Tidal volume amplitude affects the degree of induced bronchoconstriction in dogs

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Salerno, Francesco G., Norihiro Shinozuka, J effrey J. Fredberg, and Mara S. Ludwig. 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 lungs 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 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 breaths/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-
stant at 11 cmH$_2$O 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

\[ Pbr = E \cdot V + R \cdot \dot{V} + K \]

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.

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

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<tr>
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<th>Same PEEP</th>
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<th>Same Pbr</th>
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<tbody>
<tr>
<td></td>
<td>Small VT</td>
<td>Large VT</td>
<td>Small VT</td>
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<tr>
<td>Elastance, kPa/l</td>
<td>2.45 ± 0.40</td>
<td>2.56 ± 0.40</td>
<td>3.67 ± 0.45</td>
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<tr>
<td>Resistance, kPa·l$^{-1}$·s</td>
<td>0.39 ± 0.06</td>
<td>0.27 ± 0.06</td>
<td>0.32 ± 0.04</td>
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Fig. 3. Effect of VT amplitude on %increase in lung resistance (R) in same-PEEP and same-Pbr groups. Lines connect 2 lungs from same animal ventilated at different VT: small VT, 50 ml; large VT, 250 ml. n = 10 Animals. Means ± SE are shown on the side. *P < 0.05, small vs. large VT.

The E response in the same-PEEP and same-Pbr protocols is shown in Fig. 4. The increase in E was significantly greater in the small VT lungs in both the same-PEEP and the same-Pbr groups (P < 0.05).

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-

Fig. 4. Effect of VT amplitude on %increase in lung elastance (E) in same-PEEP and same-Pbr groups. Lines connect 2 lungs from same animal ventilated at different VT. n = 10 Animals. Means ± SE are shown on the side. *P < 0.05, small vs. large VT.
TIDAL VOLUME AND DEGREE OF BRONCHOCONSTRICTION

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