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Control of breathing in children with mild sleep apnoea: a 6-year follow-up study

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ABSTRACT: We have previously shown that children (average age 9 yrs) with mildly elevated obstructive apnoea/hypopnoea indices (OAHI) retained CO_2 at rest. Here, we report the results of a 6-yr follow-up study on 14 children from that study.

Minute ventilation (V'_E) and end-tidal CO_2 partial pressure (P_{ET,CO_2}) were measured during hypercapnic challenge.

OAHI decreased from 7.5±4.7 events·h^{-1} at age 9 yrs to 2.5±1.8 events·h^{-1} at age 15 yrs ($p<0.001$), despite an increase in body mass index from 20±4.6 kg·m^{-2} to 26±5.7 kg·m^{-2} ($p<0.0001$). Eupneic V'_E increased from 4.1±0.31 L·min^{-1}·m^{-2} to 5.9±0.4 L·min^{-1}·m^{-2} ($p<0.01$), while P_{ET,CO_2} fell from 44.1±0.8 to 33±1.0 mmHg ($p<0.001$). The V'_E–P_{ET,CO_2} obtained during hypercapnia was left shifted, such that V'_E at a P_{ET,CO_2} of 50 mmHg increased from 24 L·min^{-1} at age 9 yrs to 36 L·min^{-1} at age 15 yrs. Central respiratory drive did not change.

We hypothesise that somatic growth of the pharynx coupled with a regression of tonsillar tissue mass with age leads to enlargement of the upper airway lumen, a reduction in airway resistance and increased respiratory airflow at a given level of ventilatory drive.

KEYWORDS: Children, control of breathing, hypercapnia, sleep apnoea

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We have previously shown that resting end-tidal CO_2 partial pressure (P_{ET,CO_2}) was higher in 6–12-yr-old children with relatively high obstructive apnoea/hypopnoea indices (OAHI) compared with age-matched controls with lower OAHI [1]. The initial studies were performed in 1999 when the average age of our subjects was ~9 yrs. Here, we report the results of a 6-yr follow-up study of 14 children from this original sample, now with an average age of 15 yrs. All of the children in our sample have intact tonsils and adenoids. The mechanism of the CO_2 retention is unknown, but could be due to increased upper airway resistance, to blunted central chemoreceptor sensing and/or to altered regulation of central ventilatory motor output.

We were able to re-study 14 children from this original sample in 2006–2007, and our results are reported herein. Preliminary analyses from the entire Tucson Childrens Assessment of Sleep Apnoea Study (TuCASA) cohort indicate that the OAHI improves with age in children, even in the absence of adenoidectomy and tonsillectomy (table 1) [2]. We tested the hypothesis that these improvements in the OAHI are associated with improvements in ventilatory control. We were particularly interested in changes in the resting minute ventilation (V'_E), the resting P_{ET,CO_2}, and changes in the sensitivity to inspired CO_2. Our unique longitudinal study shows that although the body mass index (BMI) of the children increased with age, they also had lower OAHIs, a marked diminution in resting P_{ET,CO_2}, and a substantial leftward shift in the V'_E–P_{ET,CO_2} response curve.

MATERIALS AND METHODS

Subjects

All methods used to recruit subjects and to collect the present data set were approved both by the University of Arizona Human Subjects Committee and the Tucson Unified School District Research Committee (Tucson, AZ, USA). In all cases, we obtained written informed consent from the parents, and assent from the children. Our initial sample in 1999 was composed of subjects recruited through the Tucson Unified School District, as described in previously [1]. For the present study we selected and attempted to contact all 50 subjects from our original cohort and asked them if they would like to participate in a follow-up study. Subjects that had adenoidectomy or tonsillectomy were excluded, and a total of 14 subjects (28% of the original cohort) who met our criteria agreed to participate. Their anthropometric characteristics are given in table 1. The remaining children could not be located, had tonsillectomies or adenoidectomies (n=19) and/or refused to participate. These children, in comparison to the 14 subjects who

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TABLE 1 Anthropometric data and sleep data in 1999 and 2006

	1999	2006	p-value
Subjects n	14	14	
Sex males/females n	8/6	8/6	
Age yrs	8.7±0.91 (7–10)	15±1.3 (12–17)	<0.0001
Weight kg	38±12 (24–67)	71±18 (49.6–101)	<0.0001
Height cm	136±8.3 (120–149)	163±7.1 (149–174)	<0.0001
BMI kg·m^{-2}	20±4.6 (15–30)	26.8±5.7 (19–37)	<0.0001
BSA m^2	1.18±0.21 (0.90–1.61)	1.75±0.22 (1.4–2.1)	<0.0001
RDI events·h^{-1}	8.6±5.3 (2.7–19)	2.7±1.8 (0.5–7.8)	0.0018
OAHI events·h^{-1}	7.5±4.7 (1.8–17)	2.5±1.8 (0.3–7.6)	0.001
Total sleep time min	487±56 (314–530)	446±51 (367–528)	NS
S_{a,O_2} nadir %	89±13 (87–91)	91±2.9 (86–94)	NS
SBP mmHg	102±1.3 (72–122)	107±9.9 (88–122)	NS
DBP mmHg	65±10 (50–88)	61±7.6 (48–74)	NS

Data are presented as mean±SD (range), unless otherwise stated. BMI: body mass index; BSA: body surface area; RDI: respiratory disturbance index; OAHI: obstructive apnoea/hypopnoea index; S_{a,O_2}; oxygen saturation of arterial blood; SBP: systolic blood pressure; DBP: diastolic blood pressure; NS: not significant.

participated in the present study, did not differ with respect to mean age or BMI, sex or ethnicity distribution, or percentage of habitual snoring.

Polysomnography

In both the study in 1999 and the present study, children underwent unattended, nocturnal home polysomnography [3] using the Compumedics PS-2 system (Abbotsford, Victoria, Australia). The following signals were obtained: C_3/A_2 and C_4/A_1 electroencephalogram, right and left electrooculogram, a bipolar submental electromyogram, thoracic and abdominal displacement (inductive plethysmography bands), airflow (nasal/oral thermocouple), nasal pressure, electrocardiogram (single bipolar lead), snoring (microphone attached to a vest), body position (Hg gauge sensor), pulse oximetry (Nonin, Plymouth, MN, USA) and ambient light (sensor attached to the vest to record on/off). Using Compumedics W-Series Replay, version 2.0, release 22, sleep stages were scored according to standard criteria [4]. The respiratory disturbance index (RDI) was defined as the number of respiratory events (apnoeas and hypopnoeas) per hour of the total sleep time irrespective of any associated oxygen desaturation or arousal. Polysomnograms with <4 h of scorable oximetry were classified as failed studies and were repeated if the participant consented. Central apnoeas were scored if both airflow and thoracoabdominal effort were absent. However, central events that occurred after movement were not included. Obstructive apnoeas were identified if the airflow signal decreased to below 25% of the ''baseline amplitude''. Hypopnoeas were scored if the magnitude of any ventilation signal decreased below ~70% of the ''baseline'' amplitude, as described previously [1]. Although more recent rules for scoring respiratory events have been published [5], we elected to score apnoeas and hypopnoeas using the same algorithm used in our 1999 study in order to make valid comparisons between the two time-points, in each instance using the thermistor and/or the inductance plethysmography signal to score respiratory events.

The RDI that we routinely compute includes central apnoeas as well as obstructive apnoeas and hypopnoeas [3]. Based on the clinical and physiological uncertainty of central apnoeas in children [6, 7], we subtracted central events from the RDI to derive the OAHI. In our subjects this index primarily represents hypopnoeas. For example, in 1999 the number of frank obstructive events ranged from 0.1–0.8 obstructions·h^{-1}, except for one subject that averaged 7 obstructions·h^{-1} in 1999. In 2006 there were no frank obstructions, except in one subject who had 2 obstructions·h^{-1}.

Ventilatory control protocol

For this section of the study, participants were studied between 09:00 h and 16:00 h and were instructed to refrain from caffeinated beverages and food for 1 h prior to the time of their scheduled experiment. Subjects were studied while seated, and listened to music through headphones throughout the entire protocol. Analogue waveforms from transducers monitoring expiratory airflow, mask pressure and the fractional concentrations of O_2 and CO_2 were passed through an analogue-to-digital converter (Spike II; Cambridge Electronic Design, Cambridge, UK), sampled at 2,500 Hz per channel, and stored on the hard drive of an IBM-compatible computer (details of the measurements and equipment are given below). Estimated oxygen saturation of arterial blood was monitored and recorded manually in all studies with a pulse oximeter (Ohmeda, Madison, WI, USA).

The investigators were blinded to the OAHI status of the subject when conducting experiments and analysing data. For hyperoxic hypercapnia, the subjects breathed from humidified Douglas bags filled with 3, 5 or 7% CO_2 in O_2. Subjects started by breathing room air for 3–5 min, and then breathed, in succession, each of the three CO_2-O_2 mixtures for 3 min each, and recovered by breathing room air. In all conditions, airway occlusions were applied twice per minute, to obtain measurements of mouth occlusion pressures measured 100 ms after onset of inspiratory effort ($P_{0.1}$).

Measurement of pulmonary ventilation, inspired and expired gas concentrations and $P_{0.1}$

Subjects breathed through a tight fitting mask that covered the nose and mouth, and that allowed free breathing through either the oral or nasal airway (Hans-Rudolph paediatric rubber face mask; Hans Rudolph Inc., Shawnee, KS, USA). An additional rubber seal was created around the mask using Exaflex (GC America, Inc., Alsip, IL, USA). The mask was checked for leaks by instructing the subjects to hyperventilate, while an investigator looked for leaks by sampling CO_2 around the mask seal. When leaks were noted, they were sealed with additional Exaflex. The P_{ET,CO_2} on inspiration returned to zero under all conditions, indicating that the system dead space was sufficiently low to prevent rebreathing.

A low dead-space non-rebreathing valve (Hans Rudolph 2600; Hans Rudolph Inc.) was attached to the mask, and a short length of tubing and a pneumotachometer (Hans-Rudolph 4700; Hans Rudolph Inc.) were placed on the expiratory side of the breathing valve for the measurement of expiratory airflow. The pressure drop across the pneumotachometer was measured with a differential pressure transducer with a ± 2.5 cmH_2O diaphragm (Validyne MP 45; Validyne Engineering Corp., Northridge, CA, USA). The pneumotachometer was calibrated with a precision Matheson Rotameter before each experiment. The respiratory period was measured from the flow signal, and used to compute breathing frequency. Expired flow was integrated by the computer offline to derive expired tidal volume (V_T), which was converted from ambient temperature, pressure and humidity conditions to body temperature, pressure and humidity conditions, with the assumption that body temperature was 37°C. V'_E was computed offline as the product of V_T and breathing frequency. Breath-by-breath values for CO_2 and O_2 were measured with a rapidly responding analyser (Raytech Instruments, Cerritos, CA, USA), which was connected to the non-rebreathing valve by small-bore tubing. The output of the analyser was digitised and used to compute P_{ET,CO_2} and the end-tidal level of O_2. Mask pressure was measured by connecting a short length of PE 200 tubing to the centre of the non-rebreathing valve, and attaching the opposite end to a differential pressure transducer with a ± 56 cmH_2O diaphragm (Validyne MP 45).

For the measurement of $P_{0.1}$, a Hans-Rudolph Inc. automated balloon valve was attached to the inspiratory side of the non-rebreathing valve. The balloon was connected to a compressed air source, and was inflated or deflated with a solenoid valve and vacuum pump, respectively. The computer controlled the activation and deactivation of the solenoid valve and pump. The inspiratory port was occluded during expiration, and the occlusion was maintained for ~200 ms into the ensuing inspiration, allowing sufficient time to obtain measurements of $P_{0.1}$ [8]. The computer measured the drop in mask pressure exactly 0.1 s after the onset of the occluded inspiratory effort, and denoted this value as $P_{0.1}$.

Data processing and statistical analysis

Six to 10 breaths obtained over the last 30–40 s of control conditions and at each level of hyperoxic hypercapnia, were used to calculate average values of V_T, breathing frequency, V'_E and the end-tidal partial pressure of O_2 and P_{ET,CO_2}. All $P_{0.1}$ values obtained in each condition were averaged, so that each subject had a single $P_{0.1}$ measurement for each of the experimental conditions. All $P_{0.1}$ values were expressed in units of cmH_2O.

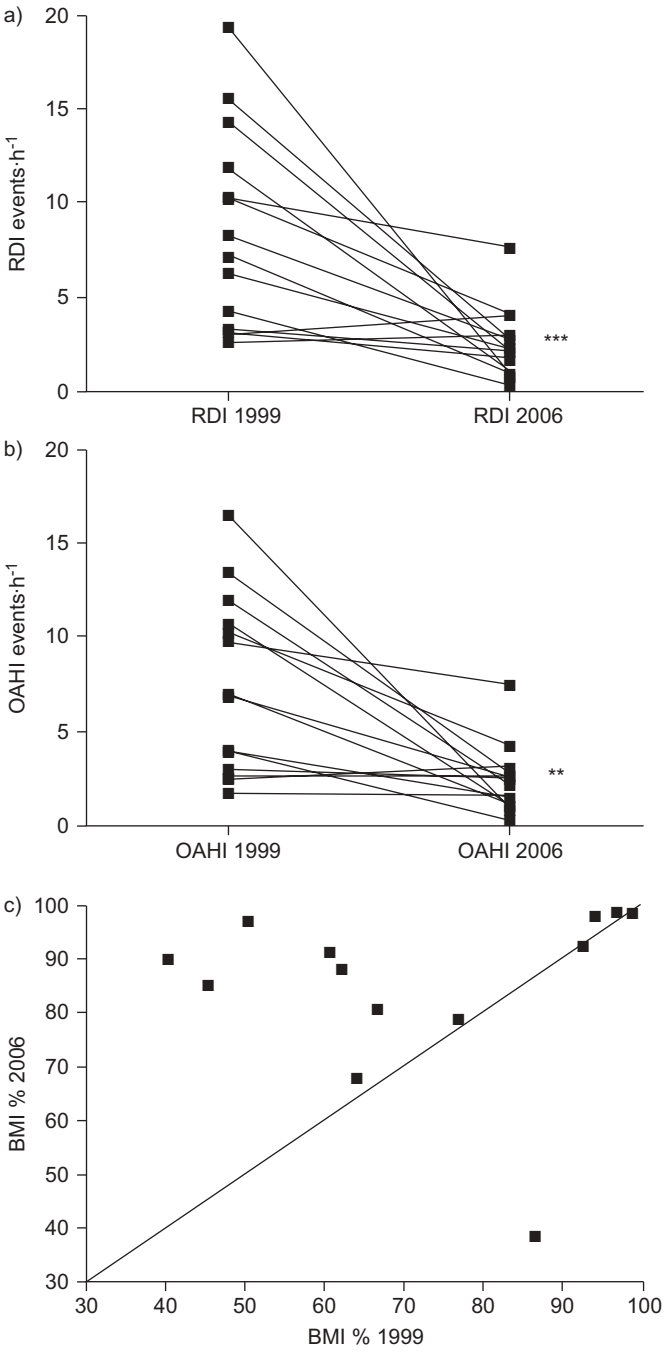

FIGURE 1. a) The respiratory disturbance index (RDI) and b) the obstructive apnoea/hypopnoea index (OAHI) recorded in 1999 and in 2006 for all 14 subjects. The OAHI declined in every subject. See table 1 for average values, and the text for description of how the RDI and OAHI values were calculated. **: $p<0.01$, different from 1999; ***: $p<0.001$, different from 1999. c) The body mass index (BMI) percentile values for each subject in 1999 and 2006. The line of identity is shown and shows that most subjects were in a much higher percentile in 2006 compared to 1999.

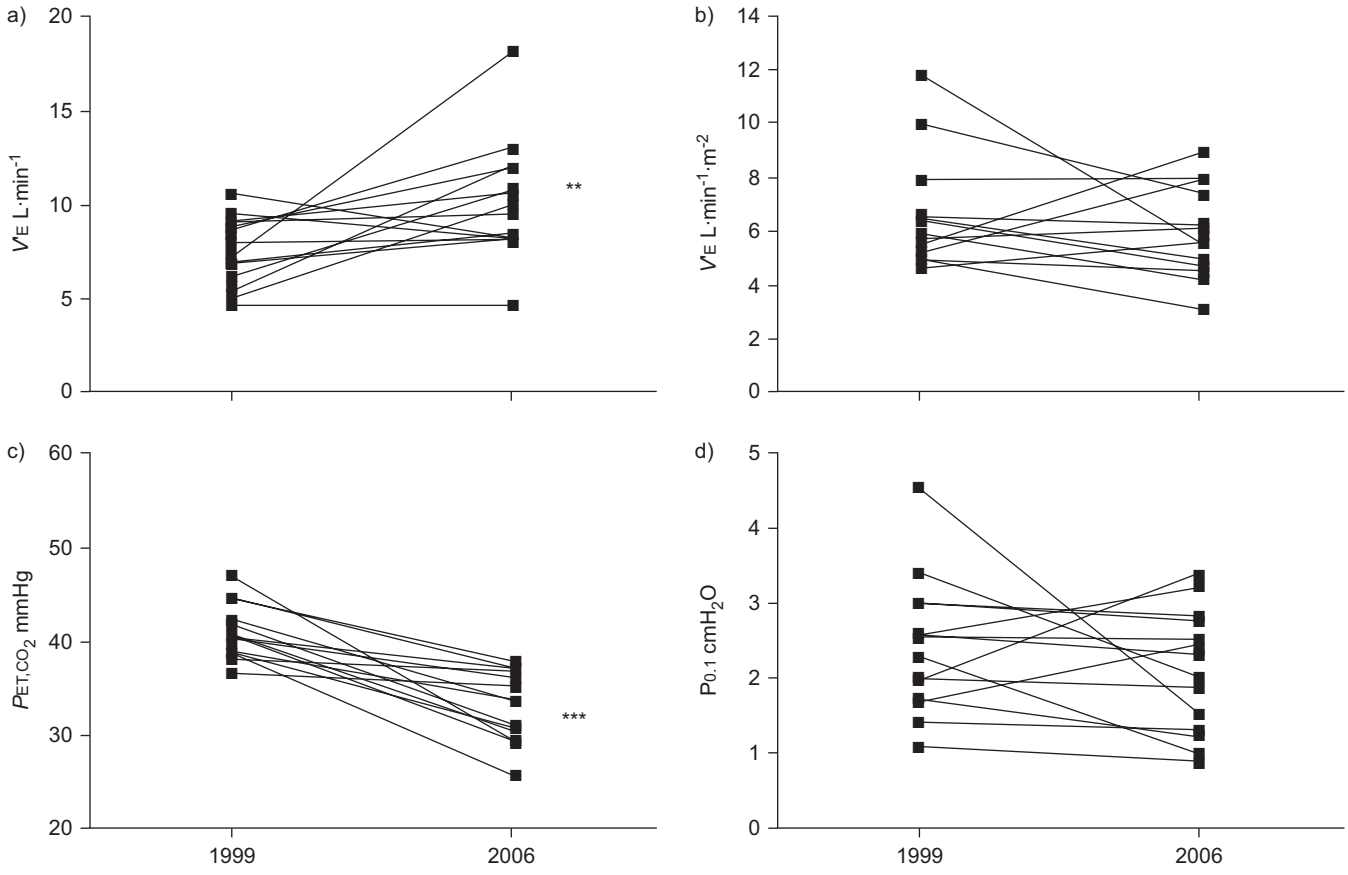

FIGURE 2. Resting values for a) absolute expired minute ventilation (V'_E), b) V'_E corrected for body surface area (BSA), c) end tidal CO_2 partial pressure (P_{ET,CO_2}) and d) mouth pressure measured 100 ms after the onset of inspiratory effort ($P_{0.1}$). V'_E was higher in every subject in 2006 compared with 1999, but V'_E corrected for BSA (b) was the same in 1999 and 2006. P_{ET,CO_2} declined in every subject (c), whereas $P_{0.1}$ did not change (d). **: $p<0.01$, different from 1999; ***: $p<0.001$, different from 1999.

The V'_E values for each subject were divided by the subject's body surface area (BSA; m^2) to account for the large differences in size (and hence V_T) over the 6-yr age range of our paediatric subject population. This analysis allowed us to compare the hypercapnic ventilatory responses of our subjects with previously published results in children of various ages.

To determine if the severity of sleep-disordered breathing (SDB) correlates with ventilatory drive, we first plotted both V'_E and $P_{0.1}$ against P_{ET,CO_2} for each subject, and computed the slope of the relationship as an index of hypercapnic ventilatory drive using linear regression analysis. We then plotted each subject's hypercapnic response slope against their OAHI, and subjected the data to a linear regression analysis. To determine if resting CO_2 retention was correlated with the OAHI, we plotted the resting level of P_{ET,CO_2} for each subject against his or her OAHI. We used a simple linear regression model followed by ANOVA (Sigma Stat 3.0) to determine if the relationship was statistically significant, with significance defined as $p<0.05$.

RESULTS

As shown in table 1, the subject's average RDI and OAHI values were significantly lower in 2006 compared to 1999. Figures 1a and 1b show the RDI and OAHI values for each subject, and it is clear that these values fell with age in all but three subjects, in whom the values were very low to begin with. Weight, height, BMI and BSA all were significantly higher in 2006 compared to 1999 (table 1). The BMI percentile adjusted for age, sex and ethnicity, calculated from the US Centers for Disease Control and Prevention growth charts [9], was higher in 2006 than in 1999 for 11 out of the 14 subjects (fig. 1c). Total sleep time and arterial oxygen saturation nadir measured in the 1999 and 2006 nocturnal sleep studies did not differ significantly (table 1).

The absolute pulmonary ventilation rate measured under resting conditions increased with age (fig. 2a), but was the same when it was expressed as a function of BSA ($p=0.26$; fig. 2b). The rise in resting ventilatory output was associated with a much lower P_{ET,CO_2}, from 44.1 ± 0.8 mmHg in 1999 to 33 ± 1.0 mmHg in 2006 ($p<0.001$; fig. 2c). In contrast to the increase in lung ventilation with age, the resting $P_{0.1}$ showed marked variability at both ages, and the mean values were not significantly different (fig. 2d). It is important to point out that our baseline $P_{0.1}$ values are within the range reported for children of similar age by MARCUS *et al.* [10].

We estimated central CO_2 sensitivity by conducting steady-state CO_2 response tests at 3, 5 and 7% inspired CO_2. The individual data points that were used to define the slope of the V'_E–P_{ET,CO_2} response for all subjects are shown in figure 3a. It is clear from this figure that although the slopes in 1999 and

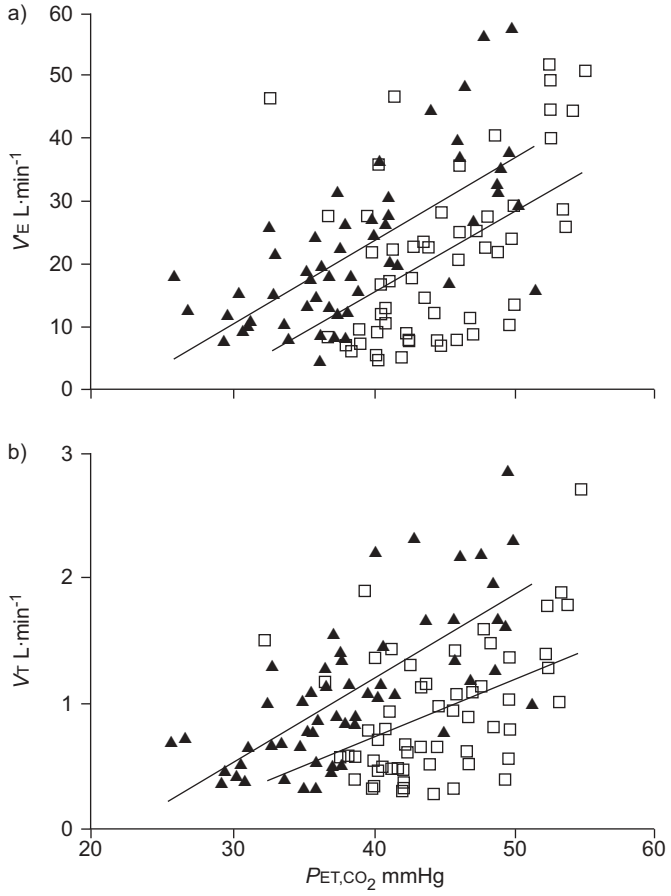

FIGURE 3. a) Minute ventilation–end-tidal CO_2 partial pressure (V'_E–P_{ET,CO_2}) relationship in 1999 (□) and 2006 (▲). Each data point represents a measurement obtained at rest, and in the steady state of breathing gas mixtures with 3, 5 and 7% inspired CO_2 in all 14 subjects. The slope of the relationship was the same in 1999 and 2006 (y=1.28(x)-35.6 and y=1.31(x)-28.6 in 1999 and 2006, respectively; t=0.08, p=0.94), but the regression line obtained in 2006 was markedly left shifted. b) Relationship between tidal volume (V_T) and P_{ET,CO_2} in all subjects. As with V'_E, the slope of the relationship was the same in 1999 and 2006 (y=0.045(x)-1.1 and y=0.066(x)-1.45 in 1999 and 2006, respectively; t=1.43, p=0.16), but the curve in 2006 was markedly left shifted. These data indicate that the left shift in the ventilatory response to CO_2 (a) was due to differences in the V_T response, as the frequency response was unaltered (data not shown).

2006 are not different (y=1.28(x)-35.6 and y=1.31(x)-28.6 in 1999 and 2006, respectively; t=0.08, p=0.94), the curve is markedly left shifted, such that V'_E was much higher at any given P_{ET,CO_2} in 2006 compared to 1999 (fig. 3a). For example, at a P_{ET,CO_2} of 50 mmHg the V'_E estimated from the data shown in figure 3a would be 28.4 L·min^{-1} in 1999 and 36.9 L·min^{-1} in 2006. Similarly, the average x-intercept calculated from the slopes, the so-called apnoea point [11], was significantly different (33.1±1.1 and 26.4±2.7 in 1999 and 2006, respectively; t=2.41, p=0.03). Figure 3b shows that the left shift in the V'_E–P_{ET,CO_2} response curves is due to a corresponding left shift in the V_T–P_{ET,CO_2} response (y=0.05(x)-1.08 and y=0.07(x)-0.34 in 1999 and 2006, respectively; t=1.43, p=0.16), coupled with a frequency response that was identical in 1999 and 2006 (data not shown). To correct for changes in V'_E secondary to growth, we also examined the

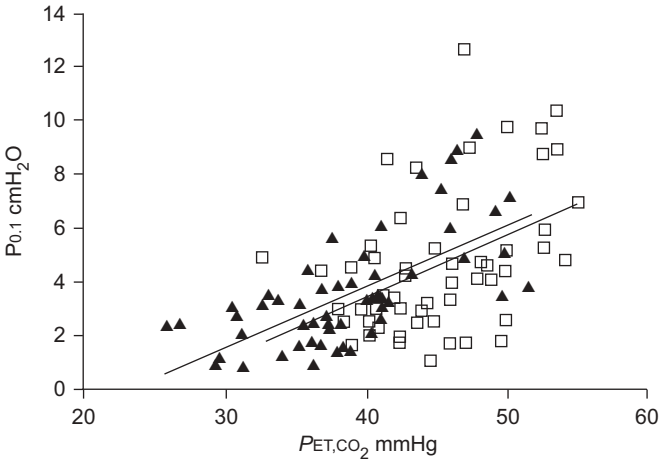

FIGURE 4. Relationship between mouth occlusion pressures measured 100 ms after onset of inspiratory effort ($P_{0.1}$) and end-tidal CO_2 partial pressure (P_{ET,CO_2}) in all subjects. The slopes calculated in 1999 and 2006 were the same (y=0.23(x)-5.7 and y=0.22(x)-5.0 in 1999 and 2006, respectively; t=0.16, p=0.87), suggesting that the central ventilatory response to CO_2 did not change.

V'_E–P_{ET,CO_2} response curves with V'_E expressed as a function of the BSA. Again, there were no significant differences in the slope of the relationship (y=0.65(x)-19.6 and y=0.72(x)-15.3 in 1999 and 2006, respectively; t=0.36, p=0.72).

Interestingly, the $P_{0.1}$–P_{ET,CO_2} slopes in 1999 and 2006 (fig. 4) were statistically identical (y=0.23(x)-5.7 and y=0.22(x)-5 in 1999 and 2006, respectively; t=0.16, p=0.87), and were only slightly left shifted, such that the apnoea point was the same in 1999 and 2006 (26.7±2.2 and 23.7±1.8 in 1999 and 2006, respectively; t=1.24, p=0.24). Individual V'_E–P_{ET,CO_2} and $P_{0.1}$–P_{ET,CO_2} slopes for each subject are shown in figures 5a and 5c. With a few exceptions, the slopes did not change with age, and the group average slopes were the same in 1999 and 2006 (V'_E–P_{ET,CO_2}: 1.7±0.24 and 1.65±0.22, in 1999 and 2006, respectively, t=0.14, p=0.89; $P_{0.1}$–P_{ET,CO_2}: 0.28±0.04 and 0.32±0.05 in 1999 and 2006, respectively, t=0.6969, p=0.49). The individual apnoea points for each subject are shown in figure 5 b and d. Statistical analysis of the individual apnoea points revealed significant differences for the V'_E–P_{ET,CO_2} curves (35.5±1.3 and 24.6±3.2 in 1999 and 2006, respectively; t=3.16, p=0.0082), but not for the $P_{0.1}$–P_{ET,CO_2} curves (29.9±2.5; 2 and 23.7±2.0 in 1999 and 2006, respectively; t=1.4, p=0.19).

DISCUSSION

This is the first longitudinal study of developmental alterations in the ventilatory control of children with SDB in early childhood. Our subjects were, on average, 9 yrs of age in the initial study and 15 yrs of age when the current study was completed. Our main finding is that subjects now have much lower OAHIs and retain much less CO_2 than they did in 1999, despite similar mass-specific resting ventilation rates and a substantial increase in BMI. We also showed that, on average, the slopes of the V'_E–P_{ET,CO_2} or $P_{0.1}$–P_{ET,CO_2} curves were not significantly different in 1999 and 2006, indicating that CO_2 sensitivity during steady state hypercapnic challenge was unchanged. However, the V'_E–P_{ET,CO_2} response was markedly left shifted in 2006 compared to 1999, indicating greater V'_E at

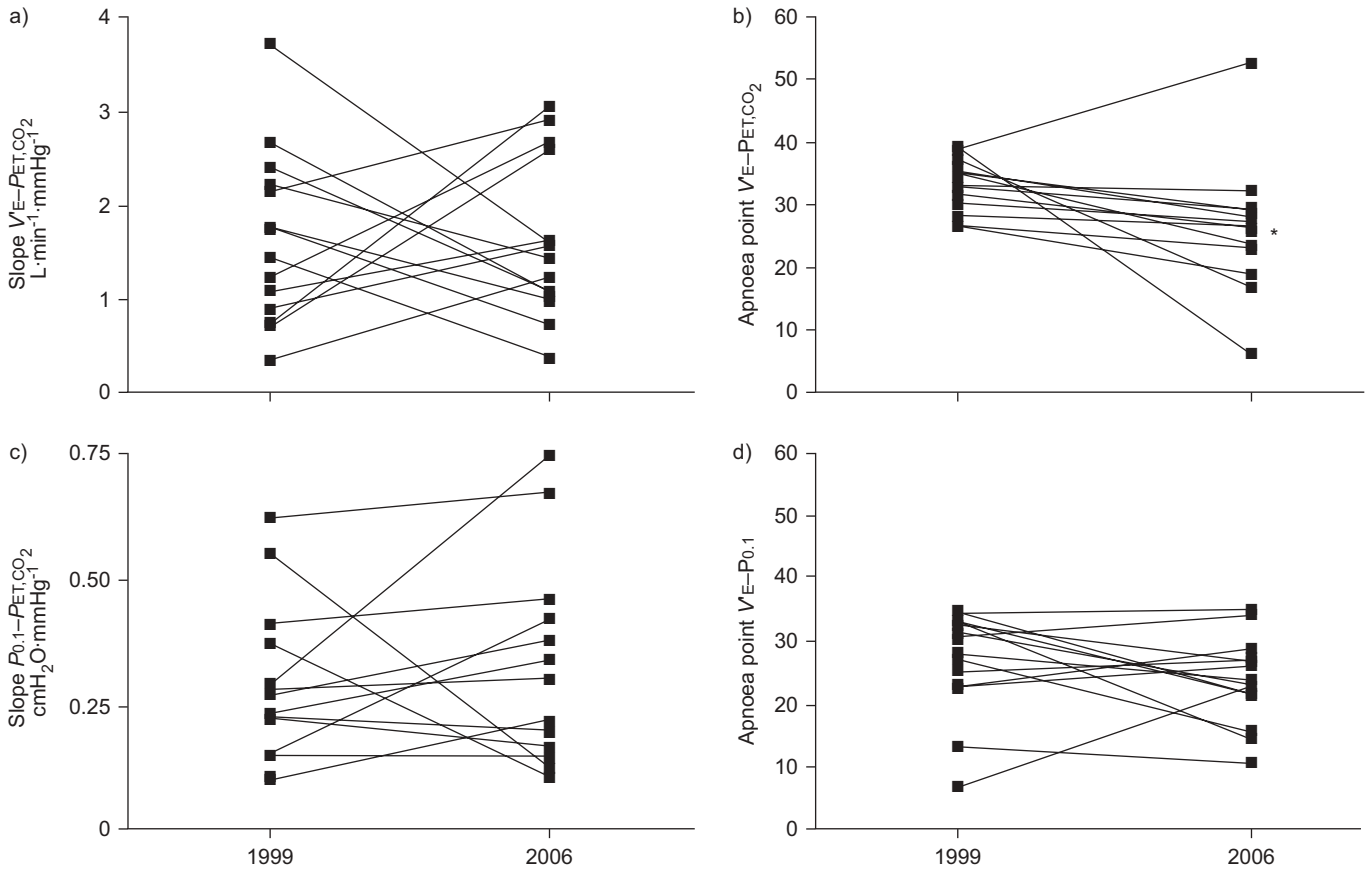

FIGURE 5. a) Individual minute ventilation–end-tidal CO_2 partial pressure (V'_E–P_{ET,CO_2}) and c) $P_{0.1}$–P_{ET,CO_2} slopes in 1999 and 2006 for each of the 14 subjects. These data demonstrate the variability between subjects with respect to the V'_E–P_{ET,CO_2} and $P_{0.1}$–P_{ET,CO_2} relationships, and that on average there was no age-dependent change in either of these relationships. b, d) The apnoea points computed from V'_E–P_{ET,CO_2} and $P_{0.1}$–P_{ET,CO_2} curves, respectively. The apnoea point derived from the V'_E–P_{ET,CO_2} curve was significantly lower in 2006 compared with 1999 (b), consistent with the left shift in the V'_E–P_{ET,CO_2} calculated from the composite data (fig. 3a). The apnoea points derived from the $P_{0.1}$–P_{ET,CO_2} curve were the same in 1999 and 2006, consistent with the lack of change in central ventilatory drive, as shown for the composite data in figure 4. *: $p<0.05$, different from 1999.

a given P_{ET,CO_2}, despite no change in CO_2 sensitivity. This left shift also resulted in much lower apnoea points [11]. Interestingly, there was no left shift in the $P_{0.1}$–P_{ET,CO_2} curve. As will be discussed later, our observations are most likely explained by changes in mechanical factors, *e.g.* a decrease in airflow resistance, rather than changes in the central control of breathing. The fact that the left shift in the V'_E–P_{ET,CO_2} response curve was the result of changes in V_T rather than breathing frequency also supports the idea that the effects were mechanical and not central.

In theory, the increased lung ventilation rate at a given P_{ET,CO_2} with no change in the sensitivity to CO_2 could be explained by a reduction in airway resistance. This is due, in a large part, to somatic growth of the airway as children grow taller [12]. Using the regression equations derived by ZAPLETAL and CHALUPOVA [12], we estimate that nasopharyngeal resistance in our subjects would have fallen by 23% on the basis of the change in height alone (136 cm tall in 1999 *versus* 163 cm tall in 2006, table 1). In addition, it is well known that tonsil size declines with age after reaching a peak size between 4 and 8 yrs of age [13]. There have been anecdotal suggestions that enlarged tonsils, and thus a narrow pharyngeal airway, predispose children to nasal breathing, which in turn leads to hypoventilation through the high-resistance nasal pathway. When our subjects were initially studied, in 1999, we found that their resting P_{ET,CO_2} during wakefulness was significantly elevated, and that it was correlated with the OAHI [1]. Our previous magnetic resonance imaging (MRI) studies showed that a sub-sample of the group studied in 1999 had large adenoids, tonsils and soft palates [14]. We analysed those data by computing the sum of the cross-sectional areas of these soft tissue structures and expressed the sum as a percentage of the nasopharyngeal cross-sectional area. We found that the children with SDB had a narrow nasopharynx as a result of increased soft tissue mass. The present data suggest that this ratio is now smaller. In other words, if their pharyngeal airway grew at a faster rate than the surrounding soft tissue structures, the lumen of the nasopharynx would be enlarged, leading to lower airway resistance. Although we do not have MRI data as part of this study, the increased ventilation and lack of CO_2 retention in the absence of a change in sensitivity to P_{ET,CO_2} is consistent with a larger upper airway lumen. The results of this study and our earlier one are consistent with other data showing hypoventilation and CO_2 retention in young children with enlarged tonsils and SDB [15, 16].

We observed that both the RDI and OAHI decreased over the approximate 6-yr interval between polysomnograms (PSGs) in these subjects. Preliminary examination of data from the entire TuCASA cohort confirms this finding [2]. In contrast to our findings, a previous study in Thai children showed that five out of seven children with obstructive sleep apnoea (OSA) had a higher OAHI over a 3-yr interval [17]. However, PSG was performed in these children because they had symptoms of OSA, and thus there may have been some selection bias. As discussed previously, we suspect that in our study the observed decrease in RDI and OAHI is related to somatic growth of the pharynx, coupled with regression of tonsillar tissue with age. At the initial TuCASA examination, children were studied between the ages of 6 and 11 yrs. This is the age range where some children will have large tonsils resulting in an elevated RDI and OAHI. With normal regression in tonsil size as they become adolescents, there should be a decrease in RDI and OAHI as we found.

Although our observations are consistent with changes in airway resistance, the exact mechanism of the CO_2 retention during quiet breathing at an average age of 9 yrs, but not approximately 6 yrs later remains unknown. One possibility is that the young children ''chose'' to hypoventilate rather than fight the increased flow resistance and, thus, higher work of breathing, that would have been required to drop their P_{ET,CO_2}. This is consistent with the strategy employed by highly trained athletes during peak exercise, wherein they allow themselves to become hypoxic and relatively hypercapnic rather than consume the extra energy that would be required to elevate alveolar ventilation sufficiently to fully correct the blood gas and acid base derangements [18].

The left-shifted ventilatory response to P_{ET,CO_2} is often considered to be due to an ''extra'' stimulus to breathe. If this were the case, we would have expected a left shift in the relationship between $P_{0.1}$ and P_{ET,CO_2}, which we did not observe (fig. 4). Complicating the relationship between $P_{0.1}$ and P_{ET,CO_2} is that the former can be influenced by both respiratory muscle strength and end-expiratory lung volume. Weak inspiratory muscles lead to lower $P_{0.1}$ values during hypercapnic challenges, although the effects are small until the P_{ET,CO_2} exceeds 60 mmHg [19]. This would have little or no impact on our data, as the P_{ET,CO_2} values were $<$60 mmHg in every case (figs 3 and 4). Inspiratory muscle strength increases by ~20% from age 9 yrs to 15 yrs in males [20], suggesting that changes in strength alone as the subjects grew would result in slightly higher $P_{0.1}$ values in 2006 compared to 1999 (fig. 4), but this was not seen.

The $P_{0.1}$ can also be influenced by changes in end-expiratory lung volume, with lower volumes associated with a greater $P_{0.1}$, due to improved muscle length-tension properties and thus improved mechanical advantage [21, 22]. However, the pertinent issue is the end-expiratory lung volume as a percentage of an individual's total lung capacity, as this dictates the length–tension relationship of the respiratory muscles for that particular system [23]. End-expiratory lung volume as a percentage of total lung capacity increases from ~46% in 9-yr-olds (the average age of our subjects in 1999), to 53% in 15-yr-olds (average age in 2006), corresponding to a volume increment of ~400 mL [24]. It has been shown that an increase in functional residual capacity of 500 mL reduces respiratory muscle pressure development by ~10% [23]. In our subjects this would translate into, at most, an 8% decrease in the $P_{0.1}$ ($400/500 \times 10\%$), which would result in only a negligible shift in the $P_{0.1}$–P_{ET,CO_2} curve (fig. 4). Obesity can reduce end-expiratory lung volume independently of age and height, although the effects are small and variable [25, 26] except in severe obesity [27]. Most of our subjects were in a higher BMI percentile in 2006 than they were in 1999 (fig. 1c), with some of them exhibiting severe obesity (*i.e.* BMI values $\geqslant$95th percentile). This could also contribute to a slight leftward shift in the $P_{0.1}$–P_{ET,CO_2} relationship, but again, this was not observed. Finally, although it is possible that hypercapnia could increase airway resistance to a variable extent across the subject population, the $P_{0.1}$ is uninfluenced by airway resistance and behavioural adjustments in ventilatory output [8, 23]. Taken together, our longitudinal data support the contention that the elevated resting P_{ET,CO_2} and the left-shifted V'_E–P_{ET,CO_2} curve in younger children is the result of reduced flow resistance, and probably not due to the addition of an ''extra'' excitatory stimulus to breathe.

The functional consequences of the elevated eupneic P_{ET,CO_2} when the children were younger are unknown. Given that the apnoea point was significantly higher in 1999 than in 2006, one might surmise that the tendency for apnoea was greater in the young children. However, the difference between the apnoea point and the eupneic P_{ET,CO_2} was the same in 1999 and 2006 (1999: 7.7 ± 1; 2006: 6.9 ± 3; p=NS). This difference has been called the CO_2 reserve, and it has been suggested that a smaller reserve increases the propensity for apnoea in adult human subjects [28]. Our subjects had higher RDI values in 1999 than in 2006 despite a similar CO_2 reserve, suggesting that the CO_2 reserve may not predict a predisposition to apnoea in children.

In conclusion, we have examined changes in the control of breathing from childhood to adolescence in a group of subjects that had mild SDB as young children. The main finding is that the rate of pulmonary ventilation at a given P_{ET,CO_2} was much higher, and the eupneic P_{ET,CO_2} much lower at an average age of 15 yrs compared to an average age of 9 yrs. This occurred in the absence of changes in sensitivity to inspired CO_2, suggesting that upper airway resistance decreased as the children grew, leading to improved alveolar ventilation in the absence of significant changes in central ventilatory drive.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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