Computational fluid dynamics endpoints to characterize obstructive sleep apnea syndrome in children

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Wootton DM, Luo H, Persak SC, Sin S, McDonough JM, Isasi CR, Arens R. Computational fluid dynamics endpoints to characterize obstructive sleep apnea syndrome in children. J Appl Physiol 116: 104–112, 2014. First published November 21, 2013; doi:10.1152/japplphysiol.00746.2013.—Computational fluid dynamics (CFD) analysis may quantify the severity of anatomical airway restriction in obstructive sleep apnea syndrome (OSAS) better than anatomical measurements alone. However, optimal CFD model endpoints to characterize or assess OSAS have not been determined. To model upper airway fluid dynamics using CFD and investigate the strength of correlation between various CFD endpoints, anatomical endpoints, and OSAS severity, in obese children with OSAS and controls. CFD models derived from magnetic resonance images were solved at subject-specific peak tidal inspiratory flow; pressure at the choanae was set by nasal resistance. Model endpoints included airway wall minimum pressure ($P_{\text{wall min}}$), flow resistance in the pharynx ($R_{\text{pharynx}}$), and pressure drop from choanae to a minimum cross section where tonsils and adenoids constrict the pharynx ($dP/T_{\text{max}}$). Significance of endpoints was analyzed using paired comparisons (t-test or Wilcoxon signed rank test) and Spearman correlation. Fifteen subject pairs were analyzed. $R_{\text{pharynx}}$ and $dP/T_{\text{max}}$ were higher in OSAS than control and most significantly correlated to obstructive apnea-hypopnea index (oAHI), $r = 0.48$ and $r = 0.49$, respectively ($P < 0.01$). Airway minimum cross-sectional correlation to oAHI was weaker ($r = -0.39$); $P_{\text{wall min}}$ was not significantly correlated. CFD model endpoints based on pressure drops in the pharynx were more closely associated with the presence and severity of OSAS than pressures including nasal resistance, or anatomical endpoints. This study supports the usefulness of CFD to characterize anatomical restriction of the pharynx and as an additional tool to evaluate subjects with OSAS.

human; nasal resistance; pharynx; pressure; airway

Obstructive Sleep Apnea Syndrome (OSAS) is characterized by narrowing of the pharyngeal airway that results in repeated episodes of airflow limitation, complete airflow cessation, oxygen desaturation, and sleep disruption (29). OSAS affects as many as 1–4% of normal children (16) and up to 50% of obese children (14, 17, 28), and obesity measured by body mass index (BMI) increases the risk for OSAS in children (16). Several upper airway anatomic variables correlate with OSAS in children: magnetic resonance imaging (MRI) studies of the upper airway show that children with OSAS frequently have a structurally narrowed pharynx (1, 3) located in the “overlap region,” where the tonsils, soft palate, and adenoids overlap (2, 12). A recent study comparing obese children with OSAS to BMI z-score-matched control subjects found that children with OSAS had a smaller oropharynx, larger adenoid, tonsils, and retropharyngeal nodes, as well as larger parapharyngeal fat pads (5), suggesting that upper airway narrowing and adverse pharyngeal mechanics play an important role in OSAS independent of obesity. The recurrence of OSAS after adenotonsillectomy surgery in obese children has been reported to be 54–76% (21, 22, 30, 31), and reductions in apnea-hypopnea index (AHI) after adenotonsillectomy correlate strongly to postsurgical reduction in tonsil and adenoid volume (24), further emphasizing the importance of anatomical restriction in OSAS.

Recent fluid mechanics studies of the static upper airway of both children and adults reported on the effects of anatomical shape, especially airway restriction, on airflow resistance. Computational fluid dynamics (CFD) based on static MR images obtained during tidal breathing was used to compare internal pressure loads and flow resistances in the upper airways of sedated children aged 3 to 7 with OSAS and matched controls (35); the models showed higher flow resistance and lower airway wall pressure in the pharynx of children with OSAS, compared with the pharynx in control subjects, and compared with the nasal passages in both subject groups. CFD-derived variables were correlated to OSAS severity as measured by AHI in an unselected group of adults with OSAS; significant correlation to AHI was found with several variables, including minimum cross-sectional area and pharyngeal flow resistance (32). The effects of adenotonsillectomy (20) or adenoidectomy alone (33) on airway pressure drop and flow resistance have been assessed by CFD modeling based on presurgical and postsurgical MR or CT imaging, in small pilot studies, where statistical testing was not possible. Changes in airway flow resistance estimated by CFD have also been statistically correlated to the clinical outcome of mandibular advancement devices, based on CT imaging (9) or MRI (37) before and after device placement. Very strong correlations can be observed when CFD endpoints and clinical parameters are normalized by presurgical values. These and other studies show the potential for CFD to quantify clinically significant flow- and pressure-related effects of anatomical narrowing and perhaps serve as guides for treatment.

The current study focuses on the relationships between CFD-derived endpoints and OSAS specifically in obese chil-
dren. CFD based on anatomical MR imaging and measured flow waveforms in awake, obese subjects was used to quantify flow variables that may be related to risk or severity of obstructive sleep apnea. Several endpoints that quantify the effect of local airway anatomical restriction in the pharynx are compared with endpoints that quantify the internal pressure loads and account for nasal flow resistance. Comparing endpoints between subjects with OSAS and controls, and comparing the strength and significance of correlations between CFD endpoints and polysomnography endpoints could provide additional insight about the interaction of anatomy, mechanical properties, and pathophysiology of OSAS in these subjects.

METHODS

Subjects from an anatomical study of airway structure, body fat composition, and OSAS in obese children (5) were further analyzed using CFD. The study was approved by the Committee of Clinical Investigations at Albert Einstein College of Medicine (Bronx, NY). Informed consent was obtained from each subject and/or parent. All subjects underwent overnight polysomnography scored by standard criteria; sleep-disordered breathing events were classified as obstructive apneas (zero flow without respiratory effort), and hypopneas (flow limitation $\geq 50\%$ and arousal, awakening, or oxygen desaturation $\geq 3\%$) (13), and aggregated as apnea-hypopnea index (AHI is the total number of apneas and hypopneas per hour) and obstructive AHI ($o$AHI is the number of obstructive apneas and hypopneas per hour). Subjects were diagnosed with OSAS based primarily on obstructive apnea index (OAI $\geq 1$ event/h) or apnea-hypopnea index (AHI $\geq 5$ events/h). An upper airway MRI study was performed in the Department of Radiology at the Children’s Hospital at Montefiore (5) using a 16-channel Philips 3.0-Tesla Achieva Quasar TX scanner (Philips Medical Systems, Best, Eindhoven, Netherlands). Subjects were awake and relaxed with mouth closed during imaging. Immediately prior to imaging, resting nasal tidal breathing waveforms were recorded in the supine position using a pneumotachometer (Hans Rudolf). Bilateral nasal flow resistance curves were recorded (3 times for each nasal passage) using an anterior rhinomanometer (NR-6; GM Instruments, Kilwinning, Scotland) with 150-Pa threshold (8). Segmentation. CFD model meshing was performed using methods previously described (25, 35). CFD model airway geometry was defined by segmenting axial image stacks (0.5 mm $\times$ 0.5 mm $\times$ 3.3 mm) using commercial software (Micromics and 3-Matic, Materialise, Plymouth, MI). The airway was segmented primarily on the basis of image intensity with the threshold set midway between the soft tissue and clear airway value. Manual editing and automated volume-preserving smoothing during reconstruction were used to minimize the effects of noise and stair-step artifacts due to coarser axial image spacing. The surface mesh was exported to commercial CFD preprocessing software (Gambit, ANSYS) for tetrahedral volume meshing; typical volume edge lengths were 300–400 $\mu$m, based on a grid convergence study (see APPENDIX).

Modeling. Recorded flow waveforms from at least 10 normal tidal breaths were averaged for each subject, and peak inspiratory flow was computed. Airway velocity and pressure fields at peak inspiratory flow were computed using commercial software ( Fluent 14, ANSYS) with a low Reynolds number k-ω turbulence model (34). Air was assumed incompressible because of the low variations in absolute pressure: density $= 1.127$ kg/m$^3$ and viscosity $= 1.87 \times 10^{-5}$ kg/m$^s$. The flow rate was imposed by uniform velocity at the tracheal exit boundary; the nasal boundary conditions were uniform stagnation pressure with 5% turbulence intensity. Although the boundary conditions are steady in time, an unsteady solver with 0.1-ms time step was used in cases where vortex shedding causes an unsteady flow field; the time step sensitivity study is given in the APPENDIX.

The CFD methods have been verified by comparing wall pressure distributions to published experimental measurements of steady flow through an asymmetric 89% area reduction stenosis at a Reynolds number of 900 based on inlet conditions (36). The pressure distributions computed along the airway wall have been validated by in vitro steady and unsteady flow experiments, in an anatomical model of a child’s airway (35). The methods were further validated in vivo in a normal adult volunteer, who underwent posterior rhinomanometry study simultaneously measuring flow rate and oral cavity pressure during nasal breathing (Fig. 1), followed immediately by MR imaging. A CFD model was segmented from the MR image set and the pressure field simulated at flow rates of 0, 200, 400, and 600 mL/s. The pressure flow curve of the pneumotachometer was measured and used to set the nasal pressure boundary condition. The CFD pressure predictions agreed very well with the measurements and were well within the scatter of the experimental data (Fig. 1). Similar CFD methods employing the k-ω turbulence model have been verified by several independent research groups using in vitro models (23, 37); the pressure accuracy is comparable to large eddy simulation models under these flow conditions (23).

For this study, although the nasal passages were included in the modeling domain, pressure at the choanae was set using rhinomanometer nasal resistance Rohrer coefficients, at the average peak inspiratory flow rate.

CFD model endpoints. Our underlying hypothesis is that anatomical abnormalities resulting in airway narrowing may contribute to the risk and severity of OSAS, by decreasing the maximum inspiratory flow rate and by creating increased negative (collapsing) pressure on the nasal surface leading to obstructive apneas and hypopneas. There is some evidence (9) that fluid mechanical parameters, particularly related to pressure drop within the pharyngeal airway, are related to severity of obstructive sleep apnea, so several anatomical and flow model endpoints related to airway wall pressure and flow resistance were defined (see Fig. 2). After identifying the choanae, a tracheal outlet cross section, and the region where tonsils, soft palate, and adenoids constrict the pharynx, the minimum cross section in the region constriicted by tonsils and adenoids was identified ($A_{min}$), and the minimum cross-sectional radius and hydraulic diameter at this cross section were calculated. Area-averaged pressures were computed at each cross section, and the pharyngeal flow resistance ($RP_{pharynx}$ was calculated by dividing the pressure drop from choanae to trachea by the flow rate. The minimum airway wall pressure in the overlap region, $P_{max}$, was identified to quantify airflow loading on the airway. The effect of the pharyngeal airway narrowing on the flow field was quantified by two other endpoints: the average pressure drop from choanae to the minimum area where tonsils and/or adenoids maximally restrict the airway ($dP_{Tanus}$) and the ratio of $dP_{Tanus}$ to the flow rate ($PQR_{Tanus}$). $PQR_{Tanus}$ is calculated like a flow resistance, but should be interpreted as the flow sensitivity of the internal pressure due to airway narrowing. To assess the potential for simplified image-based flow modeling methods, the maximum air velocity in the pharynx was estimated from flow rate and cross-sectional area, and $dP_{Tanus}$ was estimated using Bernoulli’s equation.

Statistical analysis. OSAS subjects were matched with control subjects (polysomnography studies with AHI $< 5$ and oAHI $< 1$), based on sex, age, weight, height, and BMI z-score. Statistical calculations were conducted using Microsoft Excel and MatLab. Sample mean, median, and standard deviation were tabulated for all variables. Comparisons between the OSAS and control groups used two-tailed paired t-tests where data appeared normally distributed, and Wilcoxon signed rank paired tests on log-transformed data for pressure-related endpoints, which were asymmetric and not normally distributed. Spearman’s correlation coefficient ($r$) was computed between the total obstruction event rate oAHI and CFD and anatomical endpoints for the pooled normal and OSAS subject groups.
RESULTS

Fifteen pairs of obese OSAS and control subjects were analyzed using CFD. Several subject pairs from the previous study (5) were not analyzed because of unavailability of flow measurements or rhinomanometry data or because of subject motion problems that made reconstructed surfaces too noisy for CFD analysis. Demographic and physiological parameters are summarized in Table 1. Mean AHI, obstructive apnea-hypopnea index (oAHI), and hypopnea index (HI) were significantly higher in OSAS, while oAI and central apnea index (cAI) trended higher but did not reach statistical significance. A majority of events in most subjects with OSAS were hypopneas. Nasal resistance measured by rhinomanometry and peak inspiratory flow rate were similar in both groups, as were height, weight, BMI, and BMI z-score.

Figure 2 shows airway anatomy and internal airway pressure (computed by CFD) at peak inspiratory tidal flow for a representative OSAS subject. Most airways in both OSAS and control subjects had some anatomical narrowing in the “overlap region” (12), and in some subjects, this narrowing extended into the retrolingual oropharynx between enlarged tonsils. The narrowing due to adenoids, soft palate, and tonsils creates a zone of low internal airway pressure during inspiration due to the “Bernoulli effect”, usually followed by a much smaller rise

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Fig. 1. In vivo computational fluid dynamics (CFD) verification study. A: CFD model of adult volunteer airway. B: in vivo anterior rhinomanometry experiment configuration. The subject breathes through the nose, keeping the lips sealed around a small tube and the oral cavity slightly open to the pharynx. Nasal flow rate is measured by a pneumotachometer on a nasal mask, while pressure in the static oral cavity is measured through the oral tube. C: inspiratory rhinomanometer oral pressure vs. flow rate, compared with CFD model pressure vs. flow rate. Rhinomanometer data (Rhino) is from two representative inspiratory breaths. Error bars on the CFD data indicate range of CFD pressure on the airway wall model cells in the retrolingual oropharynx.

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Fig. 2. Sample CFD airway model geometry (left) and airway wall pressure distribution (right). Cross sections normal to the flow direction were established at the choanae (slightly posterior to the vomer, where left and right nasal merge) and trachea. The pharyngeal airway from the nasopharynx to oropharynx is usually constricted by the adenoids, soft palate (S.P.), and tonsils. The area minimum (A_min) was identified as the minimum cross section in the region where tonsils, soft palate, and adenoids constrict the pharynx, perpendicular to the airway. Cross-section average pressures were computed at each cross section. The local airway wall pressure minimum in the region constricted by adenoids and tonsils was identified (P_min), as was the minimum pressure for the entire pharynx in cases in which the minimum pressure was below the tonsils.
in internal pressure downstream in the lower oropharynx, an effect called “pressure recovery”. As a result, most airways have a local minimum in the internal pressure, located in the constricted region near the minimum cross section. In many subjects, airway curvature around the soft palate and uvula, and other local curvatures of the airway wall, lead to a more pronounced local minimum pressure on the airway wall. Because the degree of pressure recovery is usually quite small compared with the pressure drop upstream of the minimum cross section, the CFD endpoint $P_{\text{min}}$ not only gives the local pressure minimum in the maximally constricted pharynx, but $P_{\text{min}}$ is usually also a reasonably good estimate of the pressure in the retrolingual oropharynx.

Figure 3 shows the airway wall pressure distribution in three OSAS subjects and three matched control subjects. In 13 of 15 subject pairs, the pressure drop from choanae to $A_{\text{min}}$ was larger in OSAS than in control. In one of the two pairs in which the control pressure drop was higher, the control subject had an unusually high-pressure drop due to airway restriction. In the other exception, the OSAS subject had an unusually wide pharynx and very low pressure drop. The range of internal pressures was relatively wide; minimum pressure was as little as $\frac{1}{1000} \text{cmH}_2\text{O} (\approx 40 \text{ Pa})$ in some airways, and as much as $\frac{1}{1000} \text{cmH}_2\text{O}$ in others. Higher flow rate, higher nasal resistance, and more restricted pharynx anatomy all contributed to lower airway pressures and higher flow resistances.

CFD model endpoint statistics are summarized in Table 2. Flow resistance in the pharynx was significantly higher in OSAS than in controls ($P < 0.025$). Similarly, the maximum pressure drop in the overlap region $dP_{\text{Tmax}}$ and the overlap region pressure flow ratio $PQR_{\text{Tmax}}$ were significantly higher (both $P < 0.005$). Dividing $dP_{\text{Tmax}}$ by flow rate slightly increased the average difference between OSAS and control, but not to statistical significance. Both of these endpoints were higher in 13 of the 15 subject pairs (Fig. 4). In contrast, the
CFD Upper Airway Flow Model Endpoints in OSAS • Wootton DM et al.

Table 2. Selected CFD endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OSAS (n = 15)</th>
<th>Control (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_{\text{pharynx}} ) Pa·ml⁻¹·s⁻¹</td>
<td>0.69 ± 0.31</td>
<td>0.27 ± 0.25</td>
<td>&lt;0.025†</td>
</tr>
<tr>
<td>( P_{\text{min}} ), cmH₂O</td>
<td>-5.57 ± 5.99</td>
<td>-2.59 ± 2.91</td>
<td>&gt;0.05†</td>
</tr>
<tr>
<td>( dP_{\text{TAmax}} ), Pa</td>
<td>229.4 ± 289.5</td>
<td>68.8 ± 91.8</td>
<td>&lt;0.005†</td>
</tr>
<tr>
<td>( P_{\text{QR}} ), Pa·ml⁻¹·s⁻¹</td>
<td>0.80 ± 0.86</td>
<td>0.23 ± 0.22</td>
<td>&lt;0.005†</td>
</tr>
<tr>
<td>( R_{\text{Amin}} ), mm</td>
<td>2.7 ± 0.8</td>
<td>3.2 ± 1.3</td>
<td>0.03*</td>
</tr>
<tr>
<td>( V_{\text{TAmax}} ), m/s</td>
<td>15.4 ± 10.0</td>
<td>8.1 ± 5.7</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

\( R_{\text{pharynx}} \) is the pressure drop from choanae to tracheal end of the model/flow rate; \( P_{\text{min}} \) is the minimum cross-sectional average pressure in pharynx segments constricted by tonsils and adenoids; \( dP_{\text{TAmax}} \) is the maximum pressure drop from choanae into area minimum; \( P_{\text{QR}} \) is the maximum pressure drop from choanae to tracheal end of the model/flow rate; \( R_{\text{Amin}} \) is the average air velocity at minimum area. *P value calculated by two-tailed Student’s t-test for paired subjects, for normally distributed endpoints. †P value calculated using Wilcoxon rank sum test of log-transformed data for paired subjects.

Table 3. Correlation coefficient of selected upper airway flow variables to oAHI, in pooled control and OSAS subjects

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>( oAHI )</th>
<th>( r )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( dP_{\text{TAmax}} )</td>
<td>0.48</td>
<td>0.007</td>
</tr>
<tr>
<td>( P_{\text{QR}} ), Pa·ml⁻¹·s⁻¹</td>
<td>0.48</td>
<td>0.007</td>
</tr>
<tr>
<td>( R_{\text{pharynx}} )</td>
<td>0.47</td>
<td>0.008</td>
</tr>
<tr>
<td>( P_{\text{min}} )</td>
<td>-0.26</td>
<td>0.17</td>
</tr>
<tr>
<td>( R_{\text{Amin}} )</td>
<td>-0.39</td>
<td>0.03</td>
</tr>
<tr>
<td>( V_{\text{TAmax}} )</td>
<td>0.45</td>
<td>0.014</td>
</tr>
<tr>
<td>( P_{\text{QR}} ), Pa·ml⁻¹·s⁻¹</td>
<td>0.46</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Unbolded rows are CFD model endpoints; bolded cells are computed using MR image analysis endpoints and measured peak average flow data. \( dP_{\text{pharynx}} \) is the pressure drop from choanae to tracheal end of the model; \( P_{\text{QR}} \), Pa·ml⁻¹·s⁻¹ is the estimate of \( P_{\text{QR}} \), Pa·ml⁻¹·s⁻¹ using Bernoulli’s equation.

Minimum airway internal pressure in the overlap region, \( P_{\text{min}} \), which includes the effect of nasal flow resistance, had only a trend to lower values in OSAS that was not significant, possibly due to the large variability in both nasal and pharyngeal pressure drops.

Several CFD endpoints were significantly correlated to obstructive apnea-hypopnea index (oAHI). Correlations between oAHI and CFD or anatomical endpoints (Table 3) were relatively consistent with the paired comparisons between OSAS and control groups. The strongest correlations with oAHI were found with \( dP_{\text{TAmax}} \) and \( P_{\text{QR}} \), Pa·ml⁻¹·s⁻¹ (both \( r = 0.48 \), \( P < 0.01 \)) (Fig. 3), and with \( dP_{\text{pharynx}} \) and \( R_{\text{pharynx}} \) (\( r = 0.47 \) and 0.49 respectively, \( P < 0.01 \)) (Fig. 5). The minimum cross-sectional area radius was the most strongly correlated airway anatomical endpoint and had a slightly weaker correlation with oAHI compared with the best CFD endpoints. Hydraulic diameter at \( A_{\text{min}} \) had a slightly lower correlation to oAHI. Because of the significant correlation of radius to oAHI, several anatomically based flow field estimates that depend on the minimum cross section but do not require CFD were compared: average velocity at the minimum airway cross section, and an estimate

Fig. 4. Distribution of pressure drop \( dP_{\text{TAmax}} \) (top) and pressure flow ratio \( P_{\text{QR}} \), Pa·ml⁻¹·s⁻¹ (bottom) from choanae to \( A_{\text{min}} \) for \( n = 15 \) subject pairs (OSAS, ■). Pressure drop and pressure flow ratio are higher in OSAS than control in 13 of 15 pairs, and mean values are significantly higher (\( P < 0.005 \)). Pressure flow ratio amplifies the difference between most OSAS and control subjects. Both endpoints were significantly correlated to oAHI (\( P < 0.01 \)).

Fig. 5. Pharyngeal pressure drop \( dP_{\text{pharynx}} \) (top) and flow resistance \( R_{\text{pharynx}} \) (bottom) vs. oAHI. Both endpoints are significantly correlated with OSAS (\( P < 0.01 \)).
of $dP_{T\text{max}}$ using Bernoulli’s equation at peak inspiratory flow. Compared with the minimum radius, each of these endpoints was more significantly correlated with oAHI, but the correlation was slightly weaker than the CFD-computed endpoints (Table 3). The correlation between $P_{\text{min}}$ and oAHI was lower and not statistically significant. Correlations of these endpoints to the hypopnea index followed the same trend and were consistently slightly stronger than correlations to oAHI. Conversely, correlations of these endpoints to AHI (including central apneas) and to obstructive apnea index alone were weaker, and there was no significant correlation between CFD endpoints and central apnea index.

**DISCUSSION**

The present study demonstrates that the CFD endpoints that best correlate with the presence and severity of OSAS in this particular group of obese children are based on the magnitude of the pressure change between the entrance to the pharynx and the point of maximum airway restriction in the overlap region: $dP_{T\text{max}}$ and $PQR_{T\text{max}}$. Both the pressure drop and pressure drop-to-flow ratio were on average more than 3.3 times higher in OSAS. The pharyngeal flow resistance and pressure drop, which included additional pressure losses, especially around the epiglottis and larynx in these models, were also larger in OSAS, and their correlation to oAHI was as strong as the overlap region pressure drop endpoints. The similar strength of these endpoints is reasonable because in most subjects with OSAS, the overlap region pressure drop is the most significant pressure drop in the pharynx, so that these CFD endpoints were highly correlated with each other. In contrast to these pharyngeal pressure drop endpoints, the minimum airway wall pressure, including nasal pressure drop, $P_{\text{min}}$, had lower statistical significance, as did the minimum cross-sectional size in the airway. Compared with oAHI, the correlations of CFD endpoints to AHI or cAI were lower and not statistically significant, suggesting that central apneas have a much weaker or no relationship to anatomical restriction and airway pressures.

The significance of the pressure drop from choanae to the overlap region $dP_{T\text{max}}$ is consistent with use of this endpoint by De Backer and colleagues (9, 32) and others (37). It is also consistent with our earlier findings with younger children (35), although the differences between the OSAS and control groups in the current study are smaller.

This is the first image-based CFD study to compare local pressure drops in the pharynx to internal pressure, which includes nasal pressure drop ($P_{\text{min}}$). The lower correlation of $P_{\text{min}}$ to oAHI in these subjects was somewhat surprising; one hypothesis of the study was that $P_{\text{min}}$ would have the strongest correlation with obstructive events because it represents internal air pressure loading both in the region of maximum constriction and in the retrolingual oropharynx. The lower correlation of $P_{\text{min}}$ compared with pressure drops in the pharynx, may suggest that pharyngeal mechanosensors that help to control upper airway muscle tone are responsive to differences in nasal resistance in many of these subjects regardless of OSAS. The lower correlation of $P_{\text{min}}$ to OSAS also implies that there may be limited benefit to modeling the nasal passages or measuring the nasal resistance when using CFD to model airway restriction effects in OSAS. Therefore, a model of the pharynx anatomy alone may be sufficient for a useful research or clinical CFD model, which could significantly simplify the time and complexity required for fluid dynamics analysis.

CFD is used as a state-of-the-art tool to model the effect of airway narrowing determined from noninvasively derived, three-dimensional anatomical images of awake subjects. The MR images show significant anatomical differences between the airways of subjects with OSAS and controls (5), even when obesity and other significant demographic factors are controlled. A narrowed airway is subject to more negative internal pressure and higher airflow velocity, which can destabilize a collapsible vessel more easily than slower, higher-pressure flow in a less restricted airway (10). If the mechanisms of stronger airway suction or higher airspeed contribute to risk of collapse, a CFD model can be more sensitive or accurate than anatomical parameters alone in modeling the effects of airway restriction in OSAS. The correlation coefficients between oAHI and overlap region pressure drop $dP_{T\text{max}}$ and $PQR_{T\text{max}}$ were stronger than correlation coefficients between anatomical volume measures of the airway and associated tissues (5), supporting this hypothesis. Our findings are consistent with a recent CFD study of nine adult males with OSAS and matched controls (7). The correlation of oAHI to CFD endpoints was also stronger than the correlation to minimum cross-sectional radius, which may be explained by the sensitivity of pressure drop to cross-sectional airway area, flow rate, upstream airway cross section, and three-dimensional geometric shape of the airway. The study suggests that image-based CFD analysis may have value to estimate anatomical effects on the severity of OSAS, since CFD endpoints had the highest correlation coefficient with oAHI.

The results also show promise for simpler methods of pressure drop analysis, such as a Bernoulli equation model based on anatomical narrowing. The strength of correlation with Bernoulli-based estimates in these subjects is consistent with the work of Lucey et al. (15) and may be explained by the dominant mechanisms influencing the pressure field in most subjects, which are acceleration of flow through a relatively short stenosis at moderately high Reynolds number (order 1000), followed by a poststenotic turbulent jet that dissipates the majority of the jet’s kinetic energy and recovers a small fraction of the pressure drop. The use of such a simple analysis might make image-based fluid dynamics modeling more clinically feasible. But a Bernoulli model would be inaccurate in airways with very gradual area narrowing, multiple restrictions, or long restricted segments. In such anatomies, pressure loss due to friction over the length of the narrowed airway cannot be neglected and is a function of both the cross-sectional area and the cross-sectional shape of the narrowed region. Streamline curvature may also affect local wall pressure minima (15) and will be difficult to accurately account for in one-dimensional models.

This study is the largest that we are aware of to use image-based CFD to analyze pressure and flow resistance in children with sleep apnea. The study design allows us to examine the influence of anatomical factors on airway fluid mechanics, while controlling for obesity, age, and sex, all significant factors in OSAS, using paired comparisons. The analysis of a relatively large number of cases was possible by using an efficient and relatively simple turbulence modeling
method (k-ω) that has been shown to accurately predict pressure field in several in vitro studies (23, 35).

The main limitations of the models presented here are the assumption of rigid airway walls, as well as that models are derived from images of awake subjects. The rigid wall assumption is reasonable for modeling most awake subjects, who are breathing quietly and have very limited airway motion. But these assumptions mean that differences in airway muscle tension and activation are not modeled. The two exceptional subject pairs in Fig. 3, which had higher pressure drops in control than OSAS, might be explained primarily by differences in airway muscle activity. The OSAS subject with relatively good anatomy and unusually low pressure (Fig. 3B, right), may have very weak airway activity or pressure sensitivity during sleep, with a higher propensity for airway collapse. And the control subject with restricted airway anatomy and unusually high pressure drop (Fig. 3C, left) may have more robust airway muscle activity that responds well to low pressure during sleep. The limitations of the model suggest that CFD complemented by assessment of airway compliance (25) or changes in airway anatomy between awake and asleep states, or models based on sleeping subject’s anatomy, may be better able to differentiate between control and OSAS subjects than CFD based on awake anatomy.

Another limitation of the model is that it assumes nasal breathing. Although nasal breathing is preferred over oral breathing during sleep, high nasal resistance can cause a switch to oral breathing, and in many cases, the flow resistance during sleep and the frequency of obstructive events are higher with oral breathing (11).

Some CFD upper airway model studies have reported stronger correlations between AHI and CFD endpoints. The most promising study modeled the effect of mandibular advancement on reduction of AHI in 10 patients with OSAS (9). These investigators used CT images before and after oral appliance placement to model the effect of the device on upper airway flow, and found a correlation of $r = 0.92$ between the relative change in computed pharyngeal flow resistance and the relative change in AHI after mandibular advancement. Such strong correlation may be due to normalizing both resistance and AHI to oral breathing, and in many cases, the flow resistance during sleep and the frequency of obstructive events are higher with oral breathing (11).

APPENDIX: GRID AND TIME STEP ERROR ESTIMATE STUDY

The effect of grid size was evaluated for a sample subject with OSAS by comparing endpoints $dP_{\text{pharynx}}$ and $dP_{\text{Tmax}}$ on fine, medium, and coarse grids with average edge lengths 0.2, 0.3, and 0.45 mm. The discretization error was estimated as suggested by American Society of Mechanical Engineers guidelines using the Richardson extrapolation (6). The estimated errors on the fine and medium grid solutions were less than 1% (Table A1), and the errors of the coarse grid were less than 2.5%. Average order of convergence was 2, consistent with a second-order accurate discretization scheme.

The effect of time step size on our unsteady simulations was evaluated for a sample subject with OSAS, by comparing $dP_{\text{Tmax}}$.

Table A1. Grid discretization error estimates, based on simulations on three grids and Richardson extrapolation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of volumes $N_1$, $N_2$, $N_3$</td>
<td>2194k, 714k, 335k</td>
</tr>
<tr>
<td>Grid sizes $h_1$, $h_2$, $h_3$, mm</td>
<td>0.2, 0.3, 0.45</td>
</tr>
<tr>
<td>Endpoint $dP_{\text{pharynx}}$, $dP_{\text{Tmax}}$</td>
<td>80.63, 76.74</td>
</tr>
<tr>
<td>Fine mesh result, $d_1$</td>
<td>80.27</td>
</tr>
<tr>
<td>Medium mesh result, $d_2$</td>
<td>78.78</td>
</tr>
<tr>
<td>Coarse mesh result, $d_3$</td>
<td>77.02</td>
</tr>
<tr>
<td>Order of convergence, p</td>
<td>3.47</td>
</tr>
<tr>
<td>Extrapolated result, $d^*_{\text{ext}}$</td>
<td>80.75</td>
</tr>
<tr>
<td>Error, fine vs. medium, $e^{21}_{\text{ext}}$</td>
<td>0.45%</td>
</tr>
<tr>
<td>Error, medium vs. coarse, $e^{32}_{\text{ext}}$</td>
<td>1.85%</td>
</tr>
<tr>
<td>Fine grid estimated error, $e^{21}_{\text{ext}}$</td>
<td>0.15%</td>
</tr>
<tr>
<td>Medium grid estimated error, $e^{32}_{\text{ext}}$</td>
<td>0.60%</td>
</tr>
<tr>
<td>Coarse grid estimated error, $e^{32}_{\text{ext}}$</td>
<td>2.4%</td>
</tr>
<tr>
<td>Fine grid convergence index, GCI$^{21}_{\text{ext}}$</td>
<td>0.18%</td>
</tr>
<tr>
<td>Medium grid convergence index, GCI$^{32}_{\text{ext}}$</td>
<td>0.75%</td>
</tr>
</tbody>
</table>

GCI, Grid Convergence Index error estimates (6).
averaged over 100 ms, at time steps = 1, 0.316, and 0.1 ms. The solution at zero time step was estimated using Richardson extrapolation (6), and the order of convergence and error for each time step was estimated from the extrapolated solution (Table A2). The estimated error due to time step was less than 1% for all time steps, and the estimated order of convergence was 1.91, consistent with the second-order accurate implicit solver employed.

At the longest time step, the pressure fluctuations were noticeably damped compared with the two shorter time steps, which had similar pressure fluctuations. The shortest time step, 0.1 ms, had estimated 0.01% time discretization error and was used because it had the shortest CPU time, as well the lowest estimated error.

**REFERENCES**


