Density dependence of forced expiratory flows in healthy infants and toddlers

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Density dependence of forced expiratory flows in healthy infants and toddlers. J. Appl. Physiol. 87(5): 1796–1801, 1999.—In older children and adults, density dependence (DD) of forced expiratory flow is present over the majority of the full flow-volume curve. In healthy subjects, DD occurs because the pressure drop from peripheral to central airways is primarily dependent on turbulence and convective acceleration rather than laminar resistance; however, an increase in peripheral resistance reduces DD. We measured DD of forced expiratory flow in 22 healthy infants to evaluate whether infants have low DD. Full forced expiratory maneuvers were obtained while the subjects breathed room air and then a mixture of 80% helium-20% oxygen. Flows at 50 and 75% of expired forced vital capacity (FVC) were measured, and the ratio of helium-oxygen to air flow was calculated (DD at 50 and 75% FVC). The mean (range) of DD at 50 and 75% FVC was 1.37 (1.22–1.54) and 1.23 (1.02–1.65), respectively, values similar to those reported in older children and adults. There were no significant relationships between DD and age. Our results suggest that infants, compared with older children and adults, have similar DD, a finding that suggests that infants do not have a greater ratio of peripheral-to-central airway resistance.

helium-oxygen; airway resistance; convective acceleration; turbulent and laminar flow; lung growth

IN OLDER CHILDREN AND ADULTS, the relationship between the peripheral and the central airways has been assessed by measuring the change in forced expiratory flows when subjects breathe air, compared with a less-dense gas mixture of 80% helium-20% oxygen. In healthy children and adults, forced expiratory flows are higher over most of the forced vital capacity (FVC) when the less-dense gas mixture is breathed. At 50 and 75% expired FVC, the ranges of the ratio of flows for helium-oxygen to air (density dependence) have been reported as 1.19–1.57 and 1.17–1.48, respectively. Helium is less dense but more viscous than nitrogen. Thus the pressure loss in the airways during forced expiration from turbulent flow and convective acceleration, which are density dependent, will decrease breathing helium, whereas the pressure loss secondary to laminar flow or frictional resistance (density independent, viscosity dependent) will increase. In older children and adults with peripheral airway disease, density dependence is lower than in healthy subjects and approaches 1.0, a finding consistent with increased frictional resistance in the peripheral Airways and less convective acceleration (1, 2, 4–7, 9, 11, 12, 16, 20–22, 25, 27, 29).

Using retrograde catheters in normal lungs obtained at autopsy, Hogg et al. (15) reported that peripheral airway resistance relative to central airway resistance was significantly higher in the first few years of life, compared with older children and adults. A higher ratio of peripheral-to-central airway resistance and a lower ratio of peripheral-to-central cross-sectional area in infants than in older children and adults should result in less convective accelerative and turbulent pressure losses and greater viscous frictional losses in the infants. In contrast to Hogg et al. (15), Hislop et al. (14) suggested from autopsy data that the airway tree of infants is a scaled-down version of the adult airway tree. Redline et al. (26) reported that density dependence at 50% FVC (DD50) increased significantly between 8 and 23 yr of age. A single study has evaluated density dependence in newborn infants (31). The findings of that study suggested that infants have significant density dependence and that infant airways are large relative to their lung volume. In that study, which was limited to newborns, density dependence was assessed from partial flow-volume maneuvers. Because functional residual capacity in the infant, particularly newborns, is dynamically controlled and often elevated, measurements of density dependence by using partial flow-volume curves in this age group are difficult to interpret.

We hypothesized that, if infants have greater peripheral airway resistance relative to central airway resistance, then they should have low-density dependence of forced expiratory flow. In addition, we anticipated that density dependence would increase with increasing age during infancy. Instead of using partial flow-volume maneuvers, we assessed density dependence in the first 2 yr of life using full flow-volume maneuvers. With the use of this newer methodology in infants, flow is referenced to stable volume landmarks and is more readily compared with values obtained from older children and adults.

MATERIALS AND METHODS

Subjects. We evaluated 22 healthy full-term infants and toddlers between the ages of 1.6 and 23.6 mo (9 girls, 13 boys). In five subjects, we repeated measurements 3–8 mo after their initial study to determine whether there were longitudinal changes with growth. The infants had no history of lung disease and had no upper respiratory symptoms for at least 3
Forced expiratory flows. Forced expiratory maneuvers from elevated lung volumes were performed by using the rapid thoracic compression technique as previously described (10). Using this methodology, we have previously demonstrated that flow limitation is achieved in normal subjects. Forced expiratory flows were initiated from a lung volume at which the airway pressure was equal to 30 cmH₂O (V₃₀). Several expiratory flows were initiated from a lung volume at which flow limitation is achieved in normal subjects. Forced expiration was initiated by rapidly inflating the jacket wrapped around the infant’s chest and abdomen. An electronic solenoid valve, which connected the jacket and the pressure reservoir, controlled jacket inflation, whereas jacket pressure was monitored with a differential pressure transducer (MP-45–871, Validyne, Northridge, CA) referenced to atmospheric pressure. The analog signals of flow and pressure were amplified and filtered ≈ 50 Hz (CD 19-A, Validyne) and digitized at 100 samples/s (DT 3001, D/A board, Data Translation). Volume was obtained by digital integration of the flow signal, and the signals were displayed on the computer monitor in real time and stored for subsequent analysis. The pneumotachometer was calibrated with known volumes of room air. Jacket and mouth pressures were calibrated by using a water manometer.

For measurements of forced expiratory flows with a less-dense gas, a certified source of 80% helium-20% oxygen was connected to the inspiratory circuit. The pneumotachometer was calibrated with known volumes of the helium-oxygen gas mixture. The ratio of the calibration factors (helium-oxygen/air) for the group of infants was 0.88, which agrees with the ratio of the viscosities of the two gas mixtures.

Half of the infants received 75 mg/kg of chloral hydrate for sedation and were tested while they were sleeping in a supine position with a face mask placed over the nose and mouth. Forced expiratory maneuvers were initially obtained while the subject was breathing room air. Jacket pressures were increased between 40 and 120 cmH₂O, until maximal flows were obtained over the lower 50% of the lung volume. We assumed that maximal flows had been obtained when increasing the jacket pressure did not lead to a further increase in flow. The helium-oxygen mixture was then connected to the inspiratory circuit, and infants breathed this mixture for a minimum of 2 min before forced maneuvers were initiated. Initial studies with the use of a nitrogen analyzer (Morgan) verified that washout was complete within 2 min. With the subject still breathing the helium-oxygen mixture, forced maneuvers were repeated at increasing jacket pressures until the maximal flows were again obtained over the lower 50% of the lung volume.

Data analysis. FVC was defined as the forced expired volume from V₃₀ to residual volume (RV). The room air and the helium-oxygen flow-volume curves with the highest forced expiratory flows over the lower 50% of the lung volume and with FVCs within 6% of each other were chosen for comparison. The air and the helium-oxygen flow-volume curves were overlaid so that they matched at RV, and the FVC obtained while the subjects breathed air was used as the reference volume. Forced expiratory flows were measured at 50% FVC (FEF₅₀) and 75% FVC (FEF₇₅). The ratio of flows for the helium-oxygen mixture and for air at these two lung volumes was calculated and expressed as the DD₅₀ and density dependence at 75% FVC (DD₇₅). The volume of isoflow (VisoV˙) was defined as the percentage of FVC above RV that the air and the helium-oxygen flow-volume curves crossed during forced expiration.

Statistical analysis was performed by using linear regression equations to assess the relationship of DD₅₀, DD₇₅, and VisoV˙ to measures of age, body length, and FVC. For comparisons among groups, parametric analysis (t-test) was used when the values were normally distributed, and a nonparametric analysis (Mann-Whitney rank sum test) was used when the values were not normally distributed.

RESULTS

Anthropometric data, forced expiratory flows, and FVC are listed for all subjects in Table 1. The group of infants and toddlers had a mean (range) age of 8.5 (1.6–23.6) mo and a mean (range) length of 68.8 (55.8–87.3) cm. There were 13 boys and 9 girls. Eight of the subjects had histories that were positive for maternal smoking during pregnancy, and 11 had a positive family history of asthma. The mean values for FVC, FEF₅₀, and FEF₇₅ were 103, 105, and 112% predicted, respectively. The predicted values were calculated from regression equations of each parameter vs. body length, based on 155 healthy subjects previously evaluated in our laboratories (17).

Forced expiratory flow-volume curves obtained from one of the subjects breathing air and then the helium-oxygen mixture are illustrated in Fig. 1. The general shape of the flow-volume curves in this infant and most of the infants was convex to the volume axis. Over most of the FVC, the forced expiratory flows with the less-dense gas mixture were higher than the flows with air. The two flow-volume curves crossed at a relatively low lung volume (VisoV˙). The individual values of DD₅₀, DD₇₅, and VisoV˙ vs. body length are illustrated in Fig. 2, A, B, and C, respectively. There were no significant relationships between density dependence and body length among these three parameters. The mean (range) of DD₅₀, DD₇₅, and VisoV˙ was 1.37 (1.22–1.54), 1.23 (1.02–1.65), and 11.3% (0–23.6%), respectively, for the 22 subjects. There were also no significant relationships between the parameters for density dependence and age (mo) or FVC (ml). Gender, maternal smoking during pregnancy, and family history of asthma also did not account for any of the intersubject variability in DD₅₀, DD₇₅, or VisoV˙.

There was a significant relationship between DD₅₀ and %FVC (Fig. 3); those infants with larger lungs for their body size had greater increases in FEF₅₀ when breathing helium-oxygen compared with air. There were no significant relationships between %FVC and either DD₅₀ or VisoV˙.

In five subjects, density dependence was assessed longitudinally. The length of time between the two studies ranged from 3 to 8 mo. For these five subjects, there were no significant changes in DD₅₀, DD₇₅, or VisoV˙ between the first and second studies when assessed by paired t-tests.
DISCUSSION

Our study found that healthy infants <2 yr of age have a 30–40% increase in forced expiratory flows in the range of midlung volumes when breathing a helium-oxygen mixture compared with air. In addition, we found that there was no relationship between density dependence and age, length, FVC, or gender in these subjects. The increase in forced expiratory flow that we observed in our infants breathing the less-dense gas mixture is similar to the increase in flow that has been reported in newborn infants with the use of partial flow-volume maneuvers (31) and in older children and adults with the use of full forced expiratory maneuvers (3–5, 7, 8, 11, 16, 18–20, 25, 26, 29, 32, 33). Our findings suggest that the relationship between the resistance of the peripheral to the central airways is similar in infants, older children, and adults.

In our study in infants, density dependence was assessed from forced expiratory maneuvers. Although the methodology for obtaining maximal flows in sleeping infants differs from that used in cooperative older children and adults, our laboratory has previously demonstrated that flow limitation is achieved in healthy infants over the lower 50% of the FVC (10). In our analysis of density dependence, the FVC for the air and the helium-oxygen gas mixture were within 6%, similar to the reproducibility used in older subjects (4, 5, 8, 13, 18, 19, 25, 32). We matched the two forced expiratory maneuvers at RV for comparison of flows and calculation of $\text{VisoV}^\prime$, a method of analysis that is similar to that used in older subjects (1, 7, 8, 13, 16, 26, 29). Rubinstein et al. (28) demonstrated that the magnitude of density dependence was not significantly different whether the curves were matched at RV or total lung capacity. When our analysis was repeated with curves matched at $V_{30}$ instead of RV, there were not significant differences in the calculated parameters of $\text{DD}_{50}$, $\text{DD}_{75}$, and $\text{VisoV}^\prime$. We also estimated the Reynolds number for flow in the central airways of an average 18-mo-old infant using oxygen mixture compared with air. In addition, we found that there was no relationship between density dependence and age, length, FVC, or gender in these subjects. The increase in forced expiratory flow that we observed in our infants breathing the less-dense gas mixture is similar to the increase in flow that has been reported in newborn infants with the use of partial flow-volume maneuvers (31) and in older children and adults with the use of full forced expiratory maneuvers (3–5, 7, 8, 11, 13, 16, 18–20, 25, 26, 29, 32, 33). Our findings suggest that the relationship between the resistance of the peripheral to the central airways is similar in infants, older children, and adults.

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airway diameters of generations 2 and 4 reported by Hislop et al. (14) and our FEF50 data of 800 ml/s. Assuming flow limitation occurred in generation 2 or 4, the calculated Reynolds numbers were 6,685 and 2,785, respectively. These values are comparable to values calculated for similar adult airways (24). Because the Reynolds numbers and the density dependence are similar in the infant and the adult, this suggests that the infant airways are a scaled-down version of the adult airway.

In our infants and toddlers, forced maneuvers were initiated from an airway pressure of 30 cmH2O, which approximates total lung capacity. However, we sometimes observed infants sigh to a lung volume 5–10% greater than V30. Therefore, FEF50 and FEF75 are at a slightly lower fraction of FVC in the infants than in the older children and adults. Because density dependence decreases with decreasing lung volume, our methodology potentially underestimates the magnitude of the density dependence in this age group. With these reservations, we believe that we can interpret and compare our findings of density dependence in infants to those previously reported in older subjects.

In our infants, the measures of density dependence are within the midrange of previously reported values for older children and adults (Table 2) (3–5, 7, 8, 11, 13, 16, 18–20, 25, 26, 29, 32, 33). In addition, density dependence did not change with age or length, nor did it change in the five infants followed longitudinally. Density dependence was higher at higher lung volumes in our infants (DD50: 1.37 ± 0.09 vs. DD75: 1.23 ± 0.18), a finding similar to that reported for healthy older children and adults (Table 2) (3–5, 7, 8, 11, 13, 16, 18–20, 25, 26, 29, 32, 33). The intersubject variabilities of the measures of density dependence (DD50, DD75, and Vdso/V˙) in our infants are also comparable to the values for older children and adults. The similarity of the intersubject variabilities for all of these parameters for the infants and the older children and adults suggests that the variability is related to physiological differences among individuals and not methodological factors. All of the above suggest that the determinants of density dependence in infants are similar to those in older children and adults. The density dependence parameters in our study were not related to gender, maternal smoking during pregnancy, or family history of asthma. These findings are consistent with the studies in older children (26, 30).

We hypothesized that, if the ratio of peripheral-to-central airway resistance was significantly greater in infants than adults, as suggested by Hogg et al. (15),

![Fig. 2. Individual values of DD50 (A), DD75 (B), and Vdso/V˙ (C) vs. body length. There were no significant relationships between the 3 parameters of density dependence and body length. Means (solid lines) and SDs (dashed lines) are shown.](image)

![Fig. 3. Individual values of DD50 vs. FVC (%predicted). There was a significant relationship (r² = 0.26, P < 0.05). Infants with larger lungs for body size had greater density dependence at DD50.](image)
then infants would have very little density dependence and they would have much lower density dependence than older children and adults. Our findings do not support this hypothesis, because the healthy infants in our study had density dependence between 30 and 40%, and \( V_{isoV} \) of 11%, which are values similar to those in older children and adults (Table 2) (1, 2, 4–7, 9, 11, 12, 16, 20–22, 25, 27, 29). In addition, the linear-to-convex shape of the flow-volume curves in our subjects does not support higher peripheral resistance in infancy. Our findings in infants using full flow-volume maneuvers are consistent with the findings of Taussig et al. (31), who assessed density dependence in 11 newborns using partial flow-volume maneuvers. For the newborns, the mean increase in maximal flows at functional residual capacity while breathing the helium-oxygen mixture was 22.6%, which is similar to our DD\(_{75} \) value of 1.23 measured with full forced maneuvers. Our findings are also consistent with the higher lung size-corrected flows and upstream airway conductance measured in intubated infants using the forced deflation technique to generate maximal flows (23).

We did find that infants with proportionately larger lungs had higher density dependence; however, there was no relationship between density dependence and flow. Castile et al. (3) found that adults with smaller central airways, as assessed by lower forced expiratory flows, also had greater density dependence. These observations in both infants and adults support the hypothesis that smaller central airways relative to peripheral airways can result in greater pressure loss from convective acceleration from the large peripheral cross-sectional area to a smaller central cross-sectional area. Fig. 4, modified from Castile et al., illustrates the two different models of central-to-peripheral airways that can produce the observed relationships in adults and infants. For the two adult lungs (Fig. 4A), the lung volumes are the same; however, the lung with the smaller central airway will have greater convective acceleration and greater density dependence. For the two infant lungs (Fig. 4B), the central airway sizes are the same; however, the lung with the larger volume will have greater convective acceleration and greater density dependence. Our infants with larger lungs for their body size could have more peripheral airways and an increased ratio of peripheral-to-central airway cross-sectional area, resulting in greater convective acceleration of gas from the peripheral to the central airways and thus greater density dependence. In our study, we did not find a significant correlation between DD\(_{75} \) and \%FVC or \( V_{isoV} \) and \%FVC. The absence of significant

### Table 2. Summary of repeated values of density dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age, yr</th>
<th>DD(_{50} )</th>
<th>DD(_{75} )</th>
<th>( V_{isoV} ), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>22</td>
<td>&lt;2</td>
<td>1.37 ± 0.09</td>
<td>1.23 ± 0.18</td>
<td>11.3 ± 7.97</td>
</tr>
<tr>
<td>Coates et al. (4)</td>
<td>7</td>
<td>7–10</td>
<td>1.28 ± 0.12</td>
<td>1.24 ± 0.17</td>
<td>8 ± 9</td>
</tr>
<tr>
<td>Landau et al. (20)</td>
<td>52</td>
<td>8–18</td>
<td>1.38 ± 0.16</td>
<td>1.17 ± 0.13</td>
<td>0.35</td>
</tr>
<tr>
<td>Fox et al. (11)</td>
<td>21</td>
<td>8–16</td>
<td>1.47 ± 0.18</td>
<td>1.44 ± 0.25</td>
<td>5 ± 6.30</td>
</tr>
<tr>
<td>Lambert et al. (19)</td>
<td>9</td>
<td>8–13</td>
<td>1.32 ± 0.07</td>
<td>1.17 ± 0.13</td>
<td>5 ± 7.4</td>
</tr>
<tr>
<td>Gurwitz et al. (13)</td>
<td>42</td>
<td>9–15</td>
<td>1.31 ± 0.02</td>
<td>1.20 ± 0.31</td>
<td>4.5 ± 4.0</td>
</tr>
<tr>
<td>Wiesemann and von der Hardt (33)</td>
<td>43</td>
<td>11 ± 2</td>
<td>1.30 ± 0.25</td>
<td>1.20 ± 0.31</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Cooper et al. (5)</td>
<td>20</td>
<td>12 ± 3</td>
<td>1.57 ± 0.13</td>
<td>1.20 ± 0.31</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Prefaut et al. (25)</td>
<td>12</td>
<td>13 ± 1</td>
<td>1.49 ± 0.12</td>
<td>1.48 ± 0.12</td>
<td>3.27 ± 1.24</td>
</tr>
<tr>
<td>Redline et al. (26)</td>
<td>103</td>
<td>15 ± 3</td>
<td>1.49 ± 0.14</td>
<td>1.37 ± 0.18</td>
<td>10 ± 10</td>
</tr>
<tr>
<td>Castile et al. (3)</td>
<td>40</td>
<td>26 ± 4</td>
<td>1.41 ± 0.12</td>
<td>1.35 ± 0.13</td>
<td>8.37 ± 4.76</td>
</tr>
<tr>
<td>Hutchison et al. (16)</td>
<td>18</td>
<td>26 ± 4</td>
<td>1.41 ± 0.17</td>
<td>1.20 ± 0.13</td>
<td>10 ± 3.5</td>
</tr>
<tr>
<td>Doman et al. (7)</td>
<td>66</td>
<td>42 ± 10</td>
<td>1.47 ± 0.27</td>
<td>1.29 ± 0.23</td>
<td>0.5–29 ± 6.88</td>
</tr>
<tr>
<td>Dull and Secker-Walker (8)</td>
<td>64–75</td>
<td>19–30</td>
<td>1.19 ± 0.10</td>
<td>1.20 ± 0.13</td>
<td>15 ± 23.55</td>
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<tr>
<td>Lam et al. (18)</td>
<td>78</td>
<td>35</td>
<td>1.51 ± 0.1*</td>
<td>1.28 ± 0.18</td>
<td>14.9 ± 6.6</td>
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<tr>
<td>Teculescu et al. (32)</td>
<td>41</td>
<td>42 ± 6</td>
<td>1.51 ± 0.14</td>
<td>1.28 ± 0.18</td>
<td>1.24 ± 0.17</td>
</tr>
<tr>
<td>Sixt and Bake (29)</td>
<td>59</td>
<td>41 ± 5</td>
<td>1.41 ± 0.14</td>
<td>1.28 ± 0.18</td>
<td>1.24 ± 0.17</td>
</tr>
</tbody>
</table>

Values are means ± SD or ranges; n, no. of subjects. DD\(_{50} \) and DD\(_{75} \), density dependence at 50 and 75% FVC, respectively; \( V_{isoV} \), volume of isoflow. *Mean ± 1.64 × SE.
correlations for DD75 and VsoV may result from the lower lung volume where these measurements are made. At lower lung volumes, the influence of convective acceleration decreases, and there is a greater influence from laminar flow or frictional resistance.

In summary, we found that healthy infants have a 30–40% increase in forced expiratory flows, in the range of midlun volumes, when breathing a helium-oxygen mixture compared with air. Density dependence does not change with age, length, or FVC during the first 2 yr of life. Because the values of density dependence in healthy infants are similar to those reported in older children and adults, our findings do not support the hypothesis that the ratio of peripheral-to-central airway resistance is significantly greater in infants than in older children and adults.

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