe in the lung ventilated with lower VT in both protocols. When VT was reset to the same amplitude in the two lungs, the difference in bronchoconstriction was abrogated. These results demonstrate that large VT inhibits airway smooth muscle contraction, regardless of mean Pbr.

methacholine; airway smooth muscle

THERE ARE A NUMBER of mechanisms potentially responsible for the increased airway narrowing observed in asthmatic patients, including factors that cause increased airway smooth muscle (ASM) contractility and factors that reduce the load opposing ASM contraction (1, 8). Under static conditions, the equilibrium between contractility and load will determine the final airway caliber. However, in vivo the lungs are continually being oscillated during tidal breathing; dynamic oscillations may affect ASM contractility and the load opposing ASM shortening. Fredberg and co-workers (3, 4) have postulated that oscillation may prevent the ASM from reaching the “latch” state, which is characterized by high force generation and low velocity of shortening.

In a recent experiment, Shen and colleagues (13) showed in vivo in rabbits that agonist-induced increases in lung resistance (R) were diminished during large tidal volume (VT) excursions. They hypothesized that the modulating effect of VT amplitude was due to the direct effect of stretch on the ability of the ASM to generate force. Experiments were carried out in these animals at a constant positive end-expiratory pressure (PEEP). However, by changing VT amplitude at a constant PEEP, important differences in mean bronchial pressure (Pbr) may have been introduced. That is, during mechanical ventilation, the mean Pbr in the lung exposed to large-volume (V) oscillations would have been relatively higher. Pbr, because of its effect on lung elastance (E) and material properties, may affect contractile responses, as the mechanical properties of the alveolar wall will, in part, determine the impedance to airway narrowing offered by the parenchymal attachments (8, 12). Indeed, Ding et al. (2) have shown that simply by lowering functional residual capacity, and thereby Pbr, in healthy humans, a dramatic increase in airway responsiveness can be induced. Hence, part of the effect observed by Shen and colleagues (13) may have been due to changes in the mean Pbr induced with altering VT amplitude.

The object of our study was to determine whether the effect of VT on airway constriction was determined simply by the amplitude of VT or, in part, by the secondary change in Pbr. To test this hypothesis, we ventilated left and right dog lungs separately during methacholine (MCh)-induced constriction using a double-lumen tracheal tube and a double ventilator. Different VT were delivered at the same PEEP. Experiments were then repeated maintaining the same mean Pbr by adjusting the PEEP. We thereby attempted to separate out the effect of mean Pbr from that of VT amplitude on the lung R response.

MATERIALS AND METHODS

Ten mongrel dogs (20–28 kg) of either sex were studied. Animals were anesthetized with xylazine (1–2 ml im) and injected intravenously with pentobarbital sodium (15–25 mg/kg). The inferior vena cava was cannulated for fluid and drug administration. Animals were tracheostomized and paralyzed with pancuronium bromide (1 mg); propranolol was given initially (2 mg/kg iv) and every 30 min thereafter (0.6 mg/kg). Supplemental doses of pentobarbital sodium (2–3 mg/kg) and pancuronium bromide (1 mg) were administered hourly. A double-lumen endotracheal tube (no. 39, Rüsch) was inserted, and animals were mechanically ventilated with a double ventilator (model 618, Harvard Apparatus, South Natick, MA) at a frequency of 20 breath/min, a VT of 150 ml for each lung, and PEEP of 5 cmH2O. The Pbr of each lung was measured by a piezoresistive microtransducer (FPM02PG, Fujikura) placed in the lateral port of each
cannula lumen, and bronchial flow (V) was measured by means of two pneumotachographs (Fleisch no. 2) separately attached to each cannula.

V values were calculated by digital integration of the flow signal. All signals were amplified, filtered at a cut-off frequency of 20 Hz, and converted by a 12-bit analog-to-digital converter (DT2801-A, Data Translation, Marlborough, MA). The signals were sampled at a rate of 50 Hz and stored on an AT-compatible computer.

Constant PEEP. Experiments were performed at a PEEP of 5 cmH₂O. After baseline measurements at a VT of 150 ml into each lung, one lung, either left or right chosen randomly, was then ventilated with a VT of 50 ml (small VT) and the other with a VT of 250 ml (large VT). Measurements were repeated after 5 min. MCh was dissolved in saline and administered by continuous intravenous infusion at a rate of 0.76 ml/min and a concentration of 10⁻³ M by using an infusion pump (model 600–950, Harvard Apparatus). The dose of MCh was adjusted (by doubling either the concentration of agonist or the infusion speed) until approximately a doubling in Pbr excursions in the lung ventilated with larger VT was observed. VT was then increased in the small VT lung to match the large VT (250 ml into each lung), and measurements were repeated after 5 min (Fig. 1).

Constant mean Pbr. The protocol was similar to that described above except that mean Pbr was maintained con-

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Fig. 1. Same-positive end-expiratory pressure (PEEP) experiment. Bronchial pressure (Pbr) and tidal volume (VT) are shown in the 2 lungs (subscript 1 and 2) of sample dog. A: baseline conditions; both lungs were ventilated at VT = 150 ml. B: lung 1 was ventilated at VT = 50 ml, and lung 2 was ventilated at VT = 250 ml. C: same conditions as B but during intravenous methacholine (MCh) infusion. D: both lungs were ventilated at VT = 250 ml.

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Fig. 2. Same-mean Pbr experiment. At each step, mean Pbr was adjusted in each lung to 11 cmH₂O. See Fig. 1 legend for details.
stant at 11 cmH₂O during the experiment by adjusting the PEEP after each VT step and after MCh infusion. Mean pressure was calculated by the integrated mean of Pbr measured during a 15-s recording (Fig. 2).

Calculations. E and R for each lung were calculated by fitting the equation of motion

\[ P_{br} = E V + R \frac{dV}{dt} + K \]  

where \( K \) is a constant term reflecting PEEP and the error linked to the residual of the least squares adjustment method (6), and \( V \) is calculated by digital integration of the flow signal. Tracheal tube R was subtracted from each lung R. The resistive properties of the two lumens of the endotracheal tube were measured as follows. The tracheal tube was attached to the double ventilator, and tube pressures and flows were measured at the proximal end. After positioning an elastic load comparable to that of the lung at the distal end of the endotracheal tube, different VT amplitudes ranging from 50 to 300 ml were applied. Tube R was then calculated by using the equation of motion. A linear relationship was observed between VT and tube R. With the use of this relationship, R was corrected for R of each tube.

All data manipulations were performed with the ANADAT software package (RHT-InfoDat, Montreal, Quebec). Unpaired t-tests were used to analyze the differences between groups. Values are reported as means ± SE.

RESULTS

Baseline values of E and R for both lungs (VT = 150 ml into each lung) in the two groups of animals are shown in Table 1. Baseline values of E and R were not statistically different for the two lungs in either the same-PEEP or the same-Pbr groups. E in the same-PEEP group was slightly lower than that in the same-Pbr group, as the actual PEEP in the former group was slightly less. These differences, however, did not achieve statistical significance. Changes in VT amplitude (50 vs. 250 ml) did not significantly affect E or R in the unconstricted state (data not shown).

At the same PEEP, R increased after MCh challenge in both the small and large VT lungs (Fig. 3). However, the increase in R was significantly larger in the small VT lungs (P < 0.05). When mean Pbr was controlled by adjusting PEEP, R again increased after MCh challenge in both small and large VT lungs. Whereas the increase in R in small VT lungs was not statistically different from that in large VT lungs, this was likely attributable to the variability in the magnitude of the response in the small VT lungs.

**DISCUSSION**

In the present study, we have shown that VT amplitude affects the degree of induced bronchoconstriction in vivo via a mechanism that is, at least in part, independent of changes in Pbr.

There has been much interest lately in the issue of how the mechanical properties of airways and lung parenchyma are modified during dynamic events such as tidal breathing and deep inspiration (14, 15). When ASM is activated under dynamic conditions, less bronchoconstriction results (5, 14). Fredberg et al. (3, 4) have hypothesized that oscillation may prevent the ASM from reaching the latch state. When ASM con-

**Table 1. Baseline values of elastance and resistance for the 2 lungs in the 2 protocols**

<table>
<thead>
<tr>
<th>VT Lung</th>
<th>Same PEEP</th>
<th>Same Pbr</th>
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<tbody>
<tr>
<td>Small</td>
<td>2.45 ± 0.40</td>
<td>3.67 ± 0.45</td>
</tr>
<tr>
<td>Large</td>
<td>2.56 ± 0.40</td>
<td>3.58 ± 0.26</td>
</tr>
</tbody>
</table>

Values are means ± SE. PEEP, positive end-expiratory pressure; Pbr, bronchial pressure; VT, tidal volume. VT = 150 ml into all lungs. See text for explanation of groups.
stricts, an early phase, characterized by high velocity of shortening, low stiffness, and low force generation, is followed by a late phase, sometimes referred to as the latch state, characterized by high stiffness, high force generation, and slow velocity of shortening (9). Oscillation, by changing muscle length, may break cross bridges and thereby maintain the smooth muscle in a state in which cross bridges rapidly cycle and force generation is less (16). Alternately, Shen et al. (14) have proposed that the decreased contractility during continuous-length oscillations is a function of the plasticity of contractile filaments within the smooth muscle cells; the cellular organization of contractile filaments allows the smooth muscle to reset its length during stretch. Large amplitude cycling of contractile elements results in the cell being "stretched"; active shortening of the contractile element must begin from a longer set point, thus resulting in lower force generation. Pratusevich et al. (11) have proposed that the number of contractile units in series in the ASM may vary as length is changed. This theory would explain the ability of smooth muscle to generate force over such a wide range of lengths. The continuous rearrangement of contractile units in series during tidal oscillations could impair ASM contractility.

VT amplitude has been shown in vivo in rabbits to modulate the degree of airway narrowing (13). In this experiment, ventilation amplitudes were changed, whereas PEEP was maintained at a constant level (13). In this circumstance, when ventilation amplitude is changed, mean Pbr will also change. Lung transpulmonary pressure and lung V are important factors in the regulation of the degree of airway narrowing during induced constriction via their effects on lung recoil, parenchymal shear properties, and impedance to airway narrowing (2, 8, 12). Nagase et al. (10) have shown, for example, that as Pbr is increased, the degree of bronchoconstriction is diminished. Therefore, a change in mean Pbr may also contribute to modulating the contractile response.

In the present study, lungs ventilated with higher amplitudes always demonstrated lesser increases in R and E during induced constriction. When mean Pbr was kept constant, the discrepancy in the contractile response between the two lungs was again evident. Whereas the magnitude of the differential response was somewhat less when mean Pbr was constant, it is difficult to directly compare the effect of amplitude in the two protocols as measurements were carried out at different PEEP. It is difficult to know, therefore, to what extent the control of Pbr modulated the response. Nonetheless, the lung ventilated with lower VT amplitude always demonstrated a larger increase in R and E relative to the other lung, suggesting that amplitude of ventilation was a major factor regulating the degree of bronchoconstriction, regardless of mean Pbr.

A further consideration in this experiment is that responses were not partitioned into airway and tissue components. It is likely that the contractile response we obtained included an important component related to changes in tissue R (7). However, there is no reason to postulate a systematic difference in the partitioning of airway and tissue responses in the same-PEEP vs. same-Pbr groups.

In conclusion, we have shown that the contractile response is modulated by the amplitude of tidal ventilation and that this mechanism is at least partially independent of any modification in transbronchial pressure. Asthmatic airways may differ from those of normal subjects in the failure of tidal ventilation to prevent excessive airway narrowing.

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