A Possible Mechanism for Mixed Apnea in Obstructive Sleep Apnea*

Conrad Iber, M.D.; Scott F. Davies, M.D., F.C.C.P.; Richard C. Chapman, M.S., and Mark M. Mahowald, M.D.

Hypopneas or pauses in respiratory effort frequently precede episodes of obstructive sleep apnea resulting in mixed apneas. We studied five subjects after chronic tracheostomy for obstructive sleep apnea. During stable non-REM (NREM) sleep, subjects breathed entirely through the tracheostomy. Tracheostomy occlusion caused experimental obstructive apnea which lasted 13.9 ± 4.7 sec and ended with transient arousal and pharyngeal opening. At the end of the apnea there was marked hyperventilation (inspired minute ventilation rose 21.6 ± 3.5 L on the first breath) followed by hypocapnia, hypopnea, and pauses in inspiratory effort as the subjects resumed NREM sleep.

Obstructive sleep apnea episodes are frequently initiated by a period of nonobstructive apnea or hypopnea followed by progressive increases in obstructed respiratory effort. Cause of initial delay and attenuation of inspiratory effort is unclear and has been ascribed to underlying exaggerated periodicity inherent in patients with obstructive sleep apnea. This initial period of attenuated or delayed inspiratory activity is felt to contribute to obstructive apnea episodes by delaying pharyngeal dilator activity relative to negative pharyngeal pressure generated by inspiratory muscles.

Hypocapnia produces central apnea in normal subjects during sleep when CO$_2$ is lowered below the “apnea threshold.” We suspected that hypocapnia might result from brief arousals terminating obstructive sleep apnea and might in turn cause periods of nonobstructive apnea or hypopnea. Nonobstructive apnea and hypopnea might therefore be a response to the preceding obstructive apnea rather than a cause of subsequent obstructions. To test this hypothesis, ventilatory pattern and end-tidal CO$_2$ were studied during experimental obstructive apneas in patients with tracheostomies for obstructive sleep apnea.

**Materials and Methods**

**Subjects**

The five subjects (Table 1) included four males and one female with chronic tracheostomies in place a minimum of six months for treatment of obstructive sleep apnea. The subjects ranged from 28 to 55 years of age and were obese (169 ± 53 percent ideal body weight) with an average awake supine oxygen saturation of 96 ± 2 percent. Polysomnography prior to tracheostomy demonstrated 62 ± 17 obstructive apneas per hour lasting 27 ± 6 sec with an average nadir in oxygen saturation of 81 ± 10 percent. The average duration of re-

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>% Ideal Body Wt</th>
<th>Sex</th>
<th>TST (hr)</th>
<th>AI (hr$^{-1}$)</th>
<th>Apnea Duration (sec)</th>
<th>O$_2$ SAT Nadir (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>91</td>
<td>125</td>
<td>M</td>
<td>7.6</td>
<td>58</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>116</td>
<td>150</td>
<td>M</td>
<td>7.4</td>
<td>72</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>185</td>
<td>262</td>
<td>M</td>
<td>5.6</td>
<td>62</td>
<td>35</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>80</td>
<td>148</td>
<td>F</td>
<td>6.1</td>
<td>81</td>
<td>22</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>139</td>
<td>162</td>
<td>M</td>
<td>6.0</td>
<td>36</td>
<td>28</td>
<td>74</td>
</tr>
<tr>
<td>Mean</td>
<td>45</td>
<td>122</td>
<td>169</td>
<td></td>
<td>6.5</td>
<td>62</td>
<td>27</td>
<td>81</td>
</tr>
<tr>
<td>± SD</td>
<td>10</td>
<td>43</td>
<td>53</td>
<td></td>
<td>.9</td>
<td>17</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

TST = Total sleep time
AI = Apneic episodes per hour

*From the Department of Medicine, Hennepin Country Medical Center, Minneapolis.
Supported by a grant from the American Lung Association.
Manuscript received July 22; revision accepted December 5.
Reprint requests: Dr. Iber, Department of Medicine, 701 Park Avenue South, Minneapolis 55415
EXPERIMENTAL APPARATUS

![Diagram of experimental apparatus](image)

Results

The experimental apparatus is shown in Figure 1. An airtight silicone rubber mask and a tracheostomy adaptor were each connected to low resistance, one-way valves and joined to common inspiratory and expiratory lines. Airway pressure was measured at the tracheostomy adaptor and at the mask. Inspiratory and expiratory flow were measured with pneumotachographs (flow linear ±2 percent at 0 to 200 L/min) calibrated with a 3 L syringe. The circuit had an inspiratory and expiratory resistance of 2.5 cm H2O/L per sec. Tracheostomy occlusion was performed by clamping the silicone rubber inspiratory line leading to the tracheostomy adaptor.

Data Collection

Control measurements were made immediately prior to tracheostomy occlusion but only after 15 to 20 min of uninterrupted nonREM (NREM) sleep. During the control period, breathing patterns were stable and no periodic breathing was observed. During both the control period and immediately following occlusion of the tracheostomy, measurements of airway pressure, ventilation, and PETCO2 were obtained. Brief arousal and immediate resumption of NREM sleep followed all experimental occlusions.

The tracheostomy was occluded until pharyngeal opening permitted resumption of ventilation, as documented by negative pressure swings at the mouth. We performed 108 occlusions in the five subjects while breathing room air (range, 12 to 40 occlusions per patient). Twenty-four additional occlusions were performed in three subjects while breathing a gas mixture with 40 percent oxygen and 4 percent CO2. In order to define the role of cortical arousal, 14 five-breath occlusions were analyzed in one individual. In these studies, the tracheostomy was opened before arousal occurred and the patient resumed breathing through the tracheostomy without pharyngeal opening.

Instrumentation

Intratracheal pressure and end-tidal PCO2 (PETCO2) were measured at the tracheostomy adaptor using a Statham P131 transducer and Almez CO2 analyser, respectively. Pressure was calibrated to a water manometer, and CO2 was calibrated to a known CO2 mixture. Mouth pressure was measured at the mask by a Statham PM15 transducer and oxygen saturation (O2, SAT) was measured by a Hewlett-Packard 47201A ear oximeter. Time delay in oxygen saturation measurements (time constant, approximately 3 sec) prohibited exact timing of oxygen saturation measurements relative to ventilation and PETCO2. Standard electroencephalography, electrooculogram and submental electromyogram measurements were recorded on a Grass 12-channel recorder with sleep staging, according to the methods described by Rechtsaffen and Kales.4 Brief arousals were defined as transient increases in EEG frequency associated with augmented EMG amplitude. Oxygen saturation, PETCO2, and integrated flow were recorded on-line using Medical Graphics' breath-by-breath waveform analyzer. Pressure, PETCO2, inspired volume and integrated flow were recorded on a Gison 5/6 recorder.

Arterial PCO2 was measured in three subjects to allow comparison with simultaneous end-tidal PCO2. An 18-gauge catheter was placed in a large hand vein; the hand was heated with a heating pad to 130°F for 20 min. Adequate arterIALIZATION was verified by O2 saturation of greater than 90 percent during wakefulness on all samples.

Pauses in inspiratory activity were determined by measurements of expiratory duration (TE) during control periods of NREM sleep preceding tracheostomy occlusion and during the brief arousal and resumption of NREM sleep which followed each experimental apnea. Breath-by-breath measurements of minute ventilation (tidal volume × respiratory cycle time) were made: 1) during control NREM sleep; 2) at the first breath terminating obstruction; and 3) at the breath when the longest TE was encountered. An apparatus leak of less than 5 percent of the inspired minute ventilation could be detected by a decrement in intratracheal PETCO2 during subsequent obstructive apnea. Occasional data collected during an apparatus leak was discarded.

A paired Student's t-test was used to compare measurements during control NREM sleep with measurements at the termination of occlusion and at maximum TE prolongation. In order to allow equal representation of expiratory durations during control periods and after airway occlusion, the longest TE was measured for an identical number of breaths both immediately before and following tracheostomy occlusion. Data is expressed as mean ± standard deviation.

Results

Reproducibility of control measurements was determined by computing intra-subject coefficients of variation during NREM sleep immediately prior to tracheostomy occlusion. Coefficient of variation was 2 percent for oxygen saturation, 3 percent for PETCO2, 10 percent for inspired minute volume (Vt), and 18 percent for TE. The reproducibility of these control
measurements verifies a stable respiratory rhythm before experimental intervention. Arterial $P_cO_2$ in three subjects was within $\pm 1$ mm Hg of simultaneous PET$CO_2$ measured at the trachea.

During unobstructed breathing in NREM sleep, $V_i$ was 7.4 $\pm 0.7$ L/min with a tidal volume of 0.43 $\pm 0.05$ L. Expiratory time was 2.3 $\pm 0.3$ sec. PET$CO_2$ was 43.7 $\pm 8.3$ mm Hg, and oxygen saturation averaged 91.7 $\pm 2.5$ percent.

An example of experimental tracheostomy occlusion is shown in Figure 2. Five subjects remained totally obstructed despite increasing respiratory effort for 13.9 $\pm 4.7$ sec. Next, transient arousal occurred and, in all cases, subjects initiated breathing by opening the pharynx. By the end of the obstructive efforts, PET$CO_2$ had increased $7.3 \pm 2.0$ mm Hg over control periods and oxygen saturation had decreased $6.7 \pm 5.4$ percent.

Transient hypercapnia and oxygen desaturation from the apnea were followed by brisk hyperventilation. On the first breath after pharyngeal opening, $V_i$ increased 21.6 $\pm 3.5$ L ($p<.005$) over baseline ventilation immediately prior to occlusion (Fig 3).

Hyperventilation caused hypocapnia, which was followed by a period of variable hypoventilation with variable pauses in inspiratory activity (TE prolongation). PET$CO_2$ was decreased 2.3 $\pm 1.6$ mm Hg below baseline ($p<.05$) and minute ventilation was decreased 3.8 $\pm 1.2$ L below baseline ($p<.005$) at the point of longest expiratory time (Fig 3). PET$CO_2$ was 4.2 $\pm 1.8$ mm Hg below baseline for longest expiratory durations lasting at least 5 sec, but only 1.2 $\pm 2.5$ mm Hg below baseline for TE prolongations less than 5 sec (Fig 4).

Increasing PET$CO_2$ markedly reduced the prolongation of expiratory time after experimental obstructive apnea. Figure 5 demonstrates expiratory durations during control periods (NREM) and for the longest expiratory duration following each experimental tracheostomy occlusion. Administration of a 4 percent $CO_2$, 40 percent $O_2$ gas mixture to three subjects increased PET$CO_2$ during NREM baseline level (breathing through open tracheostomy) by 3.0 $\pm 2.7$ mm Hg. Following experimental obstructive apnea, the longest expiratory time after termination of the apneas was only 2.9 $\pm 0.1$ sec when breathing the $CO_2$-enriched gas, as compared to 4.9 $\pm 1.3$ sec while breathing room air. In comparison to matched NREM control periods under each condition, TE was prolonged only 0.2 $\pm 0.1$ sec above control level in the post-hyperventilation period breathing excess $CO_2$, vs
2.5 ± 1.4 sec above control level while breathing room air.

Experimental tracheostomy occlusion caused a brief obstruction which ended with transient arousal and onset of breathing through the pharynx. Hyperventilation at the termination of apnea was always associated with a brief arousal, although the patient immediately returned to NREM sleep. The same sequence of obstructive apnea (causing hypercapnia) hyperventilation (causing hypocapnia), and TE prolongation was also demonstrated in one subject in whom tracheostomy occlusion was reversed after five breaths. Under these conditions, the subject resumed breathing through the tracheostomy without arousal or pharyngeal opening. Five obstructed respiratory efforts without arousal caused qualitatively similar changes to those seen when longer apneas were terminated by arousal and pharyngeal breathing. PETCO₂ had increased 5.4 ± 1.5 mm Hg by the time the obstructed tracheostomy was opened. Ventilation increased 4.9 ± 2.0 L/min over baseline level on the first unobstructed breath. Following hyperventilation, PETCO₂ fell 2.2 ± 1.2 mm Hg below baseline level, followed by a drop in ventilation (2.5 ± 1.7 below baseline) and TE prolongation of 0.7 ± 0.2 sec.

**DISCUSSION**

This study demonstrates hyperventilation and hypocapnia following pharyngeal opening in patients with obstructive sleep apnea when experimental apnea was caused by tracheostomy occlusion during NREM sleep. Hypocapnia was followed by a variable period of decreasing minute ventilation and pauses in inspiratory activity. Similar changes were seen in one subject in whom cortical arousal was prevented by early release of tracheostomy occlusion. Pauses in inspiratory activities following termination of apnea was prevented in three subjects by administration of exogenous CO₂.

There are several limitations to this model of obstructive sleep apnea. Measurements of end-tidal CO₂ and oxygen saturation are necessary approximations of input at the chemoreceptor level, and some of the variability observed may reflect gradients between these peripheral measurements and the medullary chemical environment. End-tidal CO₂ measurements in this study did accurately reflect arterial Pco₂ (documented by simultaneous samples in three subjects) and the observed change in end-tidal CO₂ during obstructive apnea was consistent with previous observations during apnea at resting lung volumes. Another problem is the shorter duration of apnea and higher oxygen nadir during experimental apnea as compared to baseline sleep studies in the same subjects prior to tracheostomy. Apnea duration was 13.9 sec compared to 27 sec and nadir of oxygen saturation was 85 percent rather than 81 percent. This improvement was probably due to chronic tracheostomy which corrects sleep fragmentation and chronic hemodynamic consequences of sleep apnea through tracheostomy should not have qualitatively changed the observed re-

---

**FIGURE 4.** PETCO₂ relative to control periods for a) all periods of TE prolongation, b) TE less than 5 sec, and c) TE greater than or equal 5 sec.

**FIGURE 5.** Average expiratory durations (TE) during NREM control periods and at the point of TE prolongation while breathing room air (solid lines) and 4 percent CO₂, 40 percent O₂ (dotted lines).
obstructive \textit{apnea} or \textit{receptor} \textit{accentuates} \textit{prolongation} \textit{events} \textit{from} \textit{baseline} \textit{tidal} \textit{volume} of \(0.43 \pm 0.05\) L. \textit{This suggests} \textit{that increased} \textit{tidal} \textit{volume is not a factor} \textit{prolonging} \textit{expiratory} \textit{duration}.

In obstructive \textit{sleep apnea}, pharyngeal dilator \textit{activation} is \textit{insufficient} \textit{relative} \textit{to activation} \textit{of the diaphragm}. Some authors suggest that \textit{periodic} \textit{breathing itself} \textit{could predispose} \textit{to} \textit{airway} \textit{obstruction} \textit{if} \textit{recovery} \textit{from nonobstructive} \textit{apnea} \textit{was associated} \textit{with} \textit{increasing diaphragm activity} \textit{out} \textit{of proportion} \textit{to} \textit{pharyngeal dilator} \textit{activity}. \textit{This hypothesis is supported} \textit{by preliminary} \textit{data} \textit{from} \textit{one model of obstructive} \textit{sleep apnea in humans in which added upper airway} \textit{resistance} \textit{during} \textit{periodic} \textit{breathing} \textit{induced} \textit{by} \textit{hypoxia} \textit{caused pharyngeal} \textit{occlusion} \textit{during the nadir of ventilation}.

However, the \textit{disappearance} \textit{of} \textit{nonobstructive} \textit{apneas} \textit{and periodic} \textit{breathing} \textit{following} \textit{tracheostomy} \textit{for obstructive} \textit{sleep apnea} suggests \textit{that nonobstructive} \textit{apneas are not likely the initiating} \textit{event}.

The present study \textit{suggests} \textit{that} \textit{posthyperventilation hypoxia} \textit{following} \textit{an obstructive} \textit{apnea} \textit{may cause the initial} \textit{attenuation} \textit{or} \textit{cessation} \textit{of respiratory} \textit{effort seen} \textit{at the beginning} \textit{of the subsequent} \textit{obstructive} \textit{apnea}. \textit{The stable} \textit{respiratory} \textit{rhythm} \textit{prior} \textit{to} \textit{experimental} \textit{obstructive} \textit{sleep apnea} \textit{suggests} \textit{that inherent} \textit{periodicity} \textit{is not necessary} \textit{for} \textit{obstruction} \textit{to occur}. \textit{Potential stimuli} \textit{for the} \textit{excessive ventilation-causing hypoxia} \textit{include hypoxia} \textit{or} \textit{cortical} \textit{input related} \textit{to transient} \textit{arousal}. However, \textit{posthyperventilation apnea} \textit{was also observed} \textit{in the absence} \textit{of hypoxia} \textit{or arousal}. \textit{There may be additional factors which contribute} \textit{to the excessive} \textit{ventilation} \textit{following} \textit{obstructive} \textit{apnea which lower} \textit{the} \textit{elevated} \textit{PCO2 below the sleep} \textit{baseline} \textit{value}.

\textbf{ACKNOWLEDGMENT:} \textit{The authors wish to thank} Rosemary Pellegrini \textit{for preparing the manuscript}.

\begin{thebibliography}{99}
\bibitem{1} Guilleminault C, Cumminskey J. \textit{Progressive Improvement of} \textit{apnea} \textit{index} \textit{and ventilatory} \textit{response} \textit{to CO2 after tracheostomy in obstructive} \textit{sleep} \textit{apnea syndrome}. \textit{Am Rev Respir Dis} 1982; \textit{126}:14-20
\bibitem{2} Martin RJ, Pennock BE, Orr WC, Sanders MH, Rogers RM. \textit{Respiratory mechanics and timing during} \textit{sleep} \textit{in obstructive} \textit{sleep} \textit{apnea}. \textit{J Appl Physiol} 1980; \textit{48}:432-37
\bibitem{3} Remmers JE, DeGroot WJ, Sauerland EK, Anch AM. \textit{Pathogenesis of upper airway} \textit{occlusion} \textit{during} \textit{sleep}. \textit{J Appl Physiol} 1978; \textit{44}:31-38
\bibitem{4} Onal E, Lopata M, O'Connor T. \textit{Pathogenesis of apneas in hypersomnia-sleep} \textit{apnea syndrome}. \textit{Am Rev Respir Dis} 1982; \textit{125}:167-74
\bibitem{5} Onal E, Lopata M. \textit{Periodic breathing and the} \textit{pathogenesis of} \textit{obstructive} \textit{sleep apnea}. \textit{Am Rev Respir Dis} 1982; \textit{126}:676-80
\bibitem{6} Longobardo GS, Goethe B, Goldman MD, Cherniack NS. \textit{Sleep} \textit{apnea as a control} \textit{system instability}. \textit{Respir Physiol} 1982; \textit{50}:311-33
\end{thebibliography}
WHO Fellowships for Travel/Study Abroad

The World Health Organization (WHO) will provide a limited number of short-term fellowships for use during 1987 for travel/study abroad related to the improvement of health status in the United States. This support is limited to United States citizens employed in the health field.

Fellowship awards are offered to persons involved in educational or service aspects of the health field with State and local government agencies, educational institutions or non-profit organizations. Applications cannot be considered for basic laboratory bench research or attendance at international meetings or seminars. In addition, Federal government employees, undergraduate or graduate students including medical interns and residents, self-employed health care providers, or individuals employed by profit making organizations are not eligible.

The fellowship award provides per diem, transportation and a small stipend to cover miscellaneous expenses. Employers of applicants are expected to endorse the application and agree to continue the applicant's salary throughout the fellowship period. Except in unusual circumstances, the fellowships will be limited to short-term programs of one or two months. The number of fellowships awarded will be governed by the funds available.

The deadline for the submission of the completed application is September 30, 1986.

Further information and application forms may be obtained from the Secretary, WHO Fellowships Selection Committee, Health Resources and Services Administration, 5600 Fishers Lane, Room 14-18, Rockville, MD 20857, telephone 301/443-6152.