Volumetric Capnography in Children

Influence of Growth on the Alveolar Plateau Slope

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Background: Lung growth in children is associated with dramatic increases in the number and surface area of alveolated Airways. Modelling studies have shown the slope of the alveolar plateau (phase III) is sensitive to the total cross-sectional area of these Airways. Therefore, the influence of age and body size on the phase III slope of the volumetric capnogram was investigated.

Methods: Phase III slope (alveolar dCO₂/dV) and airway deadspace (VDaw) were derived from repeated single-breath carbon dioxide expirograms collected on 44 healthy mechanically ventilated children (aged 5 months–18 yr) undergoing minor surgery. Ventilatory support was standardized (VT = 8.5 and 12.5 ml/kg, f = 8–15 breaths/min, inspiratory time = 1 s, end-tidal partial pressure of carbon dioxide = 30–45 mmHg), and measurements were recorded by computerized integration of output from a heated pneumotachometer and mainstream infrared carbon dioxide analyzer inserted between the endotracheal tube and anesthesia circuit. Experimental data were compared to simulated breath data generated from a numeric pediatric lung model.

Results: An increased VDaw, a smaller VDaw/VT, and flatter phase III slope were found at the larger tidal volume (P < 0.01). Strong relationships were seen at VT = 12.5 ml/kg between airway deadspace and age (R² = 0.77), weight (R² = 0.93), height (R² = 0.78), and body surface area (R² = 0.89). The normalized phase III slopes of infants were markedly steeper than that of adolescents and were reduced at both tidal volumes with increasing age, weight, height, and body surface area. Phase III slopes and VDaw generated from modelled carbon dioxide washout simulations closely matched the experimental data collected in children.


THE volumetric capnogram is a plot of expired carbon dioxide concentration or fraction that, unlike standard time-based capnography, is recorded as a function of expired volume during a single breath. The trace is typically divided into three phases (fig. 1) with the first phase marked by the relatively carbon dioxide-free washout of the proximal conducting airway. Phase II is a transitional portion of the trace characterized by a steep curvilinear upswing as alveolar gas diffuses mouthward and mixes within the conducting airway. Phase III represents gas from the acini or peripheral alveolated airway and is known as the alveolar plateau. This third phase of the volumetric capnogram contains the bulk of expired carbon dioxide and generally features a gradual linear increase in carbon dioxide concentration with respect to exhaled volume.1

Studies of continuously excreted gases have shown that the major factors influencing phase III slope of the volumetric expirogram include tidal volume (VT), re-
LUNG GROWTH AND CAPNOGRAPHY

Fig. 1. A typical volumetric capnogram (open circles) and plot of exhaled carbon dioxide volume versus exhaled volume (open triangles). The midpoint of phase III is defined at 55% of the exhaled carbon dioxide volume with margins at ±20% of the alveolar tidal volume (dotted lines). Airway deadspace (VDair) is determined by the volume intercept of a linear regression performed on the exhaled carbon dioxide volume versus exhaled volume plot (dashed line). (Modified from Neufeld et al.5)

spiratory rate, air-phase molecular diffusivity of the excreted gas, continuing evolution of excreted gas from the mixed venous blood, and the distribution of pulmonary blood flow.2-4 Modelling studies of carbon dioxide washout by Schwartz et al.5 and Neufeld et al.6 have simulated these experimental data by incorporating a source term into the airway convection-diffusion equation for gas evolved from the mixed venous blood. The resulting numeric description of airway gas mixing can be applied to anatomic dimensions from an adult Weibel lung7 to produce a “trumpet-bell” shaped single-pathway model, with the mouth and distal airways represented by the narrow and wide ends of the bell, respectively. The cross-sectional area of this model at airway generation z is proportional to the total airway cross-sectional area at generation z. This model recreates the dynamic longitudinal changes in airway gas concentration gradients during the respiratory cycle and predicts a substantial effect of total acinar airway cross-sectional area on the size of the airway gas convection-diffusion interface, thereby adding another influence on the shape of the expirogram.2,5,8

The dramatic increase in alveolar number characterizing lung growth in healthy children provides an opportunity to examine the effect of this expanding lung morphometry on the shape of the volumetric expirogram. Dunnill estimated a greater than 20-fold increase in the air-tissue interface of the lung between birth and adulthood.9 The magnitude of this increase is due to rapid multiplication of alveolated airways during the first several years of life, followed primarily by growth in size of alveolated structures thereafter.9-12 Growth of both the alveolated airways and associated capillary network will increase the alveolated airway cross-section and theoretically decrease diffusional resistance for carbon dioxide transport, reducing in turn the longitudinal gas concentration gradients in the distal airways. The diminution of these alveolated airway carbon dioxide gradients should be manifested upon exhalation by a flattening of phase III slope of the volumetric capnogram.5

Measurements derived from volumetric capnograms have been reported in infants and children (aged 1 month–11 yr) in whom the lungs were mechanically ventilated and who were undergoing cardiothoracic surgery for congenital heart disease.13,14 Qualitative observations of the carbon dioxide expirogram revealed steeper phase III slopes in children with pulmonary hyperperfusion than in those with normal pulmonary circulation.14 However, these studies lack precise control of ventilation and were not designed to accurately compare the volumetric capnograms of individuals or detect any maturational effects on phase III slope.

We hypothesized, based on prior studies of the single-pathway model, that lung growth would influence the magnitude of the phase III slope. Therefore, we collected volumetric capnograms from healthy (without cardiac or pulmonary disease) children of differing ages, weights, and heights in whom the lungs were mechanically ventilated and who were anesthetized for minor elective surgery. Additionally, breath simulations were conducted on a pediatric single-pathway lung model created by scaled reduction of a Weibel adult acinar model according to airway dimensions published by Phalen et al.15 We predicted that younger children with a smaller total acinar airway cross-section would have steeper phase III slopes than older children, and that these slopes would approach those of normal adults during late childhood in both experimental and simulation studies.

Methods and Materials

Patient Selection

Forty-four ASA physical status 1 or 2 infants, children, and adolescents without evidence of cardiorespiratory
dysfunction and undergoing elective surgery at The Children’s Hospital of Philadelphia were studied in accordance with an Institutional Review Board-approved protocol. Weight and height were measured on all patients, and body surface area was calculated according to the formula of DuBois and DuBois.16

Anesthesia and Ventilation
Anesthesia was maintained after either intravenous (propofol) or inhalation induction (halothane in nitrous oxide and oxygen) with 1.0–1.3 MAC halothane in oxygen and intravenous fentanyl (2–5 μg/kg) or morphine (0.1 mg/kg). Regional nerve blocks were employed during urologic cases (hypospadias repair, orchiopexy, hydrocele, circumcision), and nondepolarizing muscle relaxants were used uniformly. Uncuffed endotracheal tubes were placed in patients younger than 8 yr of age; inspiratory leaks were measured and occurred between 15 and 40 cmH₂O.

Mechanical ventilation (model 7800 ventilator, Ohmeda, Madison, WI) was performed through a standard circle absorber breathing circuit. Volumetric capnograms were recorded during steady-state conditions at two tidal volumes, 8.5 and 12.5 ml/kg, with an inspiratory time of 1 s. Respiratory frequencies were adjusted between 8 and 15 breaths/min to maintain end-tidal partial pressure of carbon dioxide (PETCO₂) of 30–45 mmHg. At least seven breaths within 1 ml/kg of the target expired volume were collected and the respiratory data averaged for each tidal volume. No end-inspiratory pause, positive end-expiratory pressure, or humidification of the circuit were employed during the data collection.

Respiratory Measurements
Volumetric capnograms and derived respiratory measurements were collected using a modification of a previously described computerized system.3,4 The system consisted of a mainstream infrared carbon dioxide analyzer (model 47210A, Hewlett-Packard, Palo Alto, CA) coupled with a heated screen pneumotachometer (pediatric model 3500 (<8 yr) or adult model 3700 (≥8 yr), Hans Rudolph, Kansas City, MO) and differential pressure transducer (Validyne model MP45-871, Northridge, CA). The combined deadspace of the carbon dioxide analyzer cell (neonatal model 14363A or adult model 14365A, Hewlett-Packard) and pneumotachometer equaled 6 ml for children younger than 2 yr, 19 ml for children aged 2–8 yr, and 35 ml for children older than 8 yr. Apparatus deadspace as a percentage of exhaled volume at VT = 12.5 ml/kg ranged from 3% to 12% and from 5% to 17% at VT = 8.5 ml/kg. The outputs from the infrared carbon dioxide analyzer and pressure transducer were passed through a pair of conditioning amplifiers to produce an analog output of ±5 V at full scale. The analog signals then passed to an analog-to-digital converter (Metabyte DAS8) installed in a personal computer (386 CPU, 20 MHz). The signal delay time between the adjacent infrared carbon dioxide analyzer and pneumotachometer was measured (140 ms) by generation of a square carbon dioxide waveform within a sample circuit and the infrared carbon dioxide signal aligned with the flow signal by the system software.

The nitrous oxide administered during induction was measured in exhaled breaths by mass spectrometry, and respiratory measurements began when nitrous oxide was <2%. Steady-state conditions of gas exchange, as estimated by PETCO₂ after 30–50 breaths, were achieved at each tidal volume before collecting data. Continuous acquisition of volume-based capnograms allowed the measurement and calculation of the following: inspired and expired tidal volume (V'TI and V'TE, ml), expired tidal volume per kilogram (V'TE/kg, ml/kg), respiratory rate (breaths/min), fraction of carbon dioxide in expired gas, fraction of carbon dioxide in mixed-expired gas, and PETCO₂ (mmHg). Airway or Fowler deadspace (VDair, ml), airway deadspace fraction (VDair/V'TI, %), and alveolar tidal volume (V'Talm, ml) were calculated by the method of Langley et al.17 using regression analysis on the plot of exhaled carbon dioxide volume versus exhaled volume (fig. 1).

Phase III slopes (alveolar dCO₂/dV, %/l) were quantified by first defining this phase over a fixed range of the fraction of carbon dioxide in expired gas versus expired volume plot. The midpoint of phase III for our study was defined at the volume where 55% of the expired carbon dioxide had been exhaled with the margins of phase III established at volume points ± 20% V'Talm from this midpoint (fig. 1). The definition of phase III was modified from our previously published work because of the smaller respiratory volumes of infants compared to adults3,5 or goats4 and to exclude regions of prominent cardiac oscillations at the termination of phase III. Visual inspection of cursors placed at these volume points on each expirogram ensured the exclusion of phase II or end-tidal cardiogenic oscillations from the phase III defined region. The raw phase III slopes of individual breaths (expressed as fraction/liter) derived by linear regression with respect to volume
were normalized (expressed as 1⁻¹) by dividing each slope by the corresponding fraction of carbon dioxide in mixed-expired gas, allowing comparison of breaths with differing rates of carbon dioxide excretion.

**Modelling Studies**

Based on the work of Scherer and colleagues,²⁻⁶,⁸ a series of numeric pediatric lung models were created, with anatomic geometries calculated for ages 1, 2, 4, 6, 8, 12, and 18 yr. Each model was assumed to have 23 generations of symmetric airways, the first 16 representing the conducting airways and generations 17–23 the acinar airways, as in the adult Weibel lung.⁷ The dimensions for generations 1–15 were taken from measurements of cast pediatric airway specimens by Phalen et al.¹⁵ Acinar generations were created in two steps. First, Weibel's adult 4,800-ml lung at total lung capacity was scaled to a 2,500-ml functional residual capacity (FRC) characteristic of a normal 70-kg adult.⁵ A constant scaling factor was applied to all acinar airway lengths and diameters such that the 15th scaled Weibel generation matched the measurements for generation 15 reported by Phalen et al. Airway cross-sections and volumes were calculated assuming tubular structure with circular cross-sections and fully dichotomous branching. Alveolar volume was calculated by subtracting total airway volume from published values for FRC at the given ages.¹⁸,¹⁹

A symmetric single-path trumpet-bell model of airway gas convection and diffusion²⁻⁵ was constructed to simulate carbon dioxide washout at VTₑ of 8.5 and 12.5 ml/kg. Normalized phase III slopes and VDₑ were calculated from the simulated carbon dioxide expirograms. This single-path model incorporates several assumptions regarding airway volumes and carbon dioxide concentration. First, the conducting airway volume is held constant, but adjustments are made in each breath for the average expansion caused by the tidal volume inhalation. Inspiration and expiration of tidal volumes occur through the expansion/contraction of alveolar volume. Second, the degree of acinar airway asymmetry is small relative to the magnitude of total acinar airway length or volume. Third, the average airway carbon dioxide concentration at a given cumulative volume in the actual lung is well approximated by the carbon dioxide concentration at the same cumulative volume in the single-path model.⁵

**Statistical Methodology**

Data relating tidal volume to airway deadspace, deadspace fraction, and phase III slope were compared using a paired t test (P < 0.05 indicative of statistical significance). Linear regression analysis was used to examine the effects of age, weight, height, and body surface area on airway deadspace. Data relating normalized phase III slope to age, weight, height, and body surface area were fitted to quadratic functions utilizing multiple regression analysis. The proportion of variability of phase III slope or airway deadspace explained by the regressions is presented as the coefficient of determination (R²).

**Results**

The patients ranged in age from 5 months to 17 yr. Weight, height, and body surface area ranged from 8.1–103.3 kg, 62–185 cm, and 0.35–2.27 m², respectively. An average of 24 ± 10 (mean ± SD) volume-based capnograms were analyzed at both tidal volumes for each patient. Actual measurements of exhaled tidal volume ranged from 8.3–9.1 ml/kg with a mean value of 8.7 ± 0.2 ml/kg at the target VTₑ of 8.5 ml/kg. Exhaled tidal volumes at the target VTₑ of 12.5 ml/kg ranged from 12.0–13.1 with a mean value of 12.7 ± 0.2 ml/kg.

**Effect of Tidal Volume, Age, and Body Size on Phase III Slope**

Normalized phase III slopes were positively sloping at both tidal volumes in all patients studied but decreased (flattened) at the larger tidal volume (P < 0.01). Relatively steep slopes were characteristic of infancy and flattened with increasing age, weight, height, and body surface area at both tidal volumes studied. In comparing the youngest to oldest subject, the normalized slope decreased from 3.63 to 0.22 l⁻¹ at VTₑ of 8.5 ml/kg and from 2.40 to 0.13 l⁻¹ at VTₑ of 12.5 ml/kg. There was greater variability among values for phase III slope at VTₑ of 8.5 ml/kg compared to 12.5 ml/kg. Figure 2 shows the relationship of normalized phase III slope to age, height, body surface area, and weight at both tidal volumes. The multiple regression analysis for these relationships is reported in table 1.

Normalized phase III slopes have been quantified by volumetric capnography in healthy adults during spontaneous ventilation.³ Spontaneously ventilating healthy adults had slopes of 0.22 ± 0.05 l⁻¹ for breaths with exhaled tidal volumes between 11.5–13.5 ml/kg. The normalized phase III slopes in children be-

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between the ages of 14 and 16 yr whose lungs were mechanically ventilated approximate the slopes in these adults (fig. 2A).

Effect of Lung Dimensions on the Phase III Slope in the Modelled Pediatric Lung

The slopes generated by the single-path model for children of different ages at $V_{Tn}$ of 8.5 and 12.5 ml/kg produced curvilinear plots of phase III versus age that paralleled trends seen in the experimental data (fig. 3). Observed phase III slopes tended to be somewhat higher than data derived from the model. Phase III of the simulated volumetric capnogram was positively sloping at all ages studied and both tidal volumes; flattening was noted at the larger tidal volume. Slopes were also steep in infancy and flattened with age to approximate, between the ages of 12 and 18 yr, the values seen in spontaneously ventilating healthy adults.  

Effect of Tidal Volume on Airway Deadspace

$VD_{aw}$ increased during mechanical ventilation at larger tidal volumes ($V_{Tn} = 12.5$ ml/kg vs. 8.5 ml/kg) in every patient studied (fig. 4). The increase ranged from 1.1 to 25.7 ml ($P < 0.01$). $VD_{aw}/V_{T}$ conversely decreased at the larger tidal volume ($P < 0.01$). Measurements of $VD_{aw}/V_{T}$ averaged 14.0 ± 3.3% at $V_{Tn}$ of 8.5 ml/kg and 12.5 ± 2.3% at $V_{Tn}$ of 12.5 ml/kg.

Effect of Age and Body Size on Airway Deadspace

There was a positive correlation between age and $VD_{aw}$ with strong relationships at the 8.5 and 12.5 ml/kg tidal volumes ($R^2 = 0.72$ and 0.77, respectively). Similar correlations were seen in the regression analysis of $VD_{aw}$ as a function of body size (table 2). Figure 4 demonstrates the relationships between $VD_{aw}$ and age, height, body surface area, and weight. The trend for $VD_{aw}$ derived from simulated carbon dioxide washouts plotted as a function of age paralleled the observed patient data (fig. 5). Measurements of $VD_{aw}/V_{T}$ were relatively constant at both tidal volumes; no correlation

Table 1. Multiple Regression Analysis of Normalized Phase III Slope (y) as a Function of Age, Length, Body Surface Area, and Weight at $V_{Tn} = 8.5$ ml/kg and 12.5 ml/kg

<table>
<thead>
<tr>
<th>Tidal Volume (ml/kg)</th>
<th>Regression</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.5</td>
<td>$y = 2.15 - 0.021x + 6.36E^{-5}x^2$</td>
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</tr>
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<td>12.5</td>
<td>$y = 1.78 - 0.018x + 5.53E^{-5}x^2$</td>
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<td>Length (cm)</td>
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<td></td>
</tr>
<tr>
<td>8.5</td>
<td>$y = 5.30 - 0.58x + 1.66E^{-4}x^2$</td>
<td>0.78</td>
</tr>
<tr>
<td>12.5</td>
<td>$y = 4.49 - 0.05x + 1.47E^{-4}x^2$</td>
<td>0.92</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
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<td></td>
</tr>
<tr>
<td>8.5</td>
<td>$y = 3.11 - 3.27x + 0.95x^2$</td>
<td>0.74</td>
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<td>12.5</td>
<td>$y = 2.58 - 2.75x + 0.81x^2$</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>8.5</td>
<td>$y = 2.32 - 0.61x + 4.30E^{-4}x^2$</td>
<td>0.67</td>
</tr>
<tr>
<td>12.5</td>
<td>$y = 1.90 - 0.51x + 3.55E^{-4}x^2$</td>
<td>0.77</td>
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exist between deadspace fraction and age, weight, height, or body surface area.

Discussion

Several theories have been offered to explain the shallow upward sloping alveolar plateau observed in normal individuals during inert gas or carbon dioxide washout studies. The current data are most consistent with the concept of stratified inhomogeneity, which attributes the longitudinal gas concentration gradients within the airway to interactions between gas convection and molecular diffusion, airway geometry and evolution of gas from the blood. Sequential emptying of well-mixed parallel lung regions with decreasing V/Q ratios, diffusive pendelluft, and the continuing evolution of carbon dioxide during exhalation are other explanations for the phenomenon. The concept of sequential emptying, however, underemphasizes the predominance of gaseous diffusion (rather than convection) beyond airway generation 17 and fails to explain the normally positive phase III slopes of both carbon dioxide and nitrogen, gases with concentration gradients from lung base to apex that are inversely related. Diffusive pendelluft involves the consideration of airway geometry and gaseous diffusion but not the impact of blood flow distribution and continuous carbon dioxide evolution on the alveolar plateau. Finally, the continuing evolution of carbon dioxide, though contributory to phase III slopes for carbon dioxide, is insufficient to completely account for the observed slopes.

The single-path model provides a conceptual framework for applying the theory of stratified inhomogeneity to the effect of lung growth on phase III. According to this paradigm, the phase III slope quantifies the longitudinal gas gradient within the acinar airway formed by evolution of carbon dioxide from the mixed venous blood into the FRC gas and then diffusive flux from the FRC across the moving Vt-FRC interface. The magnitude of flux is influenced by the interfacial area between Vt and FRC, the gas diffusivity, rate of evolution, and the alveolar blood flow distribution. Fick’s first law of diffusion defines the instantaneous diffusional flux (of CO₂) \( J \) across an airway cross-section as:

\[
\frac{J}{D} = A \times \frac{d_{CO₂}}{dx}
\]

where \( D \) represents the gas-phase molecular diffusivity of carbon dioxide in air and \( d_{CO₂}/dx \) the axial airway gas concentration gradient for carbon dioxide. When \( J \) and \( D \) are constant, \( d_{CO₂}/dx \) varies inversely with total cross-sectional area of the acinar airway and thus flattens with increases in acinar airway cross-section. Accordingly, the single-path model predicts a flattening of phase III, manifesting a diminution of these longitudinal concentration gradients, with larger tidal volumes, age, and body size due to an increased acinar airway cross-section.

With the understanding offered by this model, we examined the effect of lung growth during childhood on both simulated carbon dioxide washout curves and experimentally measured volumetric capnograms. No prior studies have reported the effect of age on the volumetric capnogram in children. In adults, Hoffbrand measured the rise of exhaled carbon dioxide concentration from 0.75 to 1.25 l exhaled volume as a quantitative test of ventilation-perfusion imbalance and noted an increase in this “capnogram slope” in patients older than 50 yr. In studies of children with congenital heart disease, Fletcher et al. reported steeper phase III slopes among those with pulmonary hyperperfusion than those with normal pulmonary blood flow. Pulmonary hyperperfusion may steepen phase III slopes through a reduction in airway cross-
section as engorged pulmonary veins compete for space with small airways. Several important differences emerge between the present methodology and that of previous studies. First, the standardization of tidal volume and inspiratory time in this study reduces the variation in intersubject ventilatory support that would otherwise influence the $V_E/FRC$ interface area and expiratory waveform. Second, by using mean phase III fractional concentration of carbon dioxide rather than fraction of carbon dioxide in mixed-expired gas in the denominator of the phase III slope index, Fletcher et al. could normalize only for minute ventilation but not for the inter- or intrasubject differences in carbon dioxide production. Finally, by grouping individuals ranging in age from 0.1 to 11.0 yr for comparison of phase III slopes, Fletcher et al. were unable to detect the effects of changes in the alveolated airway cross-section that occur throughout childhood.

Morphologic studies substantiate that, while FRC remains constant relative to body weight, abundant postnatal alveolar growth occurs resulting in a geometric increase in alveolated airway cross-section. However, no consensus exists on when alveolar multiplication stops and adult proportions are reached, the latter varying in one study from 212 to 605 million alveoli. Dunnill reported an increase in alveolar number from 24 to 296 million during the first 8 yr of life associated with a 26-fold augmentation of the air-tissue interface. Using radial alveolar counts of the terminal respiratory unit, Emery and Mithal noted a steady increase in alveolar number through 12 yr. Davies and Reid documented an increase of 17–336 million alveoli between birth and 11 yr but noted the majority of alveolar multiplication during the first 3 yr, after which growth occurred primarily in alveolar size. Others have described a similar pattern of lung growth. The initial rise in alveolar number parallels the rapid increase in alveolar and body surface area and is followed through adolescence by a 30% increase in alveolar linear dimensions and a doubling of alveolar volume. Details of alveolar and, to a lesser extent, pulmonary capillary development have been described elsewhere.

<table>
<thead>
<tr>
<th>Table 2. Linear Regression Analysis of Airway Deadspace.</th>
<th>Tidal Volume (ml/kg)</th>
<th>Regression</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>8.5</td>
<td>y = 0.38x + 4.36</td>
<td>0.72</td>
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<td></td>
<td>12.5</td>
<td>y = 0.48x + 6.09</td>
<td>0.77</td>
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<td>Length (cm)</td>
<td>8.5</td>
<td>y = 0.66x - 42.42</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>y = 0.85x - 54.39</td>
<td>0.78</td>
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<tr>
<td>Body surface area (m$^2$)</td>
<td>8.5</td>
<td>y = 51.89x - 14.61</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>y = 66.27x - 17.94</td>
<td>0.89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.5</td>
<td>y = 1.25x - 1.66</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>y = 1.58x - 0.92</td>
<td>0.93</td>
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</tbody>
</table>

Fig. 4. Airway deadspace ($VD_{aw}$) as a function of (A) age, (B) height, (C) body surface area, and (D) weight at $V_{IT} = 8.5$ ml/kg (closed circles) and 12.5 ml/kg (open circles).
The inverse curvilinear relationship between age and body size and the normalized phase III slope (fig. 2) may be related to the aforementioned changes in lung morphometry. This is supported by the experimental control of inspired gas composition, respiratory rate, inspiratory time, and the assumption of a relatively normal distribution of blood volumes, cardiac indexes, and pulmonary blood flow among our patients.\(^5,\)\(^6\) Additionally, the flattening of phase III could be reproduced solely by morphometric adjustments to our pediatric lung model (fig. 3). Little data exists regarding the normalized phase III slopes of mechanically ventilated adults\(^30\); however, both actual and modelled phase III slopes in this study decreased with age to approximate that of healthy spontaneously ventilating adults\(^3\) during midadolescence.

Figure 2 also demonstrates that a 50% increase in \(V_T\) tends to decrease the slope of phase III in most patients. Fletcher and Jonson\(^31\) noted a greater than 20% decrease in phase III slope in adults with an average increase in \(V_T\) of 66%. They reasoned that the larger tidal volume was associated with a longer time for gas distribution, which allowed greater gas mixing and, therefore, smaller differences in gas concentration between sequentially emptying lung units. We deliberately fixed the inspiratory time during our manipulations of \(V_T\) and preserved a physiologic \(P_{ETCO_2}\) through small adjustments in respiratory frequency. Changes in minute ventilation as a result of altering respiratory rate affect \(P_{ETCO_2}\) but, within this range, would be expected to minimally affect the normalized phase III slope.\(^5\) With a constant time for gas distribution, our data suggests that diffusion within the acinus, modified by the magnitude of the \(V_T:\)FRC interface, explains the relationship between phase III slope and \(V_T\). A similar relationship between \(V_T\) and phase III slope was seen during carbon dioxide washout simulations using the single-path lung model (fig. 3).

Age-related changes in the phase III slope may reflect growth of the alveolated airway cross-section, systematic variation in the effective alveolar tidal volume, or both. We performed respiratory deadspace measurements to demonstrate consistent alveolar tidal volume fractions (\(V_{Talv}/V_T\)) at all ages studied and support the role of growth in the observed changes of the phase III slope. \(V_{Dsw}\) was positively correlated with exhaled tidal volume (\(V_{TE}\)), as previously reported, and relates to the anatomic expansion of conducting airways with greater \(V_T,\)\(^5,\)\(^2\) \(V_{Dsw}\) also is influenced by somatic growth, as reflected in figure 4 by the positive correlations with age, height, weight, and body surface area.\(^4,\)\(^51,\)\(^33\) The measurements for \(V_{Dsw}\) in our patients approximate those generated by simulation of carbon dioxide washout (fig. 5) and those reported in children whose lungs were mechanically ventilated.\(^4,\)\(^34\) Our values for \(V_{Dsw}/V_T\) were smaller than the 0.25–0.29 determined by analysis of exhaled carbon dioxide in spontaneously ventilated children and decreased further at larger tidal volumes.\(^35,\)\(^37\) These findings are consistent with those of Fletcher and Jonson\(^31\) and may reflect positive pressure ventilation with larger tidal volumes that cause greater ventilation of dependent lung units.

There was no significant change in \(V_{Dsw}/V_T\), or by definition \(V_{Talv}/V_T\), as a function of age or body size in this study. Therefore, we have assumed little interpatient variation in the \(V_{Talv}/FRC\) fraction because strong linear relationships between FRC and body size exist throughout the age range studied.\(^18\) This assumption, combined with the observations of Fletcher et al.\(^38\) that the alveolar deadspace fraction is consistently small (0.05 ± 0.03) in healthy children, supports the concept that the effective tidal volume, when indexed for body size, was relatively consistent among our patients. Therefore, flattening of the phase III slope with age/body size is related to the morphometric changes ac-
accompanying lung growth that increases the gas-exchanging cross-section within the FRC, and not an inadvertent systematic increase in alveolar ventilation.

Several assumptions have been incorporated into this study that may affect the interpretation of the results. We presumed the effect of anesthesia on lung volumes would be uniform across the age range studied. However, the reduction in FRC accompanying anesthesia, particularly in the absence of positive end-expiratory pressure, may predispose smaller airways of the youngest patients to collapse more readily than in the older patients studied. This phenomenon could cause an increase in $V_{D_{av}}$, a smaller effective $V_T$:FRC interface, and steeper phase III slopes for the youngest children. Analysis of data from Fletcher et al., however, revealed no such correlation between age and measurements of $V_{D_{av}}/V_{T_{alve}}$ among children with normal pulmonary circulation. The observation that the measured phase III slopes tended to be greater than predicted by simulation, regardless of patient size, suggests that anesthesia and neuromuscular blockade may have caused a generalized decrease in FRC among our patients.

Tremendous development of the alveolated airways occurs during childhood. When the morphometric description of this growth is considered in a model of gas exchange, the importance of an expanding acinar cross-sectional area, where diffusion is the dominant mechanism of gas transport, becomes evident. The resulting decrease in diffusional resistance within the alveolated airways during lung growth will decrease the gradient for evolved gases within those airways and decrease the phase III slope. Our observations of the phase III slope in patients support this hypothesis.

References