Mechanisms of breathing instability in patients with obstructive sleep apnea

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The response to chemical stimuli (chemical responsiveness) and the increases in respiratory drive required for arousal (arousal threshold) and for opening the airway without arousal (effective recruitment threshold) are important determinants of ventilatory instability and, hence, severity of obstructive apnea. We measured these variables in 21 obstructive apnea patients (apnea-hypopnea index 91 ± 24 h⁻¹) while on continuous-positive-airway pressure. During sleep, pressure was intermittently reduced (dial down) to induce severe hypopneas. Dial downs were done on room air and following ~30 s of breathing hypercapnic and/or hypoxic mixtures, which induced a range of ventilatory stimulation before dial down. Ventilation just before dial down and flow during dial down were measured. Chemical responsiveness, estimated as the percent increase in ventilation during the 5th breath following administration of 6% CO₂ combined with ~4% desaturation, was large (187 ± 117%). Arousal threshold, estimated as the percent increase in ventilation associated with a 50% probability of arousal, ranged from 40% to >268% and was <120% in 12/21 patients, indicating that in many patients arousal occurs with modest changes in chemical drive. Effective recruitment threshold, estimated as percent increase in pre-dial-down ventilation associated with a significant increase in dial-down flow, ranged from zero to >174% and was <110% in 12/21 patients, indicating that in many patients reflex dilatation occurs with modest increases in drive. The two thresholds were not correlated. In most OSA patients, airway patency may be maintained with only modest increases in chemical drive, but instability results because of a low arousal threshold and a brisk increase in drive following brief reduction in alveolar ventilation.

UPPER AIRWAY OPENING at the end of obstructive apneas and hypopneas usually consists of an abrupt increase in flow that is almost always associated with cortical arousal. The “suddenness” of the flow response along with an accompanying arousal have led to the enduring notion that arousal is the mechanism responsible for opening (38). Indeed, arousal has been considered an essential survival mechanism in this disorder (33). If arousal is necessary for upper airway opening, then the mechanism of ventilatory instability is fairly simple; obstruction continues until arousal occurs and recurs on resumption of sleep.

Recently, Younes proposed that most obstructive sleep apnea (OSA) patients could open their airway without arousal (52, 53). This was based on several observations including the following. 1) Most patients develop periods of stable breathing, and sleep, in the same body position and sleep state in which they experience OSA (52), thereby signifying that upper airway dilator activity can be increased sufficiently to maintain patency in most patients during sleep. 2) In many obstructive events, airway opening preceded arousal, and the temporal relation between arousal and airway opening suggested an incidental association (53). 3) Upper airway opening occurred at the same time regardless of whether arousal occurred before or after opening or did not occur at all (53). Younes postulated that chemical drive must increase a threshold amount before the pharyngeal dilator muscles can reflexly open the airway (henceforth called effective recruitment threshold; TER). Recurrent obstructive events develop if a ventilatory overshoot occurs at the end of the event and reduces chemical drive below TER, thereby removing the very stimulus required to maintain arousal-free airway patency. According to this proposition, factors that increase the likelihood and magnitude of postevent overshoots promote recurrent obstruction (i.e., OSA). Little is known about the operation of these factors in patients with OSA.

In theory, an excessive overshoot may result from the following: 1) a high TER, since, by definition, chemical drive must increase a large amount before the airway opens reflexly [this would increase the likelihood of arousal occurring before reflex opening, and arousals greatly increase the postevent overshoot (53)]; 2) a low arousal threshold (TA), since this would trigger overshoot-augmenting arousals even if TER were low; or 3) a large, fast respiratory motor response to transient changes in alveolar ventilation (high dynamic controller gain). The obligate circulatory delay between lung and chemoreceptors dictates that chemical drive must continue to increase for a finite period after airway opening. With large and fast chemical responses, the postevent increase in drive would be large, increasing the likelihood of postevent arousal and promoting more complete opening of the airway, two factors that increase the overshoot.

In this study, TER was determined in OSA patients by transiently dialing down continuous positive airway pressure (CPAP) to a level associated with severe flow limitation at resting chemical drive (dial down from air breathing) and examining the effect, on dial-down flow, of increasing chemical drive to different levels before dial down by briefly changing the inspired gas mixture. To determine the relation between TER and arousal threshold, the increase in drive associated with arousal (TA) was also determined in each patient. Finally, to evaluate the potential for postevent increase in drive, the rate of increase in drive during the brief periods of hypercapnia and/or hypoxia was determined along with measurement of lung-to-carotid circulatory delay.

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methods

As per usual practice in Calgary, patients referred to the Sleep Center for evaluation of OSA had overnight monitoring at home using an oxyhemoglobin-saturation based monitor (Remmers Sleep Recorder model 4.2, Saga Tech Electronic, Calgary, Canada) (22, 43). Patients who had a respiratory disturbance index >15 h⁻¹ during the home study, and who did not have any of the exclusion criteria, were invited to participate. Exclusion criteria included significant comorbidities (diabetes-dependent renal failure, congestive heart failure, severe chronic obstructive pulmonary disease, previous stroke) or use of sedatives or antidepressants. The Conjoint Health Research Ethics Board at the University of Calgary approved the study protocol, and all subjects gave written informed consent to participate. Twenty-one patients were studied.

Patients underwent two studies on separate nights, a diagnostic polysomnography study followed by the dial-down study.

Diagnostic Polysomnography

The diagnosis and severity of OSA was confirmed by overnight, attended polysomnography, during which we obtained a three-channel electroencephalogram (EEG), an electro-oculogram, and a submental electromyogram using surface electrodes. Airflow was measured by monitoring nasal pressure through nasal cannulae (Ultima Dual Pressure Sensor 0585, Braebon Medical, Carp, Ontario, Canada). Respiratory effort was measured by inductance plethysmography with transducers placed on the chest and abdomen (Respirtrace, Ambulatory Monitoring, Ardsley, NY). Arterial oxyhemoglobin saturation was recorded with a pulse oximeter (Biox 3740, Ohmeda, Boulder, CO). All variables were recorded continuously by a computerized data-acquisition system and stored electronically for later analysis (Sandman, Tyco Healthcare, Kanata, Ontario, Canada). Certified polysomnographic technologists scored sleep, arousals and the presence and type of obstructive events using standard criteria (1, 1a, 37). Apnea-hypopnea index (AHI), average and minimum O2 saturation, and type of obstructive events using standard criteria (1, 1a, 37). Apnea-acquisition system and stored electronically for later analysis (Sand-recorded with a pulse oximeter (Biox 3740, Ohmeda, Boulder, CO). Monitoring, Ardsley, NY). Arterial oxyhemoglobin saturation was transducers placed on the chest and abdomen (Respitrace, Ambulatory ratory effort was measured by inductance plethysmography with Sensor 0585, Braebon Medical, Carp, Ontario, Canada). Respir-itory effort was measured by inductance plethysmography with transducers placed on the chest and abdomen (Respirtrace, Ambulatory Monitoring, Ardsley, NY). Arterial oxyhemoglobin saturation was monitored with a pulse oximeter (Biox 3740, Ohmeda, Boulder, CO). All variables were recorded continuously by a computerized data-acquisition system and stored electronically for later analysis (Sandman, Tyco Healthcare, Kanata, Ontario, Canada). Certified polysomnographic technologists scored sleep, arousals and the presence and type of obstructive events using standard criteria (1, 1a, 37). Apnea-hypopnea index (AHI), average and minimum O2 saturation, and number of respiratory events with arousal were calculated for the supine and lateral positions in non-rapid eye movement (NREM) sleep.

Dial-Down Study

This was done 9.4 ± 13.3 days after diagnostic polysomnography, before institution of CPAP. CPAP was applied via nasal mask con-nected to a multipurpose ventilator research prototype, described previously (52–54), that allowed reduction of CPAP to 1.0 cmH2O. The variables recorded were the same as in the clinical polysomnography study except for respiratory flow, which was recorded from a pneumotachograph inserted in the hose of the ventilator. Mask pressure was recorded from a side port in the mask. All signals were sampled at 120 Hz and recorded using a Windaq data-acquisition system (DATAQ Instruments, Akron, OH).

Studies were initiated in the supine position except in four patients who could not sleep in this position. Patients were encouraged to remain in the supine position throughout the night, but many unconsciously turned to the lateral position. When this happened, they were left in that position until they awoke spontaneously and were in-structed to resume the supine position. Pressure was titrated to the first level associated with no snoring or flow limitation. This level was maintained thereafter (holding pressure). If flow limitation appeared during ventilatory stimulation, holding pressure was increased appropriately.

Preliminary testing. During stable sleep and breathing room air, CPAP was reduced in steps each lasting three breaths (dial downs). Three to four levels of dial-down pressure were selected that spanned the range between holding pressure and the pressure associated with complete obstruction, or 1 cmH2O, if only a hypopnea was observed at 1 cmH2O. Each level was administered two to four times. The purpose of this preliminary step was to determine the dial-down pressure at which the airflow just closes (PcLOSs). Typically, at this dial-down pressure some dial downs resulted in complete obstruction, while others resulted in severe flow limitation.

Tests with altered inspired gas concentrations. Subsequently, dial downs were done only at PcLOS. If complete obstruction was not observed at 1 cmH2O, the subsequent dial-down pressure was 1 cmH2O. With some observations, dial down was applied while the patient breathed room air (air dial downs, e.g., Fig. 1A). Alternately, inspired gas was altered for ~30 s before dial down (gas dial down, e.g., Fig. 1, B and C). This was done using a pair of proportional solenoid valves, one connected to a nitrogen tank and the other to a tank containing 25% CO2, 21% O2, balance nitrogen. Flow through the solenoid valves was made proportional to flow through the ventilator’s hose (obtained from the flowmeter in the CPAP hose) so that the inspired concentrations of CO2 and O2 were fairly independent of airflow. The proportionality dial used by the technologists was calibrated to result, on applying a manual switch, in CO2 concentrations between 0 and 10% and O2 concentrations between 11 and 21%. Five different inspired gas mixtures were typically applied at random before dial downs. These were 3, 6, and 9% CO2 in air; 3% CO2 with either 15% or 11% O2; and 1% CO2 with either 15% or 11% O2. The choice of whether to use 15% or 11% O2 was based on the magnitude of oxyhemoglobin desaturation; reduction in arterial O2 saturation (SaO2) below 80% was avoided. In patients who experienced frequent arousals with the 3% CO2 challenge, the CO2 concentrations used were 2, 4, and 6% instead of 3, 6, and 9%. In two patients the highest CO2 delivered was 3%; at higher levels the patient aroused before dial downs with nearly every test. One patient did not receive hypoxic mixtures because the N2 solenoid was inoperative.

A change in gas mixture was maintained for ~30 s unless arousal occurred earlier. If sleep continued for 30 s, dial down was applied and maintained for three breaths, unless arousal occurred earlier. Enough time was allowed between tests for stable sleep to resume.

analyses

Analysis was limited to periods of non-rapid eye movement (NREM) sleep since the large breath-by-breath variability typical of rapid eye movement (REM) sleep precluded confident estimates of drive at any given breath. Except for the four patients who could not sleep in the supine position, analysis was limited to periods spent in the supine position; because of deliberate efforts to maintain the patient in that position, periods in the lateral position were usually brief and did not provide an adequate amount of data.

Leak during holding pressure was estimated from a 30-s moving average of flow. Leak level during dial downs was estimated by selecting a breach during which Respirtrace end-expiratory volume did not change and determining the flow offset that would result in equal inspired and expired volumes in the integrated flow signal in that breath. Leak levels were subtracted from the primary flow signal at the appropriate times to obtain patient flow.

ventilatory measurements during periods on holding pressure. Tidal volume (VT), respiratory rate (RR), minute ventilation (VT = VT × RR), mean inspiratory flow (VT/inspiratory time), and peak inspiratory flow were determined breath by breath from the corrected flow signal. Baseline ventilatory data are reported as the average of the 10 breaths preceding an air dial down or preceding a change in inspired gas concentration. For tests with gas challenges, breath-by-breath ventilatory data between the onset of gas delivery and dial down, or arousal, whichever occurred first, were tabulated and grouped according to the gas mixture used. Data for the last breath preceding the dial down or, if an arousal occurred first, preceding arousal were noted (“last breath”). The level of chemical drive achieved before dial down or arousal is reported as the difference between values in this last breath and the corresponding baseline.
values. This difference is expressed in absolute units (e.g., l/min, l/s) and as percentage of baseline.

Calculation of lung-carotid delay. \( V_\text{E} \) at breaths 2, 3, and 4 following a gas change were compared with \( V_\text{E} \) of the first exposed breath by paired t-test. Time interval between the onset of first inspiration receiving an altered gas mixture and the first breath to show a significant increase in \( V_\text{E} \) was taken as the circulatory delay. End-tidal \( \text{PCO}_2 \) (PE\( \text{T}\text{CO}_2 \)) was measured in the expiratory phase during which CPAP was reduced at the onset of the dial down. This expiratory phase invariably provided a technically adequate expiratory \( \text{CO}_2 \) trace from which to estimate PE\( \text{T}\text{CO}_2 \). Oxygen saturation at baseline was noted. To determine Sa\( \text{O}_2 \) at the chemoreceptor during altered gas tests, the interval between upper airway opening at the termination of an obstructive apnea and the corresponding increase in the oximeter signal was determined. This duration reflects the delay between a change in alveolar \( \text{PO}_2 \) and first indication of this change in the oximeter signal. Carotid-to-oximeter delay was calculated from this lung-to-oximeter delay minus the lung-to-carotid delay, estimated as described above. Carotid oxygen saturation at the chemoreceptor just before dial down, or just before arousal, was estimated from the oximeter signal at a time corresponding to the carotid-to-oximeter delay beyond the time point of interest.

Dial-down measurements. A senior certified polysomnography technologist (M. Ostrowski) determined whether a cortical arousal occurred during the dial down according to standard criteria (1a). A cortical arousal was identified if there was a visible shift to higher frequencies in any of the three EEG leads. If a cortical arousal was detected, she identified its onset to the nearest 0.1 s. Measurement of inspiratory flow during the dial down (dial-down flow) was limited to periods preceding identified arousals, if any. If no cortical arousal was present during the first two breaths, the higher of the inspiratory flow values in these two breaths is reported. If arousal occurred during breath 2, flow during breath 1 is reported. The absence of cortical or autonomic arousal at the times of measurement of dial-down flow (i.e., values to be reported here) was further confirmed by Fourier analysis and by beat-to-beat changes in heart rate (see below).

Estimation of TER. The objective of this analysis was to determine whether increasing chemical drive before dial down results in a higher inspiratory flow during the dial down in the absence of arousal and, if so, the level of increase in drive at which dial-down flow begins to increase relative to the value obtained at resting drive (air dial downs). An increase in dial-down flow at the same dial-down pressure without arousal would signify that upper airway dilators can be effectively recruited during sleep when chemical drive increases (see DISCUSSION for the meaning of “effective recruitment” and mechanisms by which chemical drive may result in dilator recruitment).

Some gas challenges resulted in arousal before dial down. These were not used for determining TER. In others, dial down was possible before arousal (Fig. 1). Dial downs during which at least one breath occurred before arousal were used to determine TER as follows. For each eligible dial down, \( V_\text{E} \) during the last breath before dial down (pre-dial-down \( V_\text{E} \)) and dial-down flow were noted. Dial-down flow was plotted against pre-dial-down \( V_\text{E} \) for all dial downs obtained in the patient, including those preceded by air breathing (e.g.,
Fig. 2. A–C: Relation between minute ventilation in the last breath before dial down and dial-down flow in 3 patients. Each point represents the result of one dial down, and each panel contains all the data obtained in the same body position throughout the night in 1 patient. ○, Dial down while breathing room air; ●, dial down ∼30 s after changing inspired gas to different CO₂ and O₂ mixtures; solid horizontal line, average flow in air dial downs; dotted horizontal line, average + 2SD of flow in air dial downs. Diagonal lines in A and B are regression lines over the ventilation range containing significantly higher flow. In such cases, effective recruitment threshold (TER) is ventilation at the intersection between the regression line and average flow in air dial downs. Note that in patient 18, the slope and mean dial-down flow in air tests (Fig. 2, A and B).

Estimation of arousal threshold (Tₐ). VE values preceding dial downs or preceding arousal, if arousal occurred, for all tests in each patient were arranged in ascending order. VE values associated with arousal were identified. A Kaplan-Meier survival curve (6) was generated that reflected the probability of having no arousal as a function of VTₐ reached (e.g., Fig. 2, D–F). TA is reported as the VE associated with 50% probability of arousal (TA₅₀, Fig. 2) and also the value that could not be exceeded without arousal (TA₀, Fig. 2). TA₀ defines the outer limit of the ventilatory range over which TER can be explored.

Confirmation of lack of arousal at the time of measurement of dial-down flow. An important question is whether observations in which dial-down flow increased significantly with the increase in chemical drive were associated with cortical arousals that were too subtle to be detected by the naked eye. To address this issue, we identified the two observations with the greatest increase in dial-down flow (i.e., upper airway opened during the dial down) in each patient who demonstrated an increase in dial-down flow with chemical stimulation (no. of patients = 12; no. of observations = 24). With each of these observations, we performed Fourier analysis on successive 3-s epochs of a central EEG channel. Analysis was performed in the 3-s epoch centered around the time of upper airway opening during dial down and for the preceding 60 s (20 epochs). This encompassed all the time during which inspired gas composition was altered and 10 epochs (30 s) of baseline. For each observation, we calculated mean ± SD of EEG power in the alpha/sigma range (7.3–14.0 Hz) and in the beta range (14.0–35.0 Hz) in the 10 baseline epochs, and we determined whether the power in these two frequency ranges was significantly higher (i.e., >mean ± 2SD of baseline) in the epoch containing upper airway opening. The average power in these two frequency ranges in the 24 epochs containing upper airway opening was also compared with the corresponding values during baseline and during the last epoch before dial down by ANOVA for repeated measures (ANOVA-R). In each of these 12 patients, a similar analysis was performed on the two observations with the greatest increase in pre-dial-down VE that were not associated with a significant increase in dial-down flow.

We also determined whether there was a significant increase in heart rate that may suggest autonomic/subcortical arousal at the time of upper airway opening. In the same 24 observations demonstrating airway opening during gas dial downs, we calculated beat-by-beat heart rate for the beat encompassing upper airway opening and for the preceding 60 s. To filter out sinus arrhythmia, a five-beat moving average of heart rate was calculated up to, but not including, the beat encompassing upper airway opening. Heart rate in the latter beat was compared with average heart rate at baseline and just before dial down by ANOVA-R. A similar analysis was performed in the 24 corre-
sponding observations with the greatest increase in pre-dial-down $\dot{V}E$ that were not associated with a significant increase in dial-down flow.

In patients who received 2, 4, and 6% CO₂, instead of 3, 6, and 9%, the values obtained with 2 and 4% were averaged and are reported as results with 3% CO₂. Values obtained under similar conditions in a given patient were averaged (e.g., $\dot{V}E$ during administration of 6% CO₂) so that each patient is represented only once in any group data. Group data are reported as means ± SD, unless otherwise indicated.

**RESULTS**

Table 1 shows polysomnography data. All patients had severe OSA in the body position in which dial-down results are reported, with the AHI ranging from 41 to 123 min⁻¹.

Apnea or severe flow limitation, recognized by the characteristic flat or gently down-sloping flow contour (10), was evident in all patients during air dial downs (e.g., Fig. 1A). In two patients, severe hypopneas, but no apneas, were observed at 1 cmH₂O. In these two patients, the estimated $P_{CLOSE}$ (by back extrapolation) was 0 and −2 cmH₂O. In all others, $P_{CLOSE}$ and hence dial-down pressure used, was ≥1 cmH₂O (3.3 ± 2.3 cmH₂O). There were 9.1 ± 3.4 air dial downs per patient. Flow during air dial downs was 0.058 ± 0.052 l/s, representing 13.9 ± 11.8% of peak flow on CPAP.

Seventy-four percent of all observations occurred in stage 2 sleep. Slow-wave sleep occurred sporadically in several patients. Fraction of observations in slow-wave sleep ranged from 0 (7 patients) to 82% (26 ± 26%). The inconsistency of presence and percentage of observations in slow-wave sleep within patients precluded a systematic analysis of effect of sleep stage (i.e., stage 2 vs. slow-wave sleep) on the results. Accordingly, the data from all NREM observations were pooled.

**Ventilatory Responses to Chemical Stimulation Before Dial Down**

Table 2 shows baseline ventilatory data. The first significant increase in $\dot{V}E$ following a gas challenge occurred during the next breath (breath 2) in four patients, during breath 3, in 14 patients, and during breath 4 in 3 patients. Estimated lung-to-carotid delay was 9.9 ± 2.4 s.

Respiratory rate of the “last breath” was 14.8 ± 2.5 min⁻¹, which was not different from baseline (14.7 ± 2.3 min⁻¹). Changes in $\dot{V}E$, $V_T$, and mean inspiratory flow were accordingly similar in proportion. Only changes in $\dot{V}E$ are reported.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP level, cmH₂O</td>
<td>11.8 ± 2.6</td>
</tr>
<tr>
<td>$V_T$, liters</td>
<td>0.49 ± 0.11</td>
</tr>
<tr>
<td>Respiratory rate, min⁻¹</td>
<td>14.7 ± 2.3</td>
</tr>
<tr>
<td>Mean inspiratory flow ($V_T/T_i$, l/s)</td>
<td>0.26 ± 0.06</td>
</tr>
<tr>
<td>Peak inspiratory flow, l/s</td>
<td>0.42 ± 0.09</td>
</tr>
<tr>
<td>$\dot{V}E$, l/min</td>
<td>7.0 ± 1.3</td>
</tr>
<tr>
<td>Coefficient of variation of $\dot{V}E$</td>
<td>0.17 ± 0.07</td>
</tr>
<tr>
<td>$PET_{CO_2}$, mmHg</td>
<td>37.6 ± 4.4</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>93.7 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. CPAP, continuous positive airway pressure; $V_T$, tidal volume; $T_i$, inspiratory duration; $\dot{V}E$, minute ventilation; coefficient of variation of $\dot{V}E$, breath-by-breath variability of $\dot{V}E$ during baseline, expressed as SD/average $\dot{V}E$; $PET_{CO_2}$, end-tidal PCO₂.

Table 3 shows average breath-by-breath changes in $\dot{V}E$ following the change in inspired gas, and the corresponding changes in $PET_{CO_2}$ and O₂ saturation during the last breath. The five mixtures resulted in a wide range of stimulation before dial down (last breath, Table 3). Oxyhemoglobin desaturation associated with the hypoxic mixtures was modest (≈4%). During hypoxia in 1% CO₂, the ventilatory response was essentially isocapnic ($\Delta PET_{CO_2} = −0.7 ± 1.3$; $P < 0.05$). Hypoxia in 3% CO₂ resulted in mild hypercapnia ($\Delta PET_{CO_2} = 3.3 ± 2.2$; $P < 0.0001$). The hypercapnic mixtures were associated with progressively higher $PET_{CO_2}$ with little changes in O₂ saturation. With all five gas mixtures, the ventilatory response began in earnest by breath 3 and progressed rapidly through breath 5 (Table 3). With pure hypoxia (hypoxia in 1% CO₂), the ventilatory response had leveled off before dial down or arousal (penultimate $\Delta \dot{V}E$, Table 3). Where hypercapnia was produced, $\dot{V}E$ continued to increase beyond the 5th breath, albeit at a slower rate.

The last data set in Table 3 is an estimate of what the ventilatory response might be if the pulmonary gas changes were similar to those expected during an obstructive apnea or moderate hypopnea in which O₂ saturation decreased by ≈4% and $V_T$ decreases below the anatomic dead space [≈1 ml/pound ideal body wt (9)]. Under these conditions, there is essentially no alveolar ventilation, and the situation is analogous to the patient rebreathing his or her own expired gas. It was derived by adding the response to 6% CO₂, which was essentially isoxic (Table 3), and the response to hypoxia in 1% CO₂, which was essentially isocapnic, and multiplying the product by 1.3 to account for the multiplicative relation between hypoxic and hypercapnic responses (see APPENDIX for justification). The estimated increase in respiratory drive during an obstructive apnea or severe hypopnea was, on average, very large, reaching a $\Delta \dot{V}E$ of 187% baseline by breath 5 (Table 3, hypoxia in 6% CO₂). The response was, however, highly variable among patients; the 5th breath response [$\Delta \dot{V}E5 (%)$] ranged from 56 to 477% (Table 4).

**Arousal in Response to Increased Respiratory Drive ($TA_{50}$ and $TA_0$)**

The frequency of cortical arousals before dial down (i.e., within 30 s of altering gas mixture) was 10.5%, 23.4%, and
Table 3. Ventilatory responses to changes in inspired gas composition

<table>
<thead>
<tr>
<th>Gas Mixture</th>
<th>ΔPETCO₂, mmHg</th>
<th>ΔO₂Sat, %</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>B5</th>
<th>Last Breath Penultimate ΔV̇E</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% CO₂ (n = 21)</td>
<td>5.9 (2.2)</td>
<td>0.7 (0.8)</td>
<td>0 (0)</td>
<td>0.4 (0.4)</td>
<td>1.4 (1.0)</td>
<td>3.1 (1.5)</td>
<td>3.9 (2.0)</td>
<td>5.0 (1.9)</td>
</tr>
<tr>
<td>6% CO₂ (n = 19)</td>
<td>13.4 (3.4)</td>
<td>0.7 (1.0)</td>
<td>0 (0)</td>
<td>0.1 (0.7)</td>
<td>1.7 (2.2)</td>
<td>4.4 (2.7)</td>
<td>6.1 (3.3)</td>
<td>8.6 (3.4)</td>
</tr>
<tr>
<td>9% CO₂ (n = 12)</td>
<td>24.6 (5.5)</td>
<td>0.3 (1.2)</td>
<td>0 (0)</td>
<td>2 (14)</td>
<td>43 (70)</td>
<td>85 (56)</td>
<td>118 (58)</td>
<td>175 (65)</td>
</tr>
<tr>
<td>Hypoxia in 1% CO₂ (n = 20)</td>
<td>-0.7 (1.3)</td>
<td>-4.4 (1.7)</td>
<td>0 (0)</td>
<td>0.0 (0.9)</td>
<td>1.0 (0.9)</td>
<td>2.5 (1.9)</td>
<td>3.3 (2.5)</td>
<td>3.8 (1.7)</td>
</tr>
<tr>
<td>Hypoxia in 3% CO₂ (n = 17)</td>
<td>3.3 (2.2)</td>
<td>-3.7 (1.6)</td>
<td>0 (0)</td>
<td>0.1 (1.0)</td>
<td>2.7 (2.5)</td>
<td>5.8 (4.4)</td>
<td>6.9 (4.1)</td>
<td>7.4 (3.1)</td>
</tr>
<tr>
<td>Hypoxia in 6% CO₂ (estimated) (n = 18)</td>
<td>12.5 (4.2)</td>
<td>-3.7 (1.6)</td>
<td>0 (0)</td>
<td>0.1 (1.5)</td>
<td>3.4 (3.7)</td>
<td>8.9 (5.6)</td>
<td>12.3 (7.4)</td>
<td>15.6 (6.4)</td>
</tr>
</tbody>
</table>

*For ΔV̇E, except for the last column, reported values are means (SD) of differences from the first breath receiving the altered gas (B1). For ΔV̇E, values in the first row are in l/min and values in the second row are %baseline. Last breath refers to last breath before dial down or before arousal. Penultimate ΔV̇E refers to difference between last breath and the immediately preceding breath. Change in PETCO₂ (ΔPETCO₂) and oxygen saturation (ΔO₂Sat) values are means (SD) and were obtained during the last breath before dial down or arousal. Estimated response if hypoxia in 6% CO₂ were tested, obtained by adding the nearly isoxic responses to 6% CO₂ and the nearly isocapnic responses to hypoxia in 1% CO₂ and multiplying by 1.3 to account for the multiplicative interaction between hypoxia and hypercapnia (see discussion for detailed explanation).

59.4% for the 3%, 6%, and 9% CO₂ mixtures, respectively. It was 7.5% and 20.3% for the hypoxia with 1% CO₂ and hypoxia with 3% CO₂, respectively. In two patients, arousal occurred infrequently, before or after dial down, even with the highest level of stimulation (ΔV̇E 174% and 268% baseline). In these patients TA could not be determined. In the other 19 patients, T A50, determined taking into account arousals before and during dial down, ranged from 40% to 282% increase in V̇E over baseline (112 ± 58%, Table 4). T A0 ranged from 90% to 348% baseline (168 ± 72%).

Table 4. Individual patient characteristics and results of chemical responsiveness dV̇E5, effective recruitment threshold (T ER) and arousal threshold (T A50)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
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<th>P close, cmH₂O</th>
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<th>dV̇E5, %</th>
<th>T A50, %</th>
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BMI, body mass index; AHI, apnea-hypopnea index (h⁻¹) during clinical polysomnography. P close, airway pressure at which the pharynx just closes; dV̇E5 (%), estimated % increase in ventilation at breath 5 following inhalation of 6% CO₂ along with 4% O₂ desaturation. ↑ in DD flow: numerator is no. of observations in which dial-down flow increased significantly relative to air dial downs; denominator is number of dial-downs preceded by gas challenges. Difference between denominator in this column and the no. in the “No. of Gas Challenges” column reflects gas challenges that resulted in arousal before dial down. T A0 (%), percent increase in ventilation associated with a significant increase in dial-down flow; T A50 (%), percent increase in ventilation associated with 50% probability of arousal.

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Response of Dial-Down Flow to Increased Respiratory Drive in the Absence of Arousals

The range of chemical stimulation over which dial-down flow could be assessed was limited by the highest $\dot{V}E$ that could be obtained without arousal ($TA_0$). There were $17.0 \pm 9.9$ gas challenges per patient (Table 4). Not all these challenges were followed by dial downs because of the frequent occurrence of arousal before 30 s had elapsed. The number of dial downs that were preceded by some degree of chemical stimulation was $12.1 \pm 8.1$ (range 1–32, Table 4). Figure 1 shows tracings from a patient who demonstrated a clear increase in dial-down flow in response to stimulation (patient 8, Table 4). Figure 2B shows the relation between last-breath $\dot{V}E$ and dial-down flow in this patient. In 12 patients a significant increase in dial-down flow was observed in at least two observations following chemical stimulation (Table 4). The pattern of response varied among patients. In four patients significant responses occurred over a wide range of pre-dial-down $\dot{V}E$, and the response was orderly such that a significant correlation was obtained between last-breath $\dot{V}E$ and dial-down flow (e.g., Fig. 2, A and B). In these four patients, $T_{ER}$ ranged from 0 to 2.2 l/min (0 to 31%) above baseline $\dot{V}E$. In the other eight patients the relation was not orderly. Typically, there was a range of last-breath $\dot{V}E$ over which dial-down flow was consistently not different from air dial downs, and a higher range in which some dial downs were associated with a significant increase in flow, while in others flow was not different from baseline (e.g., Fig. 2C). In these patients $T_{ER}$ ranged from 2.2 to 8.0 l/min above baseline ($5.0 \pm 2.2$ l/min), representing 33 to 109% of baseline $\dot{V}E$ (74 $\pm 28$% baseline).

In nine patients there was no increase in dial-down flow over the entire range of pre-dial-down $\dot{V}E$ (Table 4). An example is shown in Fig. 3. Although in these patients the precise value of $T_{ER}$ could not be determined, it was clearly higher than the highest chemical drive that can be tolerated without arousal. Six of these nine had no response despite $>100%$ increase in $\dot{V}E$ (Fig. 4A, Table 4). In three patients arousal threshold ($TA_0$) was quite low, severely limiting the range of chemical drive that could be tested, and making it impossible to determine whether failure of response was due to a high $T_{ER}$ (Fig. 4B).

Relation Between $T_{ER}$, $TA$, and Chemical Responsiveness

Table 4 shows the values of chemical responsiveness [%increase in ventilation at breath 5 ($d\dot{V}E5$; %)], $T_{ER}$, and $TA$ in individual patients, along with the corresponding $P_{CLOSE}$. Figure 5 summarizes the relation between $T_{ER}$ and $TA50$ in the 21 patients. With two exceptions, all patients demonstrated a $T_{ER} > 0$, indicating the need for a threshold increase in drive before effective reflex dilatation of the airway can take place. In at least 8 of 21 patients (38%), $T_{ER}$ was $>100%$. In patients where both thresholds were available (solid circles, $n = 12$) there was no correlation between $T_{ER}$ and $TA50$ ($r^2 = 0.03$, $P > 0.5$).

Figure 6 shows the relation between chemical responsiveness [$d\dot{V}E5$ (%)] and arousal threshold ($TA50$) in the 20 patients in whom asphyxic responses could be estimated. As
indicated earlier, TA could not be determined in two patients (vertical arrows), while in two patients the maximum CO₂ received was 3% (horizontal arrows). There was a weak but significant correlation between the two variables in the remaining 16 patients ($r^2 = 0.44$, $P < 0.005$).

There was no correlation between chemical responsiveness and $T_{ER}$ in 10 patients in whom both variables were available ($r^2 = 0.05$, $P > 0.5$). There was also no correlation between the severity of mechanical abnormality ($P_{CLOSE}$) and chemical responsiveness ($r^2 = 0.03$, $P < 0.5$), $T_{ER}$ ($r^2 = 0.02$, $P < 0.7$), or $T_{A50}$ ($r^2 = 0.09$, $P < 0.3$).

Evidence for Lack of Arousal at Upper Airway Opening

In agreement with visual assessment of lack of cortical arousal, neither alpha/sigma nor beta EEG power showed a significant increase at the time of upper airway opening in any of the 24 analyzed observations (i.e., those with the greatest increase in dial-down flow in the 12 responding patients). Likewise, the average alpha/sigma and beta powers at opening in the 24 observations were not increased relative to baseline or to the power just before dial down (Table 5). Heart rate increased slightly but significantly with the increase in chemical drive (just before dial down vs. baseline, Table 5), but there was no further increase at the time of upper airway opening. There was also no difference in the magnitude of increase in heart rate between observations with and without upper airway opening (Table 5). Peak inspiratory flow during dial downs associated with upper airway opening was significantly higher than at baseline but lower than just before dial down, indicating that opening was not complete.

DISCUSSION

We have described an approach to evaluating the various mechanisms responsible for breathing instability in OSA patients. The results confirm that in the majority of patients, even in those with severe OSA, modest increases in chemical drive can result in upper airway opening without arousal and suggest that in these patients instability develops because 1) arousals also occur, on average, with only modest increases in respiratory drive, and 2) the dynamic response of chemoreceptors to the pulmonary gas changes associated with obstructive events is, on average, sufficiently brisk to result in considerable postevent increase in respiratory drive even in the face of a
Table 5. High-frequency EEG power and heart rate at different times during chemical stimulation

<table>
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<th>Observations With Increase in Dial-Down Flow (n = 24)</th>
<th>Observations With No Increase in Dial-Down Flow (n = 24)</th>
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<td>Baseline</td>
<td>Just Before Dial Down</td>
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<td>Peak inspiratory flow, l/s</td>
<td>0.42 (0.09)</td>
<td>0.79*† (0.20)</td>
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<tr>
<td>Alpha/sigma power</td>
<td>10.8 (6.1)</td>
<td>10.8 (7.8)</td>
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<tr>
<td>Beta power</td>
<td>1.80 (0.69)</td>
<td>2.02 (1.12)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66.6 (10.2)</td>
<td>68.6*(9.3)</td>
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</tbody>
</table>

Values are means (SD). *Significantly different from baseline. †Significantly different from just before dial down. ‡Significantly different from the corresponding value in observations with no increase in dial-down flow.

normal circulatory delay. This study also suggests that the mechanisms responsible for instability may vary considerably among patients (Table 4, Figs. 5 and 6).

Critique/Limitations of Methods

1) Several studies have documented the progressive increase in inspiratory pressure during naturally occurring obstructive apneas and reported the pressure level at which the airway opens (3, 4, 25, 30, 38, 40, 46, 49, 56). Since arousal is usually present when the airway opens, and given the strong belief that arousal is responsible for opening, the threshold increase in drive required for airway opening became synonymous with arousal threshold (3, 4, 25, 30, 38, 40, 46, 49, 56).

Increases in inspiratory effort in response to mechanical loading during sleep reflect changes in blood gas tensions (51). As judged by the rate of increase in inspiratory pressure, chemical drive usually changes rapidly in the course of obstructive events (3, 4, 25, 30, 38, 40, 46, 49, 56), particularly just before opening (2a). Furthermore, the circulatory delay inherent in these chemical responses dictates that respiratory drive will continue to increase for a finite period beyond airway opening. The rapid increase in drive during natural obstructive events, and the inherent inertia of chemical responses, would make it difficult to identify a separate threshold increase in drive at which the airway may open without arousal (T_Er) since both T_Er and arousal threshold may be crossed almost simultaneously (53). A special methodological feature of the present study made it possible to identify the two thresholds separately. Here, we imposed a range of increases in chemical drive, but at each level the increase in drive was arrested, or nearly so, before the obstruction was induced (“penultimate ΔVe”, Table 3). With this arrangement, if T_Er is below arousal threshold a range of pre-dial-down chemical drive would be found where the airway would remain open during the dial down, at least for the period of circulatory delay, despite lack of arousal.

2) We studied the effect of chemical drive on dial-down flow when airway pressure was near P_Close. Under these conditions any increase in net dilating force should increase dial-down flow. This approach increases the sensitivity of detecting a change in net airway distending pressure. However, T_Er, so determined, may underestimated the increase in drive required to keep the airway open without CPAP if P_Close is >0. Under these conditions, drive must increase by T_Er plus an additional amount to overcome P_Close. We feel this is an acceptable limitation since once T_Er is reached the relation between chemical drive and extra distending force appears to be steep (see Relation Between Chemical Drive and Maximum Flow Beyond T_Er) so that the error may not be so large. Nonetheless, it is important to appreciate that when P_Close is >0, T_Er underestimates the increase in drive required to open the airway in the absence of CPAP.

3) Changes in drive were superimposed on optimal CPAP. Thus the increase in respiratory drive, as well as T_Er and T_A, could be defined by reference to the drive the individual patient has during sleep with a normal mechanical load (thereafter called eupneic drive). For example, one may say that net dilatation, or arousal, occurred when drive increased by 60% above eupnea. Defining chemical responses, T_Er and T_A in the same units and by reference to eupneic drive, is of considerable value (see Interrelation of Chemical Responsiveness, T_Er, and T_A).

4) The present results were obtained from patients before initiation of CPAP treatment. It is, therefore, not possible to tell whether the destabilizing influences identified here were pre-morbid or a consequence of long-standing OSA. A reevaluation of the responses examined here after CPAP treatment would be of considerable interest.

5) Only one value per patient is given for T_Er, T_A, and ventilatory responses (Table 4). It is clearly possible that these responses vary from night to night, or even at different times during the same night. The study was not designed to address the consistency of these responses in the same patient, and efforts to address consistency within the same night were not successful; most data reported here were obtained from a 1- to 2-h period during which body position was stable in NREM sleep and it was possible to test four to five inspired gas mixtures on at least one occasion, but usually more (Table 4). At other times, the patient may have been in a different position or spent a long time awake between observations so that we could not obtain enough data to compare results at different times of the night. Additional studies are needed to address this important issue as it may explain within- or between-night variability in the severity of OSA.

Effective Recruitment Threshold (T_Er)

Magnitude. T_Er ranged widely from zero to >175% (Fig. 5). In 12/21 patients (57%), and possibly 16/21 patients (76%), T_Er was less than 110% of eupneic drive (Fig. 5). Although this percent increase may appear large, it is in fact very small when measured against the capacity of the respiratory system to increase its output [e.g., >1,000% during moderate exercise (47)], or when one considers how little changes in blood gas tensions are typically required to increase drive by this amount. Thus, given the normal steady-state response to CO2 [≈2 l/min−1·mmHg−1 (36)], resting ventilation can be doubled through a mere 3-mmHg increase in arterial Pco2 (Paco2). It is, therefore, possible that in many, but certainly not all, patients

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the airway may remain open if respiratory drive were allowed to increase modestly, and remain increased. This finding further emphasizes the important role an excessive postapneic ventilatory overshoot, which reduces drive to eupneic levels or even lower, plays in perpetuating the obstructive apnea in many patients (53).

**Mechanism of** $T_{ER}$. Why is it necessary for drive to increase a finite amount ($T_{ER}$) before a net dilating effect is manifest, and why does the threshold differ so much among patients? Two broad mechanisms may be entertained.

1) A finite increase in respiratory drive is required before dilator activity can begin increasing. The primary stimuli for activating pharyngeal dilators during sleep are chemical drive and negative pharyngeal pressure (15). Development of an obstructive event at eupneic levels of chemical drive (e.g., at sleep onset or at the onset of air dial downs here) indicates that the negative pharyngeal pressure associated with eupneic respiratory drive is insufficient to maintain airway patency. Since inspiratory efforts are the source of negative pharyngeal pressure, and the only means by which these efforts can be increased during sleep is an increase in chemical drive (51), chemical drive must increase if upper airway patency is to be restored without arousal, regardless of whether this is accomplished directly via the increase in drive per se or indirectly via a more negative pharyngeal pressure. When breathing is stimulated by $CO_2$ in sleeping animals (13, 16, 55) and sleeping healthy humans (26, 34), diaphragm activity increases continuously with $CO_2$ whereas dilator activity increases only above a threshold level of stimulation. Activity of pharyngeal dilators increases progressively during obstructive events in OSA patients (5, 7, 28, 29, 31, 38), thereby reflecting their responsiveness to increasing chemical drive, acting directly or indirectly via the negative pressure reflex. However, the increase in chemical drive, relative to eupnea, required for dilator activation in OSA patients is not known. It may be that differences exist among patients in the magnitude of increase in chemical stimulation, or in the magnitude of negative pharyngeal pressure, required for recruitment of dilators to be initiated.

2) A finite increase in dilator activity needs to be reached before a net dilating influence can be generated. In the passive pharynx, reduction in pharyngeal pressure below values that result in flow limitation is commonly associated with a paradoxical reduction in maximum flow (negative effort dependence) (21, 42). Thus it is possible that the more negative pharyngeal pressure during stimulated breathing may, acting via negative effort dependence, offset the distending action of the activated dilators, resulting in no net dilating force until activity exceeds a threshold value. This threshold may vary among patients.

Recently, Patil et al. (32) compared OSA patients and normal subjects with respect to their ability to decrease critical closing pressure ($P_{CRT}$) during sustained reductions in airway pressure. OSA patients failed to decrease $P_{CRT}$ whereas normal subjects did. This suggests that $T_{ER}$ is higher in OSA patients than in normal subjects. Interestingly, the response of the genioglossus was not different, suggesting that the second mechanism mentioned above may be responsible for differences in $T_{ER}$. Further studies are needed to identify the reason(s) for $T_{ER}$ variability.

It is not clear whether $T_{ER}$ is a fixed property in individual patients. Given the different neural and mechanical mechanisms that may account for $T_{ER}$, it is possible that this threshold may vary with body or head and neck position, or as a result of changes in so-far-unidentified control mechanisms that affect dilator muscles recruitment. Additional studies are needed to address this important issue.

**Relation Between Chemical Drive and Maximum Flow Beyond $T_{ER}$**

In 4 of 12 patients in whom $T_{ER}$ could be determined, maximum flow ($F_{MAX}$) increased in a graded and orderly way as drive increased further (Fig. 2, A and B). In the remaining eight patients, a wide range of $F_{MAX}$ was observed over a narrow range of respiratory drive (Fig. 2C). This may reflect a very high slope between $F_{MAX}$ and drive beyond $T_{ER}$. Thus the level of drive during $F_{MAX}$ measurement (i.e., during dial down) was inferred from the last breath, which occurred 1–2 breaths earlier. Given the breath-by-breath variability in $VE$ (Table 2), it may be expected that actual drive during dial down was different from the inferred value by up to 2–3 l/min. Such random measurement errors may still be consistent with an apparent orderly response when the slope is relatively low but would result in a wide range of responses over a small range of inferred drive levels if the slope were high. Alternatively, this type of relation (i.e., as in Fig. 2C) may result if $T_{ER}$ were to vary from time to time in association with changes in head and neck position or in other unmonitored variables.

**Arousal Threshold ($T_{A}$)**

Arousal threshold in OSA patients is typically reported as the inspiratory pressure generated just before arousal at the end of obstructive events ($DPMAX$) (2a). Reported $DPMAX$ values vary considerably between patients (3, 4, 25, 30, 40, 46, 49, 56). As well, there is considerable within-patient variability in $DPMAX$ (2), reflecting differences in depth of sleep during the night. The average $DPMAX$ reported in a given patient is, therefore, the level associated with arousal nearly half the time and is comparable to the $TA$50 reported here. As with $DPMAX$, $TA$50 varied widely among patients (40 to 268% increase in drive over baseline) and displayed within-patient variability [width of the probability line (Fig. 2)]. The present study is, however, the first to report $TA$ as the increase in respiratory output above eupnea. Even though arousal threshold has been reported to be higher in OSA patients than in normal subjects (2a), when $TA$ is expressed as the percent increase in eupneic ventilatory drive that results in arousal, it becomes clear that most OSA patients arouse in the face of very modest, safe changes in blood gas tensions. Thus, in nearly half the patients (10/21), $TA$50 was <100%, and in 15/21 (71%) of patients, it was <150% (Fig. 5). As indicated earlier, such increases in drive result from very small changes in gas tensions. It therefore appears that in most OSA patients arousal mechanisms operate with an unnecessarily large safety margin.

**Chemical Responses**

To our knowledge, this is the first study in which ventilatory responses to $CO_2$ and hypoxia were assessed during sleep with normalized upper airway resistance. It is also the first in which breath-by-breath changes in drive were quantified in the course of inspired gas changes that last several breaths, thereby mimicking the pattern of pulmonary gas tensions during ob-
structive events. The selection of gas mixtures also allowed us to estimate how much respiratory drive would increase breath-by-breath in each patient if alveolar ventilation were transiently eliminated, along with a modest degree of O2 saturation, as would happen during an apnea or moderate hypopnea (Table 3). The results showed marked interindividual differences (SDs, Table 3). This is not surprising since normal ventilatory responses to CO2 and hypoxia are highly variable when measured by standard techniques (36). However, on average, chemical responses were surprisingly fast and large. Thus, with the changes in blood gas tensions expected during an apnea or moderate hypopnea, respiratory output would reach an average 287% of the eupneic level by breath 5 (hypoxia in 6% CO2, Table 3). Because of circulatory delays (~10 s), the increase in drive in breath 5 was in response to changes in pulmonary gas tensions by early breath 3 and is, therefore, unavoidable even if the airway opened at breath 3, the earliest it could do so during air breathing. Accordingly, these findings indicate that, given such chemical responses, a large ventilatory overshoot is unavoidable following even a three-breath event unless the patient’s chemical response is well below average, or airway resistance remains very high after opening to substantially damp the ventilatory response.

Our patients had severe OSA. Whether the average response observed here is excessive relative to normal subjects or to patients with milder OSA is not known. The mild, altitude-related hypoxemia in Calgary (Table 2) may have contributed. Other lines of evidence, however, suggest that dynamic ventilatory responses may be higher in OSA patients than in normal subjects. Loop gain during sleep is higher in OSA patients than in normal subjects (48, 54). Likewise, Hudgel et al. (18) found that ventilatory responses to single breath CO2 challenges were higher in awake OSA patients than in normal subjects. Furthermore, in the current patients, PETCO2 increased an average 13.4 mmHg during inhalation of 6% CO2 (Table 3). Inhalation of 6% CO2 is comparable to rebreathing in that PETCO2 cannot rise above mixed venous PCO2 before recirculation. When measured by the rebreathing technique, mixed venous PCO2 is normally only 10 mmHg higher than PETCO2 (35), thereby suggesting that mixed venous-to-alveolar CO2 gradient was above normal in our patients, perhaps reflecting the higher metabolic rate due to obesity. A higher gradient increases the dynamic ventilatory response to CO2 (23, 50).

Interrelation of Chemical Responsiveness, TER, and TA

By expressing chemical responsiveness, TER, and TA in the same units (ΔVE, relative to eupnea), it is possible to examine the interaction between these three variables in generating OSA. Figure 7 shows the estimated average change in respiratory drive associated with ~4% desaturation along with an increase in PETCO2 to mixed venous level, such as would occur during a brief obstructive event (from Table 3). Average arousal threshold (TA50) is indicated. The solid circle illustrates a situation where arousal threshold at the moment is about average. In one case, TER is lower than TA, while in the other it is higher. This display helps explain the dominant features of OSA and illustrates how instability is determined by the interaction of several unrelated variables as opposed to being a function of a single abnormality.

1) Given the average results illustrated in Fig. 7, and the impossibility of altering the time course of chemical drive until two to three breaths after opening, arousal is difficult to avoid even when the upper airway opens reflexly (i.e., TER < TA). Thus, to avoid arousal, TA must not only be higher than TER, but the difference must also exceed the obligatory increase in drive over the period of circulatory delay. According to the data of Fig. 7, this difference must be large. For example, if TER were 80% (e.g., TER2, Fig. 7), TA must be >180% (i.e., drive at breath 5), and if TER were 30%, TA must be >130% (drive at breath 4). Of course, the difference between TA and TER need not be so large in a patient in whom the rate of rise in drive is below average. However, this would require a combination of TER, TA, and chemical responsiveness that is rare in this type of patient (Figs. 5 and 6 and Table 4). This analysis explains why arousal occurs so frequently at the end of obstructive events. Furthermore, it shows why occurrence of arousal need not signify that arousal was responsible for airway opening.

2) The above analysis also explains why some individuals, whose upper airway is susceptible to closure during sleep, do not develop OSA, or may only have it intermittently (52). Thus stable breathing may occur if 1) chemical response is slow enough to reduce the difference between TA and TER required to avoid arousals, and/or 2) the difference between TA and TER is large, because TER is low, TA is high, or both. Under these conditions arousal following an obstructive event may be avoided. It has been well documented that arousals further increase respiratory output and aggravate the postapneic overshoot (17, 24, 53). Therefore, avoidance of arousal promotes a stable response with the result that the patient may develop an occasional obstructive event as opposed to repetitive OSA. Because arousal threshold varies considerably across the night (2), the difference between TA and TER is also likely to vary from time to time, and this may account for periods of stable breathing, particularly during delta sleep, in patients who have intermittent OSA (52, 53). Further studies are needed to determine the differences in these indexes of ventilatory stability.
between the patients who have repetitive OSA throughout sleep and those with OSA that occurs intermittently or not at all despite a susceptible upper airway.

3) The fast rate of increase in chemical drive coupled with the inevitable circulatory delay provide an explanation for the persistence of the characteristic discontinuous flow behavior at the end of obstructive events even in the absence of arousal (53). Thus, assume that TR and is low, at 50%. The upper airway starts to open by breath 3 (see Fig. 7). However, chemical drive continues to rise rapidly through breath 4 and possibly breath 5, reaching 130% or 180% above baseline (230% or 280% of baseline) before it begins to decline. This large additional increase in chemical drive should result in a rapid and more complete opening of the airway, particularly when the relation between FMAX and chemical drive is steep beyond TR (Fig. 2).

The frequent occurrence of arousal along with a sudden increase in flow at the end of obstructive events have been the cornerstones of the thesis that arousal is responsible for airway opening (38). The present findings and analysis indicate that both phenomena are explainable, and in fact almost unavoidable, given the intensity of chemical responses, the prevailing arousal thresholds, and the relation between FMAX and respiratory drive in the absence of arousal in patients with OSA. Accordingly, these phenomena are no longer compelling reasons for advocating an essential role for arousal in terminating obstructive events.

**Clinical Implications**

Each of the three “control of breathing” variables studied here, chemical responsiveness, TA, and TR, may be amenable to modification through appropriate, but different, nonmechanical interventions. For example, TR may be effectively reduced or eliminated by breathing CO2-enriched gas, oxygen breathing may substantially dampen brusk chemical responses, and sedatives can increase arousal threshold. However, unless these therapies are targeted to the appropriate patients, they may not be effective or may exacerbate the problem. For example, where TR and/or PLOSE is very high, it may not be possible to raise baseline respiratory drive by the required amount while maintaining sleep, and only mechanical interventions may succeed in such patients. Likewise, administering oxygen to someone in whom chemical responsiveness is not excessive may simply prolong the obstructive events, and use of sedatives where arousal threshold is already high would aggravate hypoxemia.

The values obtained for each of the three measured variables varied widely among patients (Table 4), and there was little or no correlation between them (Figs. 5 and 6). Although the extent to which the values observed on a given night/body position (as was done here) reflect fixed, or reasonably fixed, properties of individual patients remains to be determined, these findings suggest that the mechanism(s) of instability may vary considerably from patient to patient. This may explain why the use of O2 (20, 44, 45), CO2 (19, 20, 27), and sedatives (8, 14, 39) in previous studies on unselected patients produced inconsistent results. Accordingly, a reevaluation of these therapies, when used selectively, may be indicated.

The range of TR values required for reflex airway opening found here (Fig. 5) also explains why the use of pharmacological stimulants, such as acetazolamide, medroxyprogesterone, theophylline, and nicotine, proved ineffective (20, 44, 45). Thus the increase in drive produced by these agents (5- to 10-mmHg reduction in PaCO2, corresponding to 10–20% increase in drive) is trivial relative to what is required (Fig. 5).

**APPENDIX**

**Estimation of Changes in Respiratory Drive During an Obstructive Apnea or Moderate Hypoventilation**

With the 6% CO2 mixture, inspired PCO2 (~42 mmHg) was slightly above baseline PETCO2 (37.6 ± 4.4 mmHg, Table 2), thereby approximating the rebreathing situation during obstructive events in which tidal volume decreases below the anatomic dead space. Following a change to 6% CO2, PETCO2 rose rapidly to a relatively stable level (e.g., Fig. 1C), representing the mixed venous value. Thus the response to 6% CO2 reflects what would happen during an obstructive event if there were no associated hypoxemia. On the other hand, since PETCO2 changed minimally while breathing hypoxic gas in 1% CO2 (Table 3), the response to this gas mixture reflects what happens with a 4% desaturation with no associated hypercapnia.

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MECHANISMS OF OBSTRUCTIVE APNEA


