Greater airway narrowing in immature than in mature rabbits during methacholine challenge

X. Shen, V. Bhargava, G. R. Wodicka, C. M. Doerschuk, S. J. Gunst, and R. S. Tepper

Departments of Pediatrics and Physiology and Biophysics, Indiana University School of Medicine, Indianapolis, Indiana 46223; and School of Electrical and Computer Engineering, Purdue University, West Lafayette, Indiana 47907

Shen, X., V. Bhargava, G. R. Wodicka, C. M. Doerschuk, S. J. Gunst, and R. S. Tepper. Greater airway narrowing in immature than in mature rabbits during methacholine challenge. J. Appl. Physiol. 81(6): 2637–2643, 1996.—It has been demonstrated that methacholine (MCh) challenge produces a greater increase in lung resistance in immature than in mature rabbits (R. S. Tepper, X. Shen, E. Bakan, and S. J. Gunst. J. Appl. Physiol. 79: 1190–1198, 1995). To determine whether this maturational difference in the response to MCh was primarily related to changes in airway resistance (Raw) or changes in tissue resistance, we assessed airway narrowing in 1-, 2-, and 6-mo-old rabbits during intravenous MCh challenge (0.01–5.0 mg/kg). Airway narrowing was determined from measurements of Raw in vivo and from morphometric measurements on lung sections obtained after rapidly freezing the lung after the MCh challenge. The fold increase in Raw was significantly greater for 1- and 2-mo-old animals than for 6-mo-old animals. Similarly, the degree of airway narrowing assessed morphometrically was significantly greater for 1- and 2-mo-old animals than for 6-mo-old animals. The fold increase in Raw was highly correlated with the degree of airway narrowing assessed morphometrically (r² = 0.82, P < 0.001). We conclude that the maturational difference in the effect of MCh on lung resistance is primarily caused by greater airway narrowing in the immature rabbits.

METHODS

Animal Preparation

Three different age groups of New Zealand White rabbits were evaluated: 1 mo (0.5–0.7 kg), 2 mo (0.9–1.2 kg), and 6 mo (2.5–3.0 kg). Animals were anesthetized with intravenous pentobarbital sodium (50 mg/kg), and an appropriately sized tracheotomy tube was inserted and securely tied in place to prevent air leaks. Animals were mechanically ventilated (model 628, Harvard) with a tidal volume of 7 ml/kg at a frequency of 40 breaths/min and a positive end-expiratory pressure (PEEP) of 5 cmH₂O. A jugular venous catheter was inserted to administer additional anesthetic, normal saline, and MCh. The abdominal and thoracic cavities were widely opened, and a warming pad was used to prevent cooling of the animal.

Tracheal pressure was measured with a piezo-resistive pressure transducer (model 8507C-2, Endevco), and tracheal flow was measured with a screen pneumotachometer (model 8410A, Hans Rudolph) and a differential pressure transducer (±2.25 cmH₂O; model MP45, Validyne). Analog signals of flow and pressure were filtered above 50 Hz, amplified, and digitized at 100 samples/s (model DT2801-A, Data Translation). Digital signals were stored in an IBM-compatible personal computer (model 486, Zeos International) by using data-acquisition software (RHT Infodat).

Measurements of Raw

The frequency dependence of Raw was assessed by small-volume (1–2 ml) forced oscillations in flow that were
generated with a small piston attached to a linear motor as previously described (26). The motor was controlled by the microcomputer via a digital-to-analog converter. The digital signal was composed of 14 frequencies (0.146, 0.342, 0.537, 0.830, 1.123, 1.416, 1.807, 2.002, 2.294, 2.588, 2.979, 3.467, 3.857, 4.053 Hz). The frequencies were chosen as a nonsum nondifference sequence so as to minimize harmonic overlapping (23). The signal was 23 s in length.

Experimental Protocol

Oscillatory measurements were obtained under baseline nonconstricted conditions (pre-MCh) as follows. Mechanical ventilation was stopped at end expiration (PEEP = 5 cmH₂O), and the animal was apneic. The forced oscillatory signal was then applied, after which mechanical ventilation was resumed. The same sequence was followed after challenge with intravenous doses of MCh (0.01, 0.05, 0.5, 1.0, and 5.0 mg/kg). Measurements were begun when the MCh dose produced a maximal increase in tracheal pressure, which occurred ~30-60 s after MCh administration. After completion of the forced oscillation measurements for the last MCh dose administered, the lungs were rapidly removed from the chest cavity and frozen with liquid nitrogen (18). While the lung was being frozen, a PEEP of 5 cmH₂O was maintained with a bias flow of air connected to the tracheotomy tube.

Analysis

Resistance. Lung impedance at the different frequencies were estimated from the Fourier transforms of flow and pressure as previously described (26). RL was the real part of lung impedance, and RL values at the different frequencies were fit to the following equation by using least squares regression

\[ RL = \frac{Raw + B}{9.2 \cdot f} \]  

where Raw is a constant that approximates airway resistance, B is a constant that characterizes the frequency dependence of RL, and f is frequency.

Morphometry. The frozen rabbit lungs were fixed in Carnoy's solution (60% ethyl alcohol, 30% chloroform, 10% acetic acid) at -70°C for 18 h. Progressive concentrations of ethanol at -20°C were then substituted for the Carnoy's solution until 100% alcohol was reached, and then the lungs were maintained at 4°C overnight. Before sectioning, the lungs were placed at room temperature for ≥2 h. The left lower lobe was divided into four equally spaced blocks of tissue that were embedded in paraffin. With a microtome, 5-μm sections were cut and then stained with Masson's trichrome method. A light microscope with a camera lucida was used to project the image onto a digitizing board (Jandel Scientific), and the following morphometric measurements were obtained: 1) the length of the epithelial basement membrane (L(BM)); 2) the area circumscribed by the internal surface of the epithelium in the airway lumen (Ae); and 3) the area circumscribed by the external border of the airway wall. An ideal relaxed airway area (Ae) was calculated as

\[ A_e = \frac{L^2_{BM}}{4\pi} \]  

as well as the relative airway caliber, A(R) relative to A(BM/Ae). The airway wall area (Ae) was obtained as the difference between the area circumscribed by the external border of the airway wall and A(BM), and the epithelial area (Ae) was the difference between A(BM) and A0. To compare A0 and Ae among the different groups, the values were expressed as a fraction of A0 (A0/Aa; Ae/Aa).

Statistical analysis. Physiological measurements among the different age groups were compared with analysis of variance. For morphometric measurements, the airways of the animals within each age group were pooled and the airways among the different age groups were compared by analysis of variance. P < 0.05 was considered statistically significant.

RESULTS

Physiological Measurements

RL in the nonconstricted state. RL vs. frequency for a representative rabbit in each age group is illustrated in Fig. 1. The RL values at the discrete frequencies of volume oscillations are indicated by individual symbols, and the solid lines are the fitted Eq. 1. For all animals, the correlation coefficients for the fitted equations were >0.95. RL was greatest at the lowest frequency, and with increasing frequency RL rapidly decreased and approached a relatively constant value. The values of Raw and B, which were calculated from the fitted equations, decreased significantly with increasing age (Table 1).

MCh challenge. MCh produced a transient bradycardia in all animals. At the higher MCh doses, some animals developed asystole and died; thus those animals did not receive higher doses of MCh. Only one of the five 1-mo-old rabbits did not receive the highest MCh dose; all of the 2-mo-old rabbits completed the entire MCh challenge. Of the five 6-mo-old rabbits, all tolerated the first three MCh doses; however, only three animals received the fourth MCh dose and none survived through the fifth MCh dose.

Increasing RL in response to MCh challenge. The frequency dependence of RL at five different doses of MCh are illustrated in Fig. 2 for one 1-mo-old rabbit. Both the individual datum points and the fitted equations are shown. With increasing doses of MCh, there was a progressive increase in RL at all frequencies.

![Fig. 1. Lung resistance (RL) vs. frequency of volume oscillations for representative rabbits from each age group.]
MCh also produced a greater curvature or frequency dependence of $R_L$ at the lower frequencies; however, $R_L$ remained relatively frequency independent at the higher frequencies.

Greater increases in Raw for immature animals. The increases in Raw from baseline with increasing doses of MCh are illustrated for the three different age groups in Fig. 3. MCh increased Raw in all animals in all groups. At all MCh doses >0.01 mg/kg, the 1- and 2-mo-old rabbits had significantly greater increases in Raw compared with the 6-mo-old animals. At the highest MCh dose that all animals received (1.0 mg/kg), the fold increase in Raw was significantly greater for 1- and 2-mo-old animals compared with 6-mo-old animals [49 ± 20 (SE), 27 ± 2, 4 ± 1; $P < 0.05$]. The 2-mo-old rabbits had smaller increases in Raw compared with 1-mo-old animals; however, the difference was statistically significant only at the MCh dose of 0.05 mg/kg.

Greater increases in frequency dependence of RL in immature animals. $B$ increased with increasing doses of MCh (Fig. 4). The 6-mo-old rabbits had a smaller increase in $B$ than the 1- and 2-mo-old animals; however, the difference between different age groups was statistically significant only at a MCh dose of 1.0 mg/kg.

Morphometric Measurements

The average number of airways examined per animal was not significantly different for the three age groups (Table 2). There were relatively few cartilaginous airways per animal examined in each group, and there were no differences in the number of cartilaginous airways examined per animal among the groups. The average airway size assessed by $L_{BM}$ was significantly greater for the 6-mo-old rabbits compared with either the 1- or 2-mo-old animals.

The degree of airway narrowing was assessed as the relative airway caliber, $A_{BM}/A_r$, of the constricted airway divided by the calculated ideal airway caliber ($A_{BM}/A_r$). A smaller relative airway caliber ($A_{BM}/A_r$) indicates greater airway narrowing. The 1-mo-old rabbits had the smallest relative airway caliber and thus the greatest degree of airway narrowing (Table 3). The 2-mo-old animals had a greater relative airway caliber and thus less airway narrowing than the 1-mo-old animals, and the 6-mo-old rabbits had the greatest relative airway caliber and thus least airway narrowing than both the 1- and 2-mo-old animals. There was a large variability in the relative airway caliber within each age group. The coefficient of variation for $A_{BM}/A_r$ was greatest in the least mature rabbits and smallest in the most mature rabbits. When the relative airway caliber was assessed...

Table 1. Baseline values of parameters that characterize RL

<table>
<thead>
<tr>
<th></th>
<th>1 mo</th>
<th>2 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw, kPa·s·l$^{-1}$</td>
<td>2.42 ± 0.68</td>
<td>2.09 ± 0.26</td>
<td>0.92 ± 0.14</td>
</tr>
<tr>
<td>$B$, kPa/l</td>
<td>6.77 ± 1.79</td>
<td>6.28 ± 1.78</td>
<td>1.79 ± 0.28</td>
</tr>
</tbody>
</table>

Values are means ± SD. Both airway resistance (Raw) and constant that characterizes frequency dependence of lung resistance ($RL$) ($B$) decreased with increasing age. Values are significantly different for 1-, 2-, and 6-mo-old animals at $P < 0.05$. 

![Fig. 2. $R_L$ vs. frequency of volume oscillations at 5 different doses of methacholine (MCh) [0.01 (●), 0.05 (●), 0.50 (●), 1.00 (●), and 5.00 (●) mg/kg] for single 1-mo-old rabbit. Symbols represent $R_L$ values measured at single MCh dose; lines represent hyperbolic equation fitted to individual values [$R_L = \text{Raw} + B/(9.2\cdot f)$].](http://jap.physiology.org/)

![Fig. 3. Fold increase of Raw from baseline at different doses of MCh for rabbits in each age group [1 (●), 2 (●), and 6 (○) mo]. Values are means ± SE. Significantly different at $P < 0.05$ compared with values of: *1- and 2-mo-old animals; **2-mo-old animals.](http://jap.physiology.org/)

![Fig. 4. Fold increase in $B$ from baseline at different doses of MCh for 1- (●), 2- (●), and 6-mo-old animals (○). Values are mean ± SE. $B$ increases with increase in frequency dependence of $RL$. *Significantly different compared with values of 1- and 2-mo-old animals, $P < 0.05$.](http://jap.physiology.org/)
were grouped into those with relaxed airway size, as assessed by the degree of airway narrowing after MCh relative to

tions among the different-aged rabbits, we examined rabbits compared with 6-mo-old animals.

were also significantly greater in 1- and 2-mo-old L

6-mo-old animals, where the relative airway caliber and thus the smallest degree of luminal narrowing; 2-mo-old animals had the largest relative airway caliber and thus the greatest degree of luminal narrowing. The normalized values for \( A_w / (A_w + A_r) \) and \( A_r / A_w \) were also significantly greater in 1- and 2-mo-old rabbits compared with 6-mo-old animals.

Because we were not able to match airway generations among the different-aged rabbits, we examined the degree of airway narrowing after MCh relative to relaxed airway size, as assessed by \( L_{BM} \). The airways were grouped into those with \( L_{BM} < 750 \mu m \) and those with \( L_{BM} > 750 \mu m \). In Fig. 5, airway caliber after MCh for the 1-, 2-, and 6-mo-old animals is plotted for the two different-sized groups of airways. The relative airway caliber after MCh was greater in the larger sized airways than in the smaller-sized airways for both 1- and 2-mo-old rabbits, indicating that less narrowing occurred in these airways after MCh. This relationship was not observed in the airways of the 6-mo-old animals, where the relative airway caliber was similar for all airways. For the larger sized airways (\( L_{BM} > 750 \mu m \)), there were significant differences in the relative airway caliber among the three age groups. The 1-mo-old rabbits had the smallest relative airway caliber, indicating the most airway narrowing; 2-mo-old animals had a larger relative airway caliber than the 1-mo-old animals; and 6-mo-old animals had the largest relative airway caliber and thus the least degree of airway narrowing. For airways with \( L_{BM} < 750 \mu m \), the 6-mo-old animals had the greatest relative airway caliber, indicating the least airway narrowing; however, there was not a significant difference between the airway narrowing for the 1- and 2-mo-old animals. Similar results were obtained if airways were divided into small and large by using an \( L_{BM} \) of 1,000 \( \mu m \).

Correlation between physiological and morphometric measurements. The increase in \( R_{aw} \) produced by the last dose of MCh was highly correlated with the relative airway caliber measured morphometrically (\( A_{BM}/A_r \)) (Fig. 6). Those animals with a greater increase in \( R_{aw} \) had airways that narrowed to a smaller fraction of their ideal airway caliber. This relationship was present with

### Table 2. Morphometric analysis of number and size of airways

<table>
<thead>
<tr>
<th></th>
<th>1 mo</th>
<th>2 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Total no. of airways</td>
<td>112</td>
<td>141</td>
<td>79</td>
</tr>
<tr>
<td>Average no. of airways per animal</td>
<td>22.4 ± 6.5</td>
<td>28.2 ± 4.8</td>
<td>26.3 ± 4.5</td>
</tr>
<tr>
<td>Average no. of airways with cartilage per animal</td>
<td>2.4 ± 1.0</td>
<td>1.6 ± 1.6</td>
<td>1.0 ± 0.8</td>
</tr>
<tr>
<td>( L_{BM} ), µm</td>
<td>868 ± 799</td>
<td>848 ± 648</td>
<td>1,096 ± 812‡†</td>
</tr>
</tbody>
</table>

Values are means ± SD where indicated; n, no. of animals. \( L_{BM} \), length of basement membrane. Significantly different (P < 0.05) compared with values of: *1-mo-old animals; †2-mo-old animals.

### Table 3. Morphometric data

<table>
<thead>
<tr>
<th></th>
<th>1 mo (112)</th>
<th>2 mo (141)</th>
<th>6 mo (79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_{BM}/A_r )</td>
<td>0.61 ± 0.24</td>
<td>0.68 ± 0.21‡</td>
<td>0.85 ± 0.12*†</td>
</tr>
<tr>
<td>Coefficient of variation for ( A_{BM}/A_r ), %</td>
<td>35.14 ± 12.20</td>
<td>29.17 ± 9.40</td>
<td>13.78 ± 3.00‡†</td>
</tr>
<tr>
<td>( A/A_r )</td>
<td>0.30 ± 0.25</td>
<td>0.38 ± 0.25‡</td>
<td>0.65 ± 0.19*†</td>
</tr>
<tr>
<td>( A_w/A_r )</td>
<td>0.17 ± 0.06</td>
<td>0.20 ± 0.06*</td>
<td>0.14 ± 0.04*†</td>
</tr>
<tr>
<td>( A_r/A_r )</td>
<td>0.31 ± 0.17</td>
<td>0.30 ± 0.16*</td>
<td>0.20 ± 0.11*†</td>
</tr>
</tbody>
</table>

Values are means ± SD. Nos. in parentheses, no. of airways. \( A_{BM} \), measured area within epithelial basement membrane; \( A_r \), calculated area within epithelial basement membrane of relaxed airway; \( A_{aw} \), measured area within airway lumen; \( A_{ar} \), measured airway wall area; \( A_r \), measured area of airway epithelium; \( A_{BM}/A_r \), relative airway caliber; \( A_{aw}/A_r \), relative luminal caliber; \( A_{ar}/A_r \), normalized airway wall area; \( A_r/A_r \), normalized epithelial area. * Significantly different compared with 1 mo, P < 0.05. † Significantly different compared with 2 mo, P < 0.05. ‡ Significantly different compared with 1 mo, P < 0.05.
all of the rabbits combined as well as within each group of rabbits.

**DISCUSSION**

In the present study, we demonstrated that the greater pulmonary response to MCh in the immature than in the mature rabbits is related to greater airway narrowing in the immature animals. The greater airway narrowing in the immature rabbits was demonstrated both physiologically and morphologically, and we found that these two measurements were highly correlated. Although we previously reported that MCh challenge produced a greater increase in the RL of immature rabbits compared with mature rabbits (24, 27), this greater increase could have been produced by increases in Raw and/or increases in Rti. The present study, therefore, extends our previous results by demonstrating that the maturational differences in airway responsiveness can be accounted for by greater airway narrowing in the immature than in the mature rabbit.

Greater Airway Narrowing Induced by MCh in Immature Animals

In this study we assessed airway narrowing by measuring the frequency dependence of RL and fitting the values to a hyperbolic equation in which Raw was the asymptote. The hyperbolic function provided an excellent fit to RL data for all age groups (Figs. 1, 2), and changes in the values for Raw paralleled the changes in airway caliber during bronchoconstriction (Fig. 5). It has previously been demonstrated that in rabbits, as in several other species, Rti is greatest at very low frequencies and becomes negligible between 2 and 4 Hz as RL approximates Raw (4, 10, 11, 23, 26).

In this study, the increase in Raw produced by MCh was 10 times greater in the immature compared with in the mature rabbits. It has been demonstrated that RL measured at 1 Hz increases 5–10 times more in response to MCh in the immature than in the mature rabbit (24, 27). The similarity of the magnitudes of these responses suggests that the changes in RL can be attributed primarily to changes in airway narrowing.

Consistent with this conclusion is a previous study of Tepper et al. (25), which reports that airway closure occurs more frequently in isolated immature rabbit lungs compared with isolated mature rabbit lungs during maximal MCh stimulation. Greater airway narrowing in the immature rabbit lung could also account for the observation that pulmonary hyperinflation occurred in the immature but not in the mature rabbits during MCh challenge in vivo (27).

Morphometric analysis also indicated greater airway narrowing in the immature rabbit lungs than in the mature rabbit lungs after constriction with MCh. As expected, the larger more mature animals had a larger mean airway size ($L_{BM}$); however, we obtained a similar number of airways per animal for analysis from each group of lungs and most of the airways examined in all groups were noncartilaginous airways (Table 2). Although we are not able to compare specific airway generations among different age groups, we observed maturational differences in the degree of airway narrowing over the entire range of airways examined (Fig. 5).

By using similar sectioning techniques for all of the rabbit lungs, we assumed that we obtained similar generations of airways from the different age groups of animals. Thus the maturational difference in airway narrowing that we observed are not likely to be due to differences in the airway generations sampled.

We also found a high correlation between the morphometric assessment of airway caliper and the independent measurement of Raw (Fig. 6), strongly suggesting that we were examining the physiologically important airways in the three different age groups. If we assume laminar flow within the airways, then Raw should increase in a manner that is inversely proportional to the square of the decrease in airway caliber. Our results indicate an even greater fold increase in Raw relative to the degree of airway narrowing; this suggests that in addition to airway smooth muscle (ASM) shortening, luminal secretions within the airway may have also contributed to the observed increase in Raw.

Greater Heterogeneity of Airway Response to MCh in Immature Animals

Frequency dependence of RL can result from the viscoelastic properties of the lung parenchyma and from ventilation inhomogeneity within the lung (3, 9, 19). In the nonconstricted lung, the frequency dependence of RL is attributed to the viscoelastic properties of the lung parenchyma because ventilation throughout the lung is relatively homogenous (2, 10). However, it is unclear whether the increased frequency dependence of RL during bronchoconstriction is due primarily to alterations in the viscoelastic properties of the lung parenchyma or to ventilation inhomogeneity that develops within the lung. Studies of mature animals from several different species have used morphometric, physiological, and radiographic approaches to demonstrate that within the lung there is a marked heterogeneity in the degree of airway narrowing after bronchoconstriction (5–7, 9, 13). There is also recent evidence that heterogeneity of airway narrowing and not changes in lung parenchymal tissue properties can account for the increased frequency dependence of RL after bronchoconstriction and the apparent increase in Rti. Bates and Peslin (3) have demonstrated that marked ventilation inhomogeneity and not increases in static lung elastance best account for increases in RL and dynamic elastance during bronchoconstriction in mature dogs. In addition, Lutchen et al. (16) have recently demonstrated in rats that increases in Raw during bronchoconstriction can account for changes in lung mechanics previously attributed to changes in the viscoelastic properties of the parenchymal tissue.

In our study, the coefficient of variation for the distribution of airway narrowing as assessed by morphometric analysis was significantly greater in the immature than in the mature rabbit lungs (Table 3). This finding is consistent with a greater ventilation inhomogeneity in the immature lung after bronchoconstriction.
in vivo, as also suggested by our observation of a greater increase in the frequency dependence of $R_L$ in the immature than in the mature rabbit (Fig. 4). The increase in the frequency dependence of $R_L$ paralleled the increase in $Raw$ in all age groups (Figs. 3, 4), suggesting that both phenomena result from a common mechanism. The results of a previous study in which we used alveolar capsules in rabbits during bronchoconstriction in vivo also suggest that immature rabbits have greater ventilation inhomogeneity than mature rabbits (27). In that study, we calculated negative values of $R_{ti}$ in the immature rabbits after bronchoconstriction, whereas values of $R_{ti}$ remained positive in the mature rabbits. Negative values for $R_{ti}$ can occur when flow measured at the trachea is not in phase with local alveolar flow due to ventilation inhomogeneity (13). In sum, both our morphometric and physiological data are consistent with a greater heterogeneity of the airway response to MCh in immature than in mature rabbit lungs.

Mechanisms for Greater Airway Narrowing

Greater airway narrowing may have occurred in the immature rabbit lungs for any or all of the following reasons: 1) greater force generation by ASM; 2) smaller forces limiting ASM shortening; and 3) thicker airway walls. The results of Tepper et al. (25) suggest that differences in ASM contractility or quantity are unlikely to account for the large differences in airway narrowing in immature and mature rabbit lungs. This previous study also suggested that differences in the forces of interdependence between the airways and the lung parenchyma in immature and mature rabbits may be significant determinants of maturational differences in airway narrowing during bronchoconstriction. Airway closure occurs at higher transpulmonary pressures in immature compared with mature isolated rabbit lungs. In addition, there is a marked difference in the effect of transpulmonary pressure on the response of $R_L$ to MCh challenge in immature and mature rabbits (28). These findings are consistent with the hypothesis that in the immature rabbit lung there is less interdependence between the airways and the lung parenchyma and that this allows greater airway narrowing.

Airway wall geometry can also be a significant determinant of airway narrowing. For the same degree of ASM shortening, airways with thicker walls have greater luminal narrowing (17, 29). In the present study, both the normalized $A_w$ and $A_e$ were greater in the immature animals (Table 3). The airways in our study were frozen and fixed after MCh challenge, and, therefore, it is unclear whether the greater thickness of the airway wall and epithelium was present in the nonconstricted state. Our data do not address potential mechanisms for the greater normalized airway wall thickness, which could include increased collagen matrix, increased edema formation, and/or more mucus and submucosal folding. In humans, preliminary data in nonconstricted airways have suggested that infants have greater airway wall thickness relative to airway size compared with adults (12). In addition, in hamsters, bronchoconstriction produces greater airway wall edema in immature than in mature animals (1). Thus a greater normalized airway wall thickness might also contribute to the maturational differences in airway narrowing during bronchoconstriction observed in our study.

Conclusions

In the present study, MCh challenge resulted in a greater increase in $Raw$ and a greater degree of airway narrowing in immature rabbit lungs than in mature rabbit lungs. There was an excellent correlation between two independent measurements of airway narrowing, $Raw$ and the morphometric assessment of airway caliber. We also observed that the frequency dependence of $R_L$ increased more in immature than in mature rabbit lungs. The data suggest that the greater frequency dependence of $R_L$ in the immature rabbit lung during MCh challenge may be caused by greater airway narrowing and ventilation inhomogeneity. Our results also indicate that maturational differences in $R_L$ response to MCh challenge can be accounted for by differences in airway narrowing. Maturational differences in airway narrowing and airway closure may result from less interdependence between the airways and the lung parenchyma.

Address for reprint requests: R. S. Tepper, J ames Whitcomb Riley Hospital for Children, Dept. of Pediatrics, Pulmonary Section, 702 Barnhill Dr., Indianapolis, IN 46223.

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REFERENCES