

## Upper Airway Genioglossal Activity in Children with Sickle Cell Disease

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**Study Objectives:** The prevalence of obstructive sleep apnea syndrome (OSAS) in sickle cell disease (SCD) has been reported to be higher than that in the general pediatric population. However, not all subjects with SCD develop OSAS. We hypothesized that SCD patients with OSAS have a blunted neuromuscular response to subatmospheric pressure loads during sleep, making them more likely to develop upper airway collapse.

**Design:** Subjects with SCD with and without OSAS underwent pressure-flow measurements during sleep using intraoral surface electrodes to measure genioglossal EMG (EMG<sub>gg</sub>). Two techniques were applied to decrease the nasal pressure ( $P_N$ ) to subatmospheric levels, resulting in an activated and relatively hypotonic upper airway. The area under the curve of the inspiratory EMG<sub>gg</sub> moving time average was analyzed. EMG<sub>gg</sub> activity was expressed as a percentage of baseline. Changes in EMG<sub>gg</sub> in response to decrements in nasal pressure were expressed as the slope of the EMG<sub>gg</sub> vs. nasal pressure (slope of EMG<sub>gg</sub>- $P_N$ ).

**Setting:** Sleep laboratory.

**Participants:** 4 children with SCD and OSAS and 18 children with SCD but without OSAS.

**Results:** The major findings of this study were: (1) using the activated but not the hypotonic technique, the slope of EMG<sub>gg</sub>- $P_N$  was more negative in SCD controls than SCD OSAS; (2) the slope of EMG<sub>gg</sub>- $P_N$  was significantly lower using the activated technique compared to the hypotonic technique in SCD controls only; (3) similarly, the critical closing pressure,  $P_{crit}$ , was more negative using the activated technique than the hypotonic technique in SCD controls but not in SCD OSAS.

**Conclusion:** This preliminary study has shown that children with SCD but without OSAS have more prominent upper airway reflexes than children with SCD and OSAS.

**Keywords:** Critical pressure, slow wave sleep, sleep disordered breathing

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### INTRODUCTION

The prevalence of the obstructive sleep apnea syndrome (OSAS) in patients with sickle cell disease (SCD) has been reported to be over 10%,<sup>1</sup> which is manyfold higher than that among children in the general population.<sup>2</sup> The pathophysiology of OSAS in children with SCD is not fully understood. Current knowledge of OSAS suggests that both anatomical and neuromuscular factors contribute to the pathogenesis of OSAS in children.<sup>3</sup> Adenotonsillar hypertrophy is thought to be a major anatomical contributor to OSAS in patients with SCD. Children with SCD may be at increased risk for the development of adenotonsillar hypertrophy as a compensatory response to functional asplenia, or as a result of recurrent upper respiratory infections because of lack of opsonization of bacterial pathogens.<sup>4,5</sup> However, even with enlarged tonsils and adenoids, children with SCD do not develop upper airway occlusions during wakefulness. Thus, it is possible that among those children with SCD and OSAS, the upper airway during sleep is more collapsible compared to children with SCD but no OSAS because of compromised upper airway neuromuscular activity, and hence obstructive events occur.

Normal upper airway neuromuscular responses depend on a functional central nervous system. However, cerebral vasculopathy is a major cause of morbidity and mortality in subjects with SCD. Cerebral vasculopathy can be manifested as overt strokes, which are cerebral infarctions with neurological symptoms, or silent infarcts, which are not associated with focal neurological symptoms.<sup>6</sup> Ohene-Frempong et al. reported that 11% of patients with SCD had their first overt stroke by 20 years of age.<sup>7</sup> Silent infarcts were detected with brain magnetic resonance imaging (MRI) in 22% of patients with SCD aged 6 to 19 years.<sup>8</sup> In children with SCD younger than 6 years of age, the prevalence of silent infarct was reported to be similar.<sup>9</sup> It is possible that cerebral vasculopathy in children with SCD results in abnormal regulation of upper airway muscles during sleep, and hence increases the risk of OSAS.

For this preliminary study, we hypothesized that SCD patients with OSAS have a blunted neuromuscular response to subatmospheric pressure loads during sleep, making them more likely to develop upper airway collapse.

### METHODS

Subjects with SCD underwent baseline polysomnography using standard pediatric techniques.<sup>10</sup> On a separate night, measurement of activated and hypotonic upper airway flow and genioglossal electromyographic (EMG<sub>gg</sub>) activity in response to subatmospheric upper airway pressure challenges during NREM sleep was conducted. Cerebral vasculopathy was evaluated using brain MRI. The Institutional Review Board at the Children's Hospital of Philadelphia approved the study. In-

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**Table 1**—Demographic and polysomnographic data

|  | SCD OSAS<br>(n = 4) | SCD Controls<br>(n = 18) |
|--|---------------------|--------------------------|
| Age (years)                            | 15 (13 to 17)       | 14 (7 to 18)             |
| Male, (N, %)                           | 3 (75)              | 9 (50)                   |
| Body mass index Z-score                | -0.5 (-3.3 to -0.4) | -0.4 (-3.1 to 1.0)       |
| Apnea hypopnea index (N/h)             | 6.7 (3.0 to 27.0)   | 0.3 (0.0 to 1.1)*        |
| Arterial oxygen saturation nadir (%)   | 80 (69 to 91)       | 87 (71 to 96)            |
| Peak end-tidal CO <sub>2</sub> (mm Hg) | 53 (47 to 58)       | 53 (41 to 61)            |
| Cerebral vasculopathy (N)              | 0                   | 3                        |

\*P < 0.001. Data presented as median (range) unless otherwise specified.

formed consent was obtained from subjects aged 18 years and older, and from the parents or legal guardians of younger subjects. Assent was obtained from subjects aged 7 years and older.

### Study Group

Subjects with SCD, aged 5-18 years, were recruited. The lower age limit was set to exclude those who were too young to cooperate with the face mask and other aspects of the protocol. Children who were treated with hydroxyurea, chronic transfusions, or previous adenotonsillectomy were excluded. Since children with SCD have lower baseline oxygen saturation,<sup>11</sup> their oxygen saturation tends to be in the steep section of the oxygen-hemoglobin dissociation curve. Therefore, children with SCD tend to have more scorable obstructive hypopneas. For this study, subjects with an obstructive apnea hypopnea index (AHI)  $\geq$  3/h were recruited as cases of OSAS (SCD OSAS), and subjects with an AHI  $\leq$  1.5/h were recruited as controls (SCD control).<sup>12-15</sup>

### Pressure-Flow and EMG Measurements

A dental impression of the lower anterior 4-5 teeth made of dental putty (Splash!, Discus Dental, Inc., Culver City, CA) with surface stainless steel electrodes (A-M Systems, Inc., Sequim, WA) was customized for each subject.<sup>16-22</sup> The subjects wore the dental mold throughout the sleep study. The surface electrodes were fitted to rest against the base of the genioglossal muscle to obtain upper EMG signal from the airway muscles, presumably primarily from the genioglossus.

Routine polysomnographic measurements were obtained. In addition, the subjects wore a continuous positive airway pressure (CPAP) full face mask (Philips Respironics, Murrysville, PA) attached to a heated pneumotachometer (Hans Rudolph, Inc., Kansas City, MO) and differential pressure transducer (ADInstruments, Colorado Springs, CO). Nasal pressure ( $P_N$ ) was measured at the mask, using a differential pressure transducer with a demodulator (Validyne Engineering Corp., Northridge, CA) referenced to atmosphere. Signals were acquired on a PowerLab system (ADInstruments, Colorado Springs, CO) and simultaneously displayed on a Rembrandt polysomnography system (Embla, Denver, CO).  $P_N$  was altered in either a positive or subatmospheric direction, using a device provided by Philips Respironics.<sup>23,24</sup> A toggle switch allowed the patient to be switched rapidly between positive and negative nasal pressure, ranging from -25 to +30 cm H<sub>2</sub>O.

Two techniques were applied to decrease the nasal pressure to subatmospheric (negative) levels, resulting in an activated

and relatively hypotonic upper airway.<sup>19-21,25</sup> Application of negative upper airway pressure results in activation of upper airway dilator muscles,<sup>26,27</sup> whereas positive pressure suppresses EMGgg activity during sleep.<sup>28</sup> Using the activated technique, the holding pressure, i.e., the highest  $P_N$  at which flow limitation first became discernible, was determined. At that pressure level, upper airway muscle activities are relatively suppressed. The  $P_N$  was then dropped in 2 cm H<sub>2</sub>O steps every 5 breaths to lower pressure levels until arousal or obstructive apnea occurred. This technique results in upper airway activation. Using the hypotonic technique, the studies were initiated at the holding pressure.  $P_N$  was then acutely decreased by 2 cm H<sub>2</sub>O for 5 breaths, following which it was rapidly returned to the holding pressure.  $P_N$  was dropped repeatedly to incrementally lower levels, with

a return each time to the holding pressure, until either apnea or arousal occurred. Previous studies in children demonstrated that EMGgg is at a low level for the first 3 breaths of negative pressure, and begins to increase by the 4th breath.<sup>19-21</sup> This technique results in an upper airway with minimal activation during the first 3 breaths of negative pressure. Because arousal often occurred with the trials, multiple trials using both the activated and the hypotonic technique were performed during NREM sleep. Trials performed during spontaneous respiratory events or other periods of respiratory instability were excluded from analysis. For each technique, the trial reaching the lowest  $P_N$  before arousal/apnea was selected for data analysis.

### Data Analysis

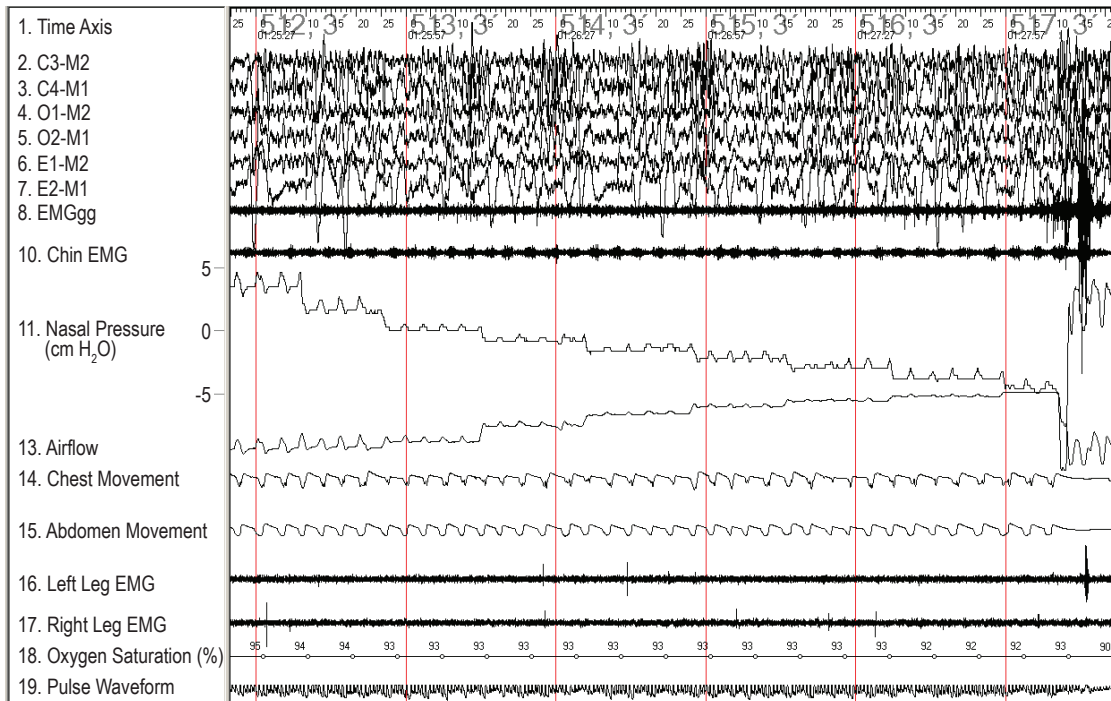
Pressure-flow curves were constructed based on analysis of flow-limited breaths, and the critical closing pressure ( $P_{crit}$ ) as well as the slope of the pressure-flow curve (SPF) were calculated.<sup>16,20,29</sup>  $P_{crit}$  was defined as the extrapolated nasal pressure at which flow reached zero. We used -25 cm H<sub>2</sub>O to represent  $P_{crit}$  when the extrapolated  $P_{crit}$  was  $<$  -25 cm H<sub>2</sub>O, since -25 cm H<sub>2</sub>O was the lowest pressure our device could provide.<sup>16,19,20,23</sup> The SPF is the ratio of changes in flow to changes in nasal pressure, and is used to represent the conductance of the upper airway. A high SPF corresponds to an upper airway with low conductance.<sup>16</sup> We used both  $P_{crit}$  and SPF to characterize the flow response to changes in  $P_N$ .

Raw EMGgg signals were rectified, and filtered at low frequency of 10 Hz and at high frequency of 100 Hz.<sup>10,17,18,21,30</sup> The signals were then moving-time averaged with a time constant of 200 ms.<sup>21</sup> The area under the curve of the inspiratory EMGgg moving-time average was calculated and corrected for inspiratory time (inspiratory EMGgg area under the curve/inspiratory time). The area under the curve of the EMGgg reflects total tonic and phasic inspiratory EMGgg activity. EMGgg activity was then presented as a percentage of baseline (the baseline being the averaged EMGgg activity over 5 breaths during inspiration at the holding  $P_N$  prior to the pressure challenge). Changes in EMGgg in response to decrements in nasal pressure were presented as the slope of the EMGgg vs. nasal pressure (slope of EMGgg- $P_N$ ).

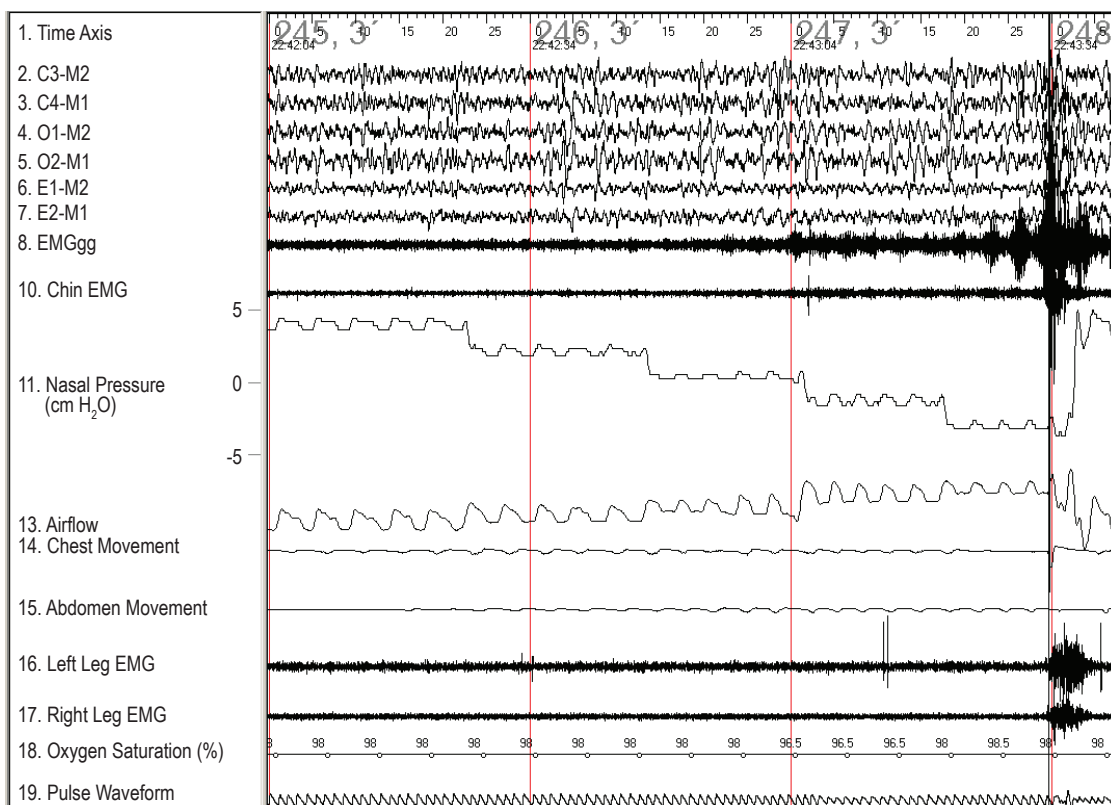
### Statistical Analysis

Statistical analysis was performed with SPSS software version 17.0 for windows (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to test for normalcy. Categorical data

### SCD OSAS



### SCD Control



**Figure 1**—Typical examples of airflow and EMGgg changes during pressure-flow runs in slow wave sleep are shown for a subject with SCD and OSAS and an SCD control subject. During inspiration, airflow and nasal pressure signal tracings have a negative deflection. Initially, nasal pressure was maintained at the holding pressure. The nasal pressure was then lowered in 2 cm H<sub>2</sub>O steplike decrements every 5 breaths until arousal or obstructive apnea occurred. The baseline of the airflow tracings for both subjects moved upwards during the pressure drops due to the change in bias flow. The subject with SCD OSAS had a decrease in airflow with no significant EMGgg increase in response to negative pressure, whereas the SCD control maintained airflow and had a gradually increased EMGgg.

**Table 2**—Slopes of pressure-flow curve, critical closing pressure and slopes of EMGgg-P<sub>N</sub> from sickle cell disease subjects with and without OSAS using activated or hypotonic technique

|   | SCD OSAS          |                   | SCD Controls   |                    |
|---|-------------------|-------------------|----------------|--------------------|
|   | Activated         | Hypotonic         | Activated      | Hypotonic          |
| <b>Slopes of EMGgg-P<sub>N</sub> (%/cm H<sub>2</sub>O)</b>      |                   |                   |                |                    |
| Median  | -3.3 <sup>a</sup> | -3.8              | -11.6          | -1.9 <sup>b</sup>  |
| Range   | -7.1 to 3.5       | -4.0 to 3.3       | -27.9 to -1.9  | -11.3 to 1.5       |
| 95% CI  | -9.6 to 4.5       | -7.8 to 3.6       | -17.8 to -8.0  | -5.9 to -1.6       |
| <b>Pcrit (cm H<sub>2</sub>O)</b>                                |                   |                   |                |                    |
| Median  | -17.4             | -14.5             | -25.0          | -25.0 <sup>c</sup> |
| Range   | -25.0 to -4.2     | -25.0 to -3.7     | -25.0 to -6.3  | -25.0 to -4.2      |
| 95% CI  | -32.9 to 0.9      | -33.9 to -5.0     | -25.0 to -19.0 | -21.6 to -14.8     |
| <b>Slopes of pressure-flow curve (mL/sec*cm H<sub>2</sub>O)</b> |                   |                   |                |                    |
| Median  | 10.6              | 25.7              | 4.5            | 10.8               |
| Range   | -5.1 to 60.3      | 1.0 to 72.7       | -10.3 to 37.4  | -21.2 to 32.4      |
| 95% CI  | -27.1 to 65.3     | -24.5 to 87.1     | 1.4 to 14.8    | 3.7 to 18.0        |
| <b>Holding pressure (cm H<sub>2</sub>O)</b>                     |                   |                   |                |                    |
| Median  | 3.1               | 3.3               | 1.2            | 1.5                |
| Range   | 1.3 to 7.0        | 1.3 to 7.8        | -1.8 to 5.1    | -1.0 to 5.0        |
| 95% CI  | -0.8 to 8.0       | -1.0 to 8.8       | 0.4 to 2.4     | 0.9 to 2.5         |
| <b>Lowest pressure before arousal/apnea (cm H<sub>2</sub>O)</b> |                   |                   |                |                    |
| Median  | -6.3 <sup>d</sup> | -3.4 <sup>e</sup> | -13.0          | -13.0              |
| Range   | -6.8 to -4.4      | -15.0 to -3.3     | -20.3 to -3.1  | -23.6 to -5.2      |
| 95% CI  | -7.7 to -4.2      | -15.6 to 3.4      | -19.2 to -9.8  | -10.4 to -15.1     |

<sup>a</sup>SCD controls had more negative slopes of EMGgg-P<sub>N</sub> than SCD OSAS when using the activated technique (P = 0.04).

<sup>b</sup>For SCD controls, the slope of EMGgg-P<sub>N</sub> using the activated technique was more negative than that using the hypotonic technique (P < 0.001).

<sup>c</sup>For SCD controls, Pcrit was more negative using the activated technique than the hypotonic technique (P = 0.03).

<sup>d</sup>SCD controls had a more negative lowest pressure before arousal/apnea than SCD OSAS using the activated technique (P = 0.03).

<sup>e</sup>SCD controls had a more negative lowest pressure before arousal/apnea than SCD OSAS using the hypotonic technique (P = 0.02).

SCD controls, the slope was significantly more negative using the activated technique compared to the hypotonic technique (P < 0.001), reflecting increased genioglossal activity. The slope of EMGgg-P<sub>N</sub> using the activated technique was more negative in SCD controls than in SCD OSAS (P = 0.04), indicating that upper airway muscle activation was more prominent in SCD controls than in SCD OSAS. EMGgg-P<sub>N</sub> using the hypotonic technique was similar between groups.

### Critical Closing Pressure (Table 2 and Figure 3)

Group Pcrit data are shown in Table 2. The activated Pcrit values from the 4 SCD OSAS subjects were -4.2, -9.8, -25, and -25 cm H<sub>2</sub>O, and the hypotonic Pcrit values from the same subjects were -3.7, -4.0, -25, and -25 cm H<sub>2</sub>O, respectively. For SCD OSAS, no difference in Pcrit was observed between the activated and hypotonic techniques. However, for SCD controls, Pcrit obtained using the activated technique was significantly lower (i.e., more negative) than that using the hypotonic technique (P = 0.03), reflecting a significant contribution of upper airway muscle activation to upper airway patency. There was a trend for a higher (more positive) Pcrit under both activated and hypotonic conditions for SCD OSAS compared to SCD controls. The difference in Pcrit between the 2 groups did not reach significance, probably due to the small number of subjects with SCD and OSAS. The difference between the activated and hypotonic Pcrit (ΔPcrit) in each group was calculated. The ΔPcrit values from the 4 SCD OSAS subjects were -6.1, -0.2, 0, and 0 cm H<sub>2</sub>O, respectively. No difference in ΔPcrit was observed between the 2 groups. Existence of a negative ΔPcrit suggests the presence of active neuromotor reflexes during sleep. Among the SCD OSAS group, only one subject (25%) had a negative ΔPcrit, whereas among the SCD control group, ΔPcrit was negative in 8 subjects (44%, P = NS).

### Slope of Pressure-Flow Curve (Table 2)

The activated SPF values from the 4 SCD OSAS subjects were -5.1, 3.7, 17.5, and 60.3 mL/sec\*cm H<sub>2</sub>O, and the hypotonic SPF values from the same subjects were 1.0, 3.4, 48, and 73 mL/sec\*cm H<sub>2</sub>O, respectively. Within the SCD OSAS and SCD control groups, no differences in SPF were observed using the activated or hypotonic technique. Similar to Pcrit, a trend for a steeper SPF using both techniques for SCD OSAS vs. SCD controls was observed.

Data on the holding pressure and the lowest pressure before arousal/apnea were compared. No difference in holding pressure was observed between the SCD OSAS and SCD control groups.

Data on slope of EMGgg-P<sub>N</sub>, Pcrit, slope of pressure-flow curve, holding pressure and lowest pressure before arousal/apnea were compared between the 3 SCD controls with cerebral vasculopathy and the rest of the SCD controls. No significant differences in the above parameters were observed between the 2 subgroups.

### DISCUSSION

This is a pilot study with a small number of subjects. The major findings of this study were: (1) using the activated but

were compared using the  $\chi^2$  test. Noncategorical data were presented as median and range, because most of the data were not normally distributed. Differences in Pcrit, SPF, and the slope of EMGgg-P<sub>N</sub> between activated and hypotonic techniques within the SCD OSAS or SCD control group were compared using the Wilcoxon signed-rank test. Differences in SCD OSAS compared to SCD controls were examined using the Mann-Whitney rank sum test. A P value < 0.05 was required for significance.

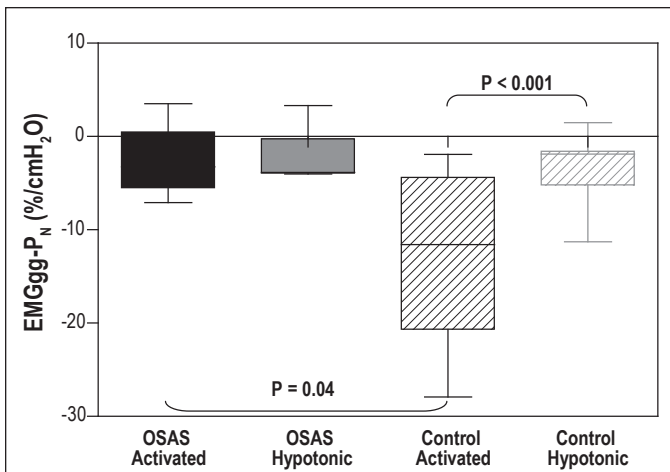
### RESULTS

Four SCD OSAS and 18 SCD controls were studied. Subject characteristics are shown in Table 1. As planned, SCD OSAS had a significantly higher AHI than SCD controls (P < 0.001). Three SCD controls but no SCD OSAS had cerebral vasculopathy diagnosed with brain MRI.

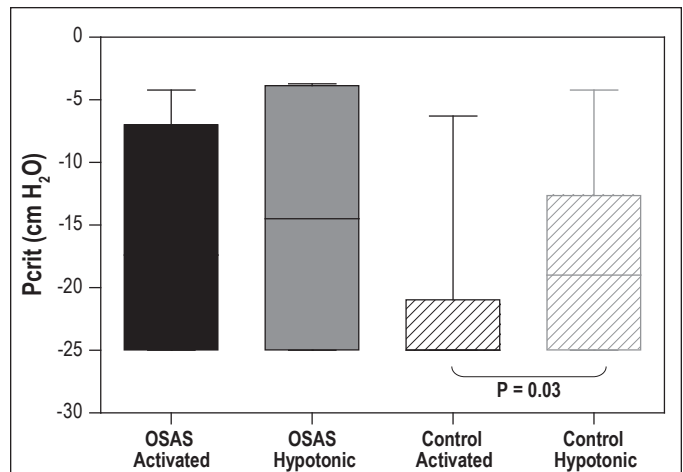
Typical examples of pressure-flow runs are shown in Figure 1.

### Slope of EMGgg-P<sub>N</sub> (Table 2 and Figure 2)

For SCD OSAS, no difference in the slope of EMGgg-P<sub>N</sub> was observed using activated or hypotonic techniques. For



**Figure 2**—Box and whiskers plot of the slopes of the EMGgg-P<sub>N</sub> data SCD OSAS and SCD controls. The boxes represent the interquartile range that contains 50% of the values. The line across each box indicates the median. The whiskers extend from the box to the highest and lowest values. Solid boxes represent data obtained from the SCD OSAS group; striped boxes represent data obtained from the SCD control group. Black boxes represent data obtained using the activated technique; gray boxes represent data obtained using the hypotonic technique. The slope of the EMGgg-P<sub>N</sub> (as a percentage of the baseline EMGgg) using the activated technique was more negative in SCD controls than in SCD OSAS (P = 0.04), but the slope of EMGgg-P<sub>N</sub> using the hypotonic technique was similar between the groups. In SCD controls but not in SCD OSAS, the slope of the EMGgg-P<sub>N</sub> was more negative using the activated technique than using the hypotonic technique (P < 0.001).



**Figure 3**—Box and whiskers plot of the critical closing pressure (Pcrit) data for SCD OSAS and SCD controls. The boxes represent the interquartile range that contains 50% of the values. The lines across the boxes indicate the median. The whiskers extend from the boxes to the highest and lowest values. Solid boxes represent data obtained from the SCD OSAS group; striped boxes represent data obtained from the SCD control group. Black boxes represent data obtained using the activated technique; gray boxes represent data obtained using the hypotonic technique. For SCD controls, Pcrit obtained using the activated technique was significantly lower than that using the hypotonic technique (P = 0.03). Note that a floor value of -25 cm H<sub>2</sub>O was used.

not the hypotonic technique, the slope of EMGgg-P<sub>N</sub> was more negative in SCD controls than SCD OSAS; (2) the slope of EMGgg-P<sub>N</sub> and Pcrit using the hypotonic technique were similar between the two groups; (3) the slope of EMGgg-P<sub>N</sub> was significantly more negative using the activated technique compared to the hypotonic technique in SCD controls only; (4) similarly, Pcrit was more negative using the activated technique than the hypotonic technique in SCD controls but not in SCD OSAS. Overall, we thus demonstrated that upper airway reflexes were more prominent in SCD controls than in SCD OSAS, indicating that decreased upper airway neuromuscular reflexes contribute to the increased upper airway collapsibility in children with SCD and OSAS.

Compared to the hypotonic technique, the activated technique results in a more activated upper airway (more negative Pcrit and steeper slope of EMGgg-P<sub>N</sub>) in normal children.<sup>19-21</sup> Differences in Pcrit using the two techniques in SCD control demonstrated the contribution of upper airway reflexes to upper airway patency during sleep. However, those reflexes were blunted in SCD OSAS. It is possible that covert cerebral vasculopathy in some children with SCD causes impairment of active upper airway reflexes during sleep, so that they are unable to maintain upper airway patency. Although none of the subjects with SCD OSAS had imaging proof of cerebral vasculopathy, it is still possible that these subjects had subclinical neurologic damage secondary to vaso-occlusive episodes. Changes in upper airway local reflexes, abnormal central processing of the afferent stimuli, and abnormal control of upper airway dilators may contribute to the impairment of upper airway responses to

subatmospheric pressure, and need to be further explored. More detailed EEG analysis, such as frequency-specific EEG power analysis<sup>31</sup> or respiratory-related evoked potentials,<sup>32</sup> or more sophisticated imaging techniques may provide further insight into the pathophysiology of OSAS in SCD.

Only a small number of children with SCD and OSAS were recruited. This is because our technique cannot be used easily in very young children, in whom OSAS is more common. Also, children undergoing treatment with hydroxyurea were excluded, and at our institution hydroxyurea has become a standard treatment for children with significant complications of SCD. Nevertheless, even with this small number of cases, we were able to demonstrate a significant difference in EMG reflexes between children with SCD with and without OSAS.

Previous studies have typically shown a higher Pcrit in children with OSAS than that found in the SCD OSAS subjects in the current study. However, this may be due to the variability typically shown in these measurements; data for Pcrit and the slope of the pressure-flow relationship are within the range previously reported.<sup>20</sup> In addition, as all the SCD OSAS subjects were underweight, they may have had a lower anatomical load on the upper airway compared to children with OSAS but no SCD. In addition, it would be beneficial to have data on the size of the tonsils and adenoids to further evaluate the contribution of anatomic factors to upper airway patency in children with OSAS and SCD. This should be a direction for future research.

It would have been ideal to have included a control group of subjects with OSAS but no SCD. However, most subjects in the study were adolescents, and OSAS is rare in otherwise normal adolescents without obesity. In contrast, children with SCD are underweight.<sup>33</sup> Previous data have demonstrated that obesity in-

creases upper airway collapsibility.<sup>34</sup> Therefore in this study, we did not include children with OSAS but no SCD.

To conclude, this preliminary study has shown that children with SCD but without OSAS have more prominent upper airway reflexes than children with SCD and OSAS. We speculate that decreased upper airway neuromuscular reflexes contribute to the increased upper airway collapsibility in children with SCD and OSAS.

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#### DISCLOSURE STATEMENT

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