ORIGINAL RESEARCH

Upper Airway Narrowing during Central Apnea in Obese Adolescents

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Abstract

Rationale: The use of real-time magnetic resonance imaging (MRI) for the evaluation during sleep-related respiratory events can lead to better understanding of airway dynamics.

Objectives: To investigate the dynamic anatomy of the upper airway during central apnea.

Methods: The study included obese adolescents who snore and were otherwise healthy. Subjects underwent an overnight baseline polysomnogram. Subjects slept during a 24-minute real-time upper airway MRI scan wearing a full face mask attached to a pneumotach. Sleep versus wakefulness during the MRI was inferred from the heart rate and respiratory patterns. Central apneas were scored using tracings of facemask airflow and abdominal bellows. The cross-sectional area of the upper airway before, during, and after each central apnea event was recorded.

Results: Eight subjects were studied and 57 central apnea events were observed during real-time MRI scanning during natural sleep. The median age of subjects was 14.0 years (interquartile range [IQR], 13.5 to 15.5). The median average reduction in cross-sectional area during central apnea events was -38% (IQR, -27 to -51) for primary snorers and -45% (IQR, -40 to -54) for subjects with obstructive sleep apnea. The percentage decrease in cross-sectional area of upper airway during a central apnea event was positively correlated to the length of the central apnea ($\rho = 0.389$; $r^2 = 0.152$; $P = 0.003$).

Conclusions: We observed that there is upper airway narrowing during central apneas during natural sleep in obese adolescent subjects, using real-time MRI.

Keywords: sleep-disordered breathing; cine magnetic resonance imaging; airway obstruction; obstructive sleep apnea

Obese children are at risk for obstructive sleep apnea syndrome (OSAS) and other forms of sleep-related breathing disorders (SRBD) (1–3). SRBD, including OSAS, contribute to serious health problems, such as daytime sleepiness, neurocognitive dysfunction, glucose intolerance, and cardiovascular disease (2, 4). SRBD is also associated with psychosocial effects, including fatigue, inattention, depressive disorders, and poor performance in school (1, 2). We performed dynamic magnetic resonance imaging (MRI) of the upper airway of obese adolescents with snoring to understand the anatomical changes during OSAS.

Upper airway narrowing in obese children is multifactorial, including fat deposition in the neck and tongue and adenotonsillar hypertrophy. The increase in soft tissue load in the upper airway can cause

alterations in mechanical function of upper airway muscles (5, 6). The stimulation and control of the upper airway muscles is centrally controlled. Most of the upper airway muscles are stimulated on inspiration to create a patent as well as stable airway under the negative pressure created during inspiration to allow adequate airflow.

Central apnea is defined by the cessation of airflow without respiratory effort. This differs from obstructive apnea, in which an ongoing respiratory effort continues during upper airway obstruction (2, 4). A mixed apnea is an event that is initiated with absent central drive followed by respiratory effort to overcome an occluded airway. The characteristics of mixed apnea suggest that there may be overlap in the mechanism of both obstructive and central apnea. Any narrowing of the upper airway during a central apnea could predispose to a subsequent obstructive apnea. The changes in airway dynamics during a central apnea have not been extensively studied or described. Bradley and colleagues studied eight subjects with idiopathic central apnea and eight weight-matched snoring control subjects (7). The study concluded that there was increased pharyngeal compliance as lung volume decreased suggesting a role of lung volume in the etiology of central apnea. Another study by Badr and colleagues performed in adults used fiber optic nasopharyngoscopy to determine pharyngeal patency during central apnea and revealed complete pharyngeal occlusion in 146 of 160 spontaneously occurring central apneas (8).

Our group and others have used dynamic MRI techniques to evaluate the upper airway in patients with OSAS (9–12). These studies have demonstrated that MRI can be a useful technique to characterize airway obstruction under dynamic conditions. Real-time MRI imaging to study the features of central apnea has not been performed. In adults with OSAS, central apneas are considered part of the pathology of OSAS and therefore included in the apnea–hypopnea index (AHI) by convention. In pediatric patients, central apneas are omitted from the AHI, as they have not been considered to be contributive to OSAS.

We hypothesized that central apneas could contribute to OSA via upper airway narrowing during an event in obese adolescents with SRBD. We used real-time MRI of the upper airway in these obese adolescents during natural sleep to explore this hypothesis. Central apnea events occurring spontaneously without local anesthesia or airway instrumentation and without external negative airway pressure or induced occlusions were analyzed.

Methods

The study was approved by both the Children's Hospital Los Angeles and University of Southern California institutional review boards referencing principles of the Declaration of Helsinki, protocols CCI-10-00177 and HS-11-00401, respectively. Informed consent from the parents and assent from the subjects were obtained. Inclusion criteria were age 13 to 21 years, history of snoring, obesity with a body mass index (BMI) percentile greater than 85%, and otherwise healthy. Individuals were excluded for chronic medical conditions other than allergic rhinitis or intermittent asthma and use of any medications other than intermittent bronchodilators or nasal steroids. Subjects were also excluded if they had metallic dental bracing or any ferromagnetic materials that would interfere with image quality or were contraindicated for MRI. Each subject underwent baseline diagnostic overnight polysomnography (PSG). The PSG was staged and scored as per American Academy of Sleep Medicine criteria (13). OSA was defined as having an obstructive AHI index of 5 events/h or greater with snoring. Subjects who did not meet OSA criteria were labeled as having primary snoring, as all subjects presented with snoring.

Dynamic Airway Imaging by MRI

On a separate occasion, the subjects underwent a dynamic MRI study in the supine position in the MRI scanner. The study was performed at night between 21:00 and 01:00 to allow for natural sleep. Before the start of the study, the subjects were placed into the MRI scanner for a 15- to 30-minute mock session to assess the comfort of the subject and tolerance of the MRI environment. Subjects lay supine in the MRI scanner on a memory foam mattress during a simulated scan. All safety precautions were reviewed, including orientation to the signaling device to be used if the subject experienced discomfort.

After the mock session, subjects were given the opportunity to ask questions and have these answered by the research team. The subjects who tolerated the mock session advanced to the study protocol. The study was performed with a General Electric HDxt 3.0 Tesla scanner system at the University of Southern California Healthcare Consultation Center. A body coil was used for radiofrequency signal transmission, and a six-channel carotid receive coil was used for radiofrequency signal reception.

Throughout the MRI scan, the research team could communicate with the subject to ensure comfort and safety. The study was paused or terminated if the subject felt uncomfortable. Physiological signals were monitored and recorded continuously during the MRI scan. An optical fingertip plethysmograph (Biopac Inc.) was used to measure heart rate and oxygen saturation. A respiratory transducer (Biopac Inc.) and the scanner's built-in respiratory bellows (GE Healthcare) were used to measure respiratory effort. A snugly fitted mask covering the nose and mouth (Hans Rudolph Inc.) was used for measurement of airway pressure as a surrogate measurement of airflow. The airway pressure from the mask port was transmitted to a pressure transducer (Validyne Engineering Inc.). Real-time imaging with an axial scan with the slice of airway midway between the soft palate and the epiglottis in two-dimensional Fourier transform gradient echo sequences was used for imaging the airway (14) (two-dimensional Fourier transform parameters: FOV = 16 cm^2; slice thickness = 5 mm; in-plane = 1.6 mm^2; repetition time = 8.02 ms or 8.66 ms; partial k-space [70/100]; scan time = 28 min). MRI images were obtained with a frame rate of 3.3 frames per second using parallel imaging (15) or Projection onto Convex Sets (POCS) formalism, the method for SENSitivity Encoded data reconstruction (16). Airway cross-sectional areas were computed using semiautomatic segmentation on the basis of seeded region growing (17).

Scoring Respiratory Events during MRI

Respiratory events were determined breath by breath using airflow, oxygen saturation, and respiratory effort signals. Airflow was determined using mask pressure. Respiratory effort was determined using

abdominal bellows. Sleep and wakefulness were inferred from the heart rate, mask pressure, oxygen saturation, and respiratory signals by American Board of Pediatrics board-certified sleep medicine specialist. Regular respiratory patterns, steady heart rate, and tracing free of movement artifact were the three criteria that were used to infer sleep. Subjects were queried after completion of the MRI scan for their subjective assessment of whether they could fall asleep during the study. A central apnea event was defined by absent respiratory effort, as demonstrated by no displacement of the respiratory bellows tracing as well as zero mask pressure recording demonstrating no airflow, both lasting longer than the duration of two baseline breaths. If there was a displacement of the respiratory bellows, the apnea would be considered obstructive. Figures 1 and 2 demonstrate typical mask pressure and abdominal bellows displacement tracings. Respiratory events were only scored during periods of presumed sleep with preceding

stable heart rate, respiratory rate, and oxygen saturation as measured by pulse oximetry (Sp_{O_2}) greater than 95%. Hypoxemia or arousal was not required to score central apnea, as the goal was to describe the characteristics of individual events and not to arrive at a clinical diagnosis.

Statistical Analysis
Descriptive statistics were used to summarize and describe the demographic characteristics and the distribution of variables. Continuous variables were summarized as mean and standard deviation for normally distributed data and median and interquartile range for nonnormally distributed data. Categorical variables were summarized as frequencies and percentages. Correlation between percentage change in airway cross-sectional area before and during central apnea events was analyzed by Pearson correlation.

Multilevel mixed-effect model was used to examine the association in airway cross-sectional area in relation to age, sex,

obstructive AHI, BMI, and sleep phenotype. Generalized estimating equations were used to examine the change in airway cross-sectional area before, during, and after central apnea events. Both of these methods of computation were used to appropriately account for nested data and repeated measures, respectively. Significance level was set at 0.05 with a two-sided test. All computations were performed using Stata/SE 15.1 (StataCorp).

Dynamic image reconstruction and computation of the cross-sectional areas were performed using custom software implemented in MATLAB (The Mathworks). The largest cross-sectional area of the upper airway just before the central apnea, the smallest cross-sectional area during the central apnea, and the largest cross-sectional area immediately after the central apnea were generated automatically by the computer. The baseline Sp_{O_2} before a central apnea event and nadir Sp_{O_2} after the central apnea event were also recorded.
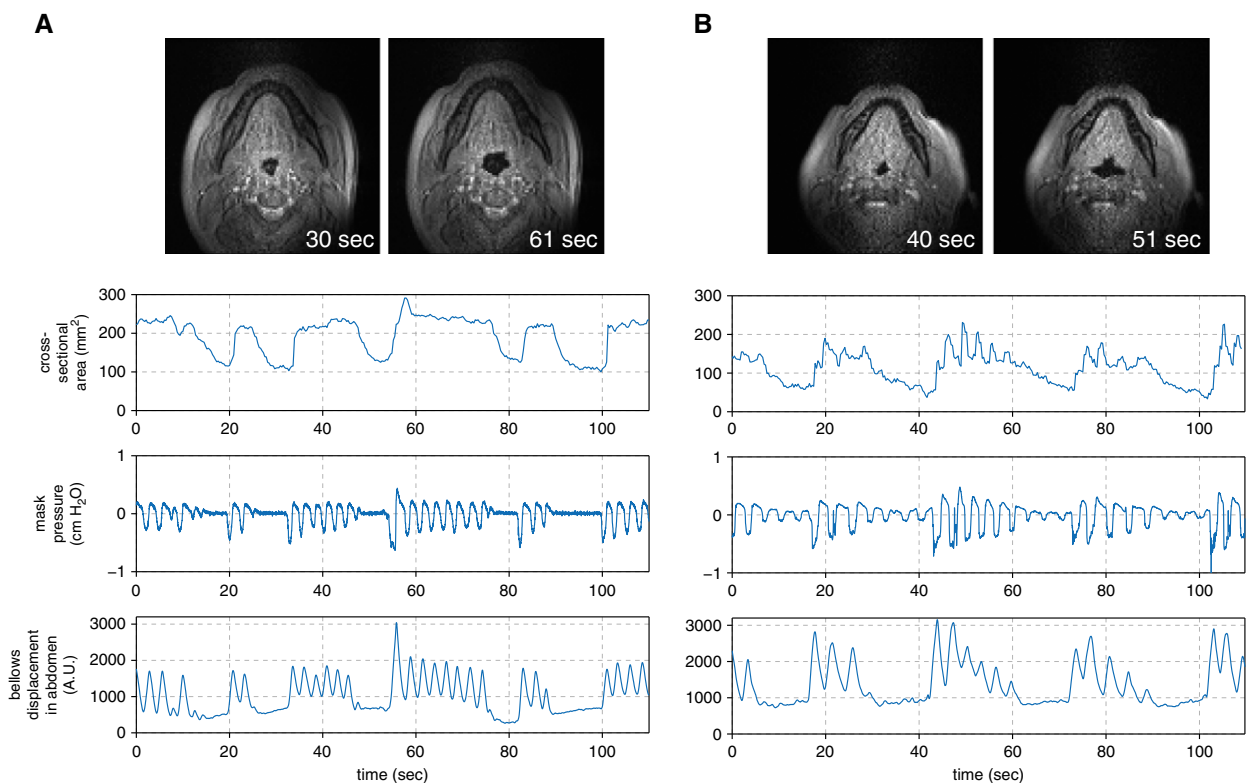
Figure 1. Selected retroglossal frames and plots of cross-sectional area, pressure, and respiratory effort from two subjects using real-time magnetic resonance imaging. These illustrate (*A*) central sleep apneas with periodic breathing (Subject 2, 14-yr-old boy); (*B*) hypopneas with periodic breathing (Subject 5, 17-yr-old girl). The left image of *A* and *B* panels depicts at minimum cross-sectional area and the right image during tidal breathing. All events and airway dynamics were obtained during natural sleep.

Figure 2. Real-time magnetic resonance imaging (MRI) of a representative central apnea event is depicted at three time points in the top panel: (*A*) indicates just before the central apnea event; (*B*) at the cross-sectional area nadir during the central apnea; and (*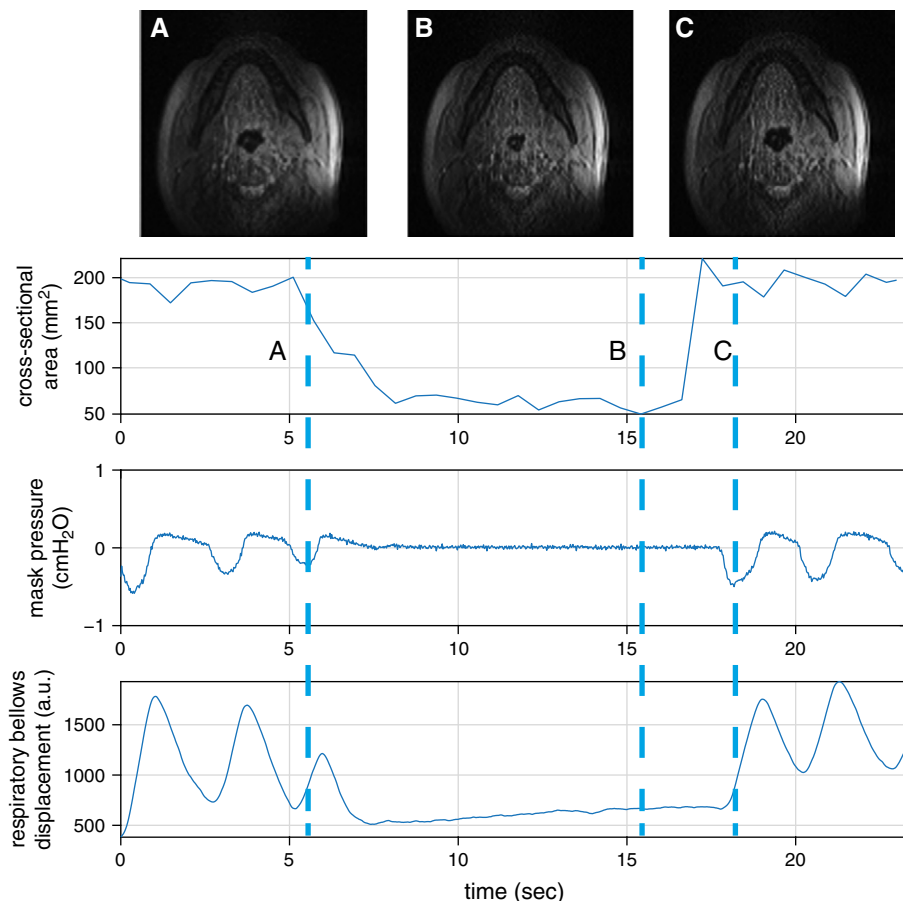C*) after breathing resumes. Airway cross-sectional area, mask airflow, and respiratory bellows displacement are also depicted, demonstrating a decrease in airway size during paused respiration during the central apnea. Video E1 shows airway narrowing during central apnea by real-time MRI over the 25-second period.

Results

Four girls and four boys were studied, with a median age of 14 years (IQR, 13.5–15.5 yr) and a median BMI of 29.4 kg/m^2 (IQR, 28.1–31.5 kg/m^2). Table 1 describes the demographic data as well as PSG results and number of central apnea events during sleep and MRI. Two subjects had an elevated obstructive AHI of 10.6 and 21.2 events/h, consistent with moderate to severe OSA. There were 57 identified central apnea events during the MRI scan periods. Figure 2 and Video E1 (online supplement) demonstrate a typical central apnea event. The data for these eight subjects showed that there was no statistical difference in airway cross-sectional area between male and female subjects when comparing measurements made before, during, and

after central apnea events (β, 26.8; 95% confidence interval [CI], −28.2 to 81.8; $P = 0.3$). However, there is a difference in airway cross-sectional area between OSA and primary snorer when comparing measurements made before, during, and after central apnea events (β, −83.7; 95% CI, −110.6 to −56.8; $P < 0.0001$). On the basis of the multilevel mixed-effects model, there are no significant associations in the cross-sectional airway area with AHI score (β, 0.9; 95% CI, −6.7 to 8.5; $P = 0.8$) and age (β, −1.9; 95% CI, −16.9 to 13.2; $P = 0.8$). However, there was a statistical association in airway cross-sectional area with BMI (β, 5.1; 95% CI, 3.7–6.63; $P < 0.0001$). In these 57 events, there was no association between airway cross-sectional area and length of events (β, −2.9; 95% CI, −6.5 to 0.7; $P = 0.1$). However, there was a statistical

difference in airway cross-sectional area comparing measurements made before, during, and after central apnea events (β, 1.8; 95% CI, 0.03–3.5; $P = 0.04$), demonstrating a decrease in airway cross-sectional area (β, −43.5; 95% CI, −53.2 to −33.8; $P < 0.0001$) during central apnea events as compared with those just before and just after the central apnea period (Table 2) for both primary snorer subjects and subjects with OSA. There was a correlation in the percentage change of airway cross-sectional area from before to during events with length of event (ρ = 0.39; $P = 0.003$), as seen in Figure 3.

Discussion

Upper airway collapse is considered a characteristic of obstructive apnea. Obesity is a known risk factor for OSA, but central sleep apnea and its association with obesity-related OSA is less well understood. PSG can identify central apnea events and demonstrate changes in oxygenation and ventilation associated with the event. However, the impact of central apneas on upper airway dynamics is not visualized during PSG. We used real-time two-dimensional and three-dimensional MRI to evaluate airway dynamics during sleep. This novel technique has the potential to be an important investigational tool that can demonstrate the anatomical characteristics of the upper airway in a dynamic fashion at rest and during respiratory events. This technique can lead to a better understanding of upper airway characteristics that could direct treatment options in patients with sleep apnea.

Hoffman and colleagues have described the appearance of central sleep apnea after the treatment of OSAS with continuous positive airway pressure (CPAP) (18). In many patients in the study, the central apneas resolved in the initial months of CPAP therapy. However, in a minority of patients, central apnea events persisted and resulted in impaired sleep despite CPAP therapy. This outcome suggests that there is an association in the underlying mechanism of obstructive and central apnea events, and it may be that the mechanisms responsible for both central and obstructive sleep apnea are interrelated.

The concept of loop gain and its relation to central apnea has been described in a number of studies (19–23). Loop gain is a concept borrowed from control theory

Table 1. Subject demographic data and polysomnography results

Subject	Sex	Age (yr)	BMI (kg/m²)	Polysomnography Results (events/h)					Real-Time MRI Central Apnea Events (n)
				Diagnosis	Obstructive AHI (Apnea Hypopnea Index)	Central Apnea Index	Apnea Index	Desaturation Index	
1	Male	15	29.2	Primary snoring	0.7	0	0.7	0.2	6
2	Male	14	46.0	OSA	10.6	0.5	11.1	12.2	16
3	Male	16	29.5	Primary snoring	0.6	0.2	0.8	0.1	12
4	Male	13	28.0	Primary snoring	3.8	5.8	9.6	3.4	3
5	Female	17	26.9	Primary snoring	1.7	0	1.7	0.2	15
6	Female	13	28.1	OSA	21.2	3.2	24.4	17.3	1
7	Female	14	30.2	Primary snoring	2.5	0.2	2.7	3.2	1
8	Female	14	32.8	Primary snoring	1.2	0.2	1.4	0.3	3

Definition of abbreviations: AHI = apnea hypopnea index; BMI = body mass index; MRI = magnetic resonance imaging; OSA = obstructive sleep apnea.
Polysomnography results include the apnea index, which combines obstructive, hypopnea, and central apnea events.

that reflects the stability of the ventilatory control system. Malhotra and colleagues categorized two mechanisms for central apnea: central apnea with high loop gain and central apnea with low central drive (4). A study conducted by Franklin and colleagues evaluating the effect of oxygen therapy in adult patients with central apnea concluded that oxygen therapy effectively reduced central sleep apnea in eucapnic patients, presumably those with ventilatory instability due to high loop gain (24). Their study suggested that there was a decrease in central apnea events as supplemental oxygen made ventilation more stable by eliminating increased ventilation in response to hypoxemia that results in a decrease in CO_2 and a temporary cessation in ventilatory drive. Our data suggest that stabilization of the ventilatory system may also decrease the risk of OSA, to the extent that upper airway narrowing via central apnea may be a contributing factor.

Chou and colleagues compared central sleep apnea in obese and nonobese children with SRBD (25). The study concluded that the central apnea index in the obese group was significantly lower than in the nonobese group. Contradicting this study, Verhulst and colleagues studied children and adolescents with SRBD and found that OSA had no association with abdominal obesity (3). However, higher levels of abdominal obesity and fat mass were associated with central sleep apnea. This study suggests that an increase in soft tissue load in the upper airway in obese patients could alter the neuromuscular activity or blunt the response from the respiratory center that is responsible for maintaining the upper airway muscle tone. It is possible that the decrease in airway cross-sectional area during central apnea events identified in our study of obese subjects may have been impacted by upper airway adiposity despite the lack of a relationship with BMI, although there was a statistical relationship between BMI and the absolute airway cross-sectional area before central apneas.

Our study identified a decrease in cross-sectional area of the upper airway during central apnea. This finding suggests that the passive airway narrowing during central apnea is related to and may contribute to the severity of OSAS. The innate collapsibility of the upper airway is unmasked during a central apnea with the cessation of input from the center of respiratory control. The airway narrowing demonstrated in our study during and after central apneas likely predisposes to airway obstruction during resumption of respiratory effort, yielding events described as mixed apneas. We have found progressive airway narrowing as the length of central apneas increased, likely making the risk of airway obstruction more probable with resumption of effort.

Limitations

We studied subjects in natural sleep; however, MRI was only during the first half of the night, and thus we presume that most of our subjects did not enter rapid eye movement (REM) sleep. We believe that it would be important to also evaluate the airways during REM sleep when the airway is innately more collapsible. In addition, using MRI-compatible electroencephalogram to document sleep stages would be ideal. In lieu of sleep staging by electroencephalogram, we inferred sleep versus wake by respiratory rate, heart rate, and motion patterns to address this challenge. Given the environment of the MRI scanner, it is also possible that our subjects were mostly in N1 sleep, with episodic arousals leading to oscillations in ventilatory control between sleep and wakefulness predisposing to central apnea. This may be one explanation for the increased number of central apneas

Table 2. Airway cross-sectional area

Phenotype	No.	Airway Cross-Sectional Area (mm²)			
		Before CA	During CA	After CA	Change
Primary snorer	40	58 (36 to 94)	39 (25 to 51)	59 (39 to 105)	−38% (−27 to −51)
OSA	17	194 (184 to 208)	105 (83 to 118)	205 (195 to 210)	−45% (−40 to −54)

Definition of abbreviations: CA = central apnea; OSA = obstructive sleep apnea.
Data are median (interquartile range) unless otherwise noted. The airway cross-sectional area was measured using real-time magnetic resonance imaging during CA events. CA events were grouped by subject sleep diagnosis as primary snorer or OSA. Median airway cross-sectional area measurements were determined just before change during CA event, during the CA event at the airway cross-sectional area nadir, and after respiratory effort resumed. The percent change in cross-sectional area during the CA event was calculated as a comparison between during the CA and before the CA.
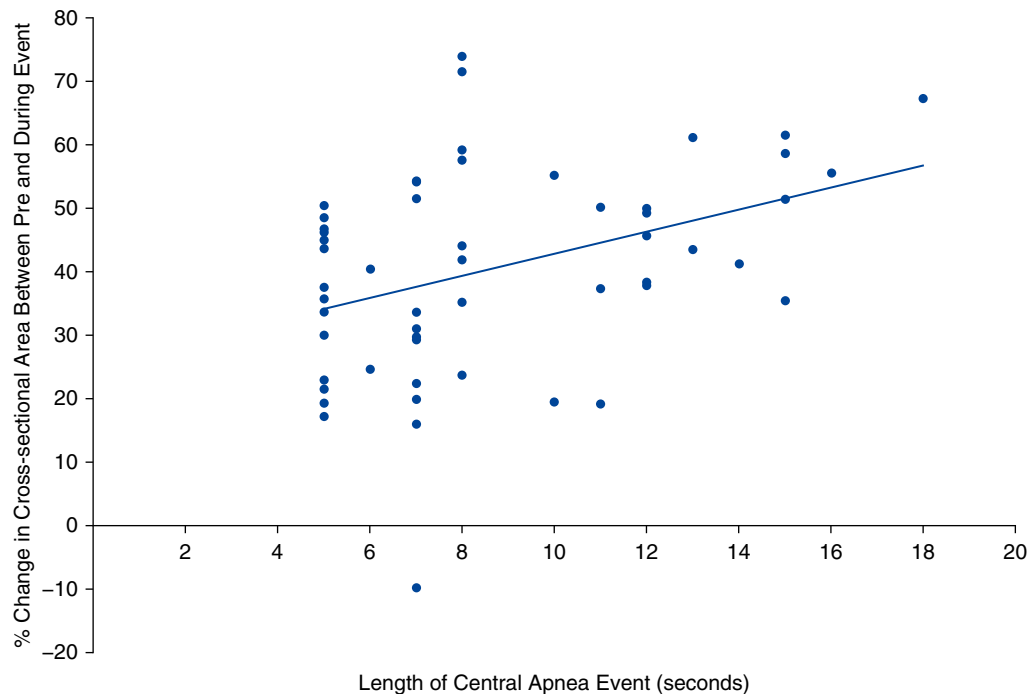
Figure 3. Change in airway cross-sectional area increases with increasing length of the central apnea event in all (*n* = 57), except for one event. As described in Table 1, the percent change in cross-sectional area during the central apnea event was calculated as a comparison between area during the central apnea and before the central apnea. $\rho = 0.34$; $r^2 = 0.15$; $P = 0.003$.

observed during the MRI study in comparison to the number seen in the baseline PSG. A second explanation is that with the oronasal mask in place there was an increase in resistance within the breathing circuit leading to an increased respiratory rate and potential for lower arterial carbon dioxide pressure that was below the apneic threshold leading to central apnea. These factors, though limitations, were to our advantage, leading to the increased number of observable events.

We used only one anatomical axial image to evaluate the airway, and there is a possibility that airway narrowing above or below the imaged slice during central apneas was not appreciated. Although MRI is an ideal investigational tool for dynamic imaging, the acoustic noise produced by the MRI scanner does not

create an ideal environment for people to fall asleep (26).

The small sample size is a limiting factor in our study. In addition, our study included only obese subjects. Similar imaging studies performed on nonobese subjects could provide additional information about central apneas and the association with other physiological factors, such as mucosal adhesiveness of upper airway and mechanoreceptor and airway muscle responsiveness, thus providing additional information about the impact of obesity on the extent of airway narrowing during central apnea.

Conclusions

Central sleep apnea is a distinct entity in patients with SRBD; however, it has received limited attention in the pediatric population

beyond infancy. AHI is an important indicator to understand the frequency and severity of obstruction, but by convention central apnea events are excluded when deriving the AHI in pediatric populations. Our study demonstrates that central sleep apneas are complex events that involve partial collapse and could contribute to the severity of OSAS. It may be prudent to reexamine the exclusion of central apnea from the AHI in the pediatric population. The use of dynamic MRI, or other emerging imaging techniques, during natural sleep could help to characterize the degree and level of airway obstruction and potentially inform the medical and surgical approaches to therapy. ∎

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