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Oxygenation and Breathing Pattern During Phasic and Tonic REM in Patients with Chronic Obstructive Pulmonary Disease

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Summary: Oxygen desaturation in chronic obstructive pulmonary disease (COPD) occurs during sleep and is most marked in REM sleep. REM is not a homogeneous state, consisting of phasic REM (PREM) (REMs, myoclonic twitches) and tonic REM (TREM) (muscle atonia, desynchronized electroencephalogram). In normals, onset of PREM produces transient changes in breathing pattern with a decrease in respiratory amplitude and an increase in frequency, which produce reductions in oxygen saturation (S_aO_2). Because it is reasonable to expect such breathing pattern changes to cause more desaturation in COPD, and because systematic all-night studies of PREM and TREM have not been reported, we studied 18 patients with severe COPD [Forced expiratory volume in one second (FEV_1) = 25.7 ± 3.5 (SEM) % predicted] during sleep and monitored S_aO_2 and breathing pattern in PREM and TREM. PREM made up 19.7% of total REM (4.6% total sleep time) but was associated with 81.7% of the total REM desaturations of >5% (57.9% of all sleep desaturations of >5%). With PREM onset, breathing pattern changed 72.5% of the time, most often with a transient decrease in amplitude and increase in frequency. Even though 27.5% of PREM was not associated with changes in breathing pattern and many PREM segments were very short, we were still able to show highly significant S_aO_2 differences between PREM and TREM. Mean TREM S_aO_2 was 88.0 ± 1.2%; mean PREM S_aO_2 was 86.6 ± 1.4%, with mean nadir S_aO_2 for individual PREM segments falling to 84.8 ± 1.5%. Mean awake S_aO_2 was 89.7 ± 0.8%. We conclude that in COPD the transition from TREM to PREM is associated with breathing pattern changes and oxygen desaturation. Differences in breathing pattern with PREM onset may be related to different effects of PREM processes on respiratory neurons and diaphragm motor neurons. **Key Words:** Chronic obstructive pulmonary disease—Phasic REM—Tonic REM.

There is considerable evidence that the oxygen desaturation that occurs during sleep in chronic obstructive pulmonary disease (COPD) is more severe during REM sleep than during NREM sleep (1–3). REM sleep is not a homogeneous state, and, while it has not formally been subdivided, there exist periods of phasic activity (occurring only intermittently) contrasting with periods of tonic activity (lasting throughout the stage).

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Muscle atonia and desynchronized electroencephalogram (EEG) are examples of tonic events, while REMs, pontogeniculooccipital (PGO) waves, and myoclonic twitches are considered phasic events (4). In 1964 Aserinsky (5) reported changes in breathing pattern and oxygenation in normal people in the transition from tonic (TREM) to phasic (PREM) REM. He found that with the onset of eye movement bursts (PREM), there was an immediate reduction in respiratory amplitude and an increase in respiratory rate relative to the preceding period where there were no eye movements (TREM) and that these changes were transient. Concomitant with these changes, there was a small but definable drop in oxygen saturation (S_aO_2) that was statistically significant.

COPD patients develop oxygen desaturation during sleep, and this fall in S_aO_2 is most marked in REM sleep (3). The degree of desaturation in COPD is a function of resting blood gases; the lower the starting point on the oxygen-hemoglobin dissociation curve, then the greater will be the maximal fall in S_aO_2. We hypothesized that COPD patients would demonstrate similar breathing patterns as do normals in the transition from TREM to PREM but that the changes in S_aO_2 could very well be much larger owing in part to the lower baseline S_aO_2.

METHODS

Patients were chosen from the outpatient respiratory clinics of the University of Manitoba. The selection criteria were a clinical diagnosis of severe COPD, the presence of severe airflow obstruction by spirometry ($FEV_1 < 40\%$ predicted), clinical stability for at least 3 weeks prior to study, and no oxygen therapy (one patient was being evaluated for home oxygen but was studied on room air). The group included 17 men and 1 woman with an age of 69 ± 1.4 years (mean ± SEM) and an FEV_1 of 0.72 ± 0.05 L (see Table 1).

The patients spent 2 consecutive nights instrumented in the sleep laboratory with polysomnographic recording on the second night. We recorded the EEG, electrooculogram (EOG), and electromyogram (EMG), and these were scored according to standard criteria (6). Respiratory movement was monitored with a respiratory inductance plethysmograph abdominal belt (Respitrace Ambulatory Monitoring, Ardsley, NY, U.S.A.). Airflow was detected by a nasal cannula that was modified to sample airflow from both the nose and the mouth, and this was attached to a CO_2 analyzer [Hewlett-Packard (HP) capnometer model no. 47210A, Waltham, MA, U.S.A.]. The electrocardiogram and derived instantaneous heart rate were recorded. S_aO_2 was measured using

TABLE 1. *Clinical characteristics (n = 18)*

	Mean ± SEM
Age (yrs)	69 ± 1.4
Sex	17 M, 1F
FEV_1 (L)	0.72 ± 0.05
FEV_1 (% predicted)	25.7 ± 3.5
TLC (L)	6.87 ± 0.37
TLC (% predicted)	110 ± 4.8
Awake Po_2 (mm Hg)	65.0 ± 2.5
Awake Pco_2 (mm Hg)	39.0 ± 1.3
pH	7.42 ± 0.01

TLC, total lung capacity.

a transmittance ear oximeter in five patients (HP model no. 47201A) with a pulse oximeter applied to the finger (model no. N-100, software version 53.0; Nellcor, Hayward, CA, U.S.A.) in 11 patients and a pulse ear oximeter (Biox 3700; Ohmeda, Boulder, CO, U.S.A.) in 2 patients. All data were simultaneously recorded on paper using a polygraph (model no. 78D; Grass Instruments, Quincy, MA, U.S.A.), while a microcomputer (MINC-11; Digital Equipment Corp., Maynard, MA, U.S.A.) continuously monitored airflow and respiratory movement and stored S_aO_2, volume (qualitative), and heart rate twice for each complete respiratory cycle on a floppy disk. The computer generated a binary time stamp on the polygraph so that polygraph data and computer-stored data could by synchronized (7).

The sleep record was staged according to standard criteria, and REM sleep was subsequently divided into PREM and TREM using bursts of eye movements in the EOG tracing to define PREM and periods of ocular quiescence to indicate TREM. The EOG was derived from electrodes in the standard positions at the outer canthi of the eyes but configured as a single channel. This configuration has been previously validated (8). The EOG signal was processed by a Grass amplifier (model no. 7P511J) that was set to record eye movement with a gain of 10 mm for 50-μV deflection and a rise time constant of 0.1 s. Eye movements that were separated by a duration of less than a single complete respiratory cycle were considered to belong to the same PREM period; those eye movements separated by a duration of >1.0 respiratory cycle were considered to belong to a separate PREM period. When only a single eye movement or a very short burst of eye movements occurred (which was shorter in duration than 1.0 respiratory cycle), it was considered as neither PREM or TREM and excluded from the analysis. A duration of 1.0 respiratory cycle was arbitrarily chosen as it was felt that this was the minimum length of time needed to produce a change in the breathing pattern and/or oxygenation [Aserinsky (5) and Schmidt-Nowara and Snyder (9) chose 1.5 respiratory cycles].

After identifying segments of the record as PREM, TREM, NREM, and awake, the sleep stage data were merged with the data stored on floppy disks. A computer program yielded S_aO_2 values for the corresponding stages. Before analyzing the data file for S_aO_2, a time correction was introduced to account for circulation time and instrument delay. Hudgel and co-workers (10) estimated this time correction in patients with COPD by having them inhale 100% O_2 and measuring the time until the S_aO_2 reading increased. This time was of the order of 10–15 s and was assumed to be the same for sleep. Because some of the TREM and PREM segments are short and in the same order of magnitude as the known delay of the oximeters, it was critical that we accurately determine the delay of the oximeters. We determined this time correction first by scanning the individual records as follows: When there was a clear reduction (<50%) in amplitude or change in frequency of breathing and an associated desaturation, the time from the change in breathing to the beginning of the desaturation was measured. As well, when there was an arousal associated with a desaturation and subsequent resaturation, the time when breathing increased to the time of the start of the resaturation was measured. Measurements were made in 323 desaturations of >5% detected in 15 patient records.

The pulse oximeter on the finger was noted to have a slower response time than the transmittance oximeter on the ear. The response also appeared to be a function of heart rate. To quantitate the pulse oximeter response delays, we simultaneously measured S_aO_2 with an HP ear oximeter, a Nellcor finger oximeter, and a Biox ear oximeter

during sleep in five apnea patients who demonstrated repetitive S_aO_2 oscillations. We analyzed 149 such oscillations (S_aO_2 range 92.1 ± 2.6 to 74.2 ± 7.7%) and found both the Nellcor and the Biox to be of comparable accuracy to the HP (Nellcor S_aO_2 = 1.006 × HP S_aO_2 + 0.67, r = 0.9, $p < 0.001$; Biox S_aO_2 = 0.868 × HP S_aO_2 + 14.15, r = 0.9, $p < 0.001$). The response delay of Nellcor relative to HP was inversely related to heart rate [Nellcor delay relative to HP (s) = heart rate × −0.22 + 27.5; r = −0.64, $p < 0.05$], but there was no appreciable delay with the Biox on the ear [Biox delay relative to HP (s) = heart rate × 0.07 − 6.3; r = 0.554, $p < 0.01$].

Thus, the time correction was patient specific and for the 11 measured with the Nellcor oximeter derived from the average of the HP time correction plus the response delay calculated using the individuals' mean heart rate during REM. Results of S_aO_2 are those using each individual's time correction. For the HP, the time correction was 15 ± 0.2 s. For the Nellcor, the response delay was 10.6 ± 2.4 s, giving the average Nellcor time correction of 25.6 ± 2.4 s.

To examine breathing patterns with TREM and PREM transition, we chose a random sample of 10 TREM-PREM segments from eight of the records; the pattern was analyzed first by visual inspection (qualitatively) and then by measuring the relative changes in the volume signal (quantitatively) from TREM to PREM.

One-way analysis of variance with post hoc Scheffé's multiple comparison test (11) was used to analyze S_aO_2 for the REM subcategories (PREM, TREM) and NREM.

RESULTS

Total sleep time was 304 ± 21.8 min. The amount of REM sleep as a percentage of the total sleep time was 23.3 ± 1.6%, which is within the normal range for age (12). We analyzed 1,072 PREM segments and 1,197 TREM segments; this totaled 94.9% of all REM was 5.1% was excluded from the analysis. The average durations of PREM and TREM were 11.4 ± 1.2 and 38.4 ± 5.4 s, respectively. PREM comprised 19.7 ± 2.3% of REM sleep, or 4.6% of total sleep time.

We examined the distribution of oxygen desaturations of >5%. Three of 18 patients had no desaturations >5% in either REM or NREM sleep, while the remaining 15 had a total of 323. Of these 323 desaturations, only 19 were due to apneas. Thirteen apneas occurred in REM, with six beginning with the start of a PREM episode (see Fig. 4 and below). Even though PREM made up only 19.7% of total REM, 81.7% of REM desaturations of >5% (187/229) were associated with PREM, while only 18.3% were associated with TREM. Figure 1 displays the distribution of NREM-REM sleep and the

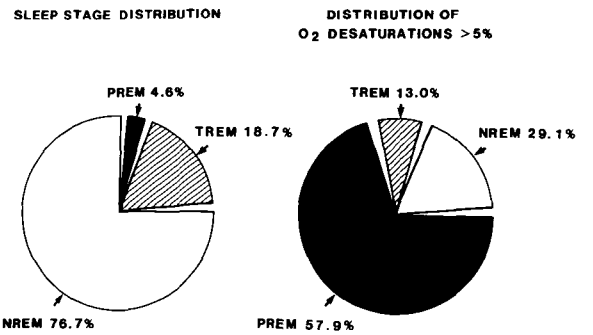

FIG. 1. Distribution of sleep in terms of stages NREM, phasic REM (PREM), and tonic REM (TREM). Sleep stage values are means for the group. Contrasting this is the concentration of desaturations in PREM.

distribution of desaturations >5%. While PREM makes up only 4.6% of the total sleep time, it is associated with 57.8% of all the sleep desaturations (187/323). In contrast, NREM makes up 76.7% of the total sleep yet is associated with only 29.1% of desaturations. To account for the variable length of PREM, TREM, and NREM, the oxygen desaturations were expressed as the number per hour of PREM, per hour of TREM, or per hour of NREM sleep (Table 2). Again, this emphasizes the concentration of desaturations in PREM.

We also examined arousals associated with these desaturations. An arousal was defined as the simultaneous appearance of an increase in amplitude in EMG, the presence of eye movements, and an increase in alpha activity in the EEG, that is, a short neurological awakening. During PREM, two patients aroused with each desaturation. This occurred 3 times in one patient but happened 30 times in another. These two patients had the greatest mean difference between phasic (PS_aO_2) and tonic (TS_aO_2) S_aO_2 (3.1 and 5.3%, respectively. With the exception of these two, the arousals occurred in association with a desaturation of >50% of the time in REM (PREM or TREM) or NREM.

The mean PREM and TREM S_aO_2 data are compared with awake S_aO_2 in Fig. 2. The PS_aO_2 and TS_aO_2 are those derived using the individual's time correction as outlined in Methods. These values for PS_aO_2 and TS_aO_2 are based on all PREM and TREM segments, whether or not a desaturation of >5% occurred, and so the number of data points is large (8,393 data points in PREM, 32,415 data points in TREM). The difference between awake S_aO_2 and TS_aO_2 was significant (89.7 ± 0.8 vs. 88.0 ± 1.2%) as was the TS_aO_2-PS_aO_2 difference (88.0 ± 1.2 vs. 86.6 ± 1.4%) ($p < 0.05$). The mean nadir S_aO_2 in PREM was 84.8 ± 1.3%. The reason that the mean TREM-PREM differences were small was related in part to the differences in breathing patterns with PREM onset, which we now present.

From the 80 TREM-PREM transition segments chosen, four breathing patterns were identified: (a) The most common pattern was that anticipated from Aserinsky's data. That is, with the onset of PREM, there was an increase in frequency and decrease in the amplitude of respiration relative to the preceding TREM with return to baseline with time (Fig. 3). This occurred in 52.5% of the segments, giving a change in S_aO_2 of −3.6 ± 0.44% and a (calculated) change in P_aO_2 of −8.2 ± 0.76 mm Hg. (b) In 27.5% of segments, there was no discernible change in the breathing pattern despite the presence of REMs. Here the change in S_aO_2 was −0.4 ± 0.4% and the change in P_aO_2 was −1.3 ± 0.72 mm Hg. (c) In 11.25% of the segments, there was an initial decrease with subsequent increase in respiratory amplitude similar to the most common breathing

TABLE 2. *Frequency of oxygen desaturations and associated arousals*

		NREM		PREM		TREM	
	Total[a]	Rate[b]	Associated Arousals[c]	Rate	Associated Arousals[c]	Rate	Associated Arousals[c]
Mean	18.0	1.3[d]	0.7	70.2[d]	36.9	3.9[d]	0.8
SE	4.7	0.5	0.3	22.8	19.1	1.6	0.5

PREM, phasic REM; TREM, tonic REM.
[a] Absolute no. of desaturations.
[b] No. of oxygen desaturations >5%/h of stage.
[c] Arousals associated with desaturations expressed as rate/hr.
[d] All three columns differ from each other ($p < 0.01$) by analysis of variance.

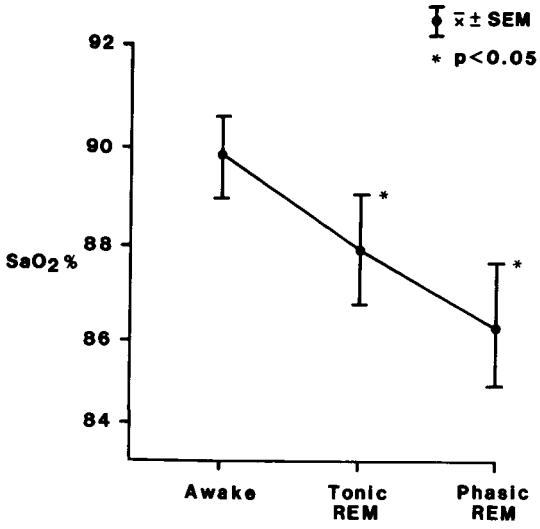

FIG. 2. Oxygen saturation (S_aO_2) (percentage) for phasic and tonic REM compared with awake. *Significant difference when compared with preceding stage.

pattern described above. However, this pattern repeated itself within the same bursts of eye movements so that there were two peaks and two troughs of respiratory amplitude. The change in S_aO_2 was $-1.2 \pm 0.4\%$, and the change in P_aO_2 was -2.5 ± 2.3 mm Hg. (d) A small number of segments (8.75%) showed an increase in respiratory amplitude with the onset of PREM without further change despite ongoing eye movements. The change in S_aO_2 for these was $1.3 \pm 0.3\%$ and that for P_aO_2 was $+3.9 \pm 1.1$ mm Hg. Of interest, we could document only 19 apneas (11 obstructive, 8 central) in our 18 records. Six apneas (all obstructive) began with the onset of PREM (Fig. 4).

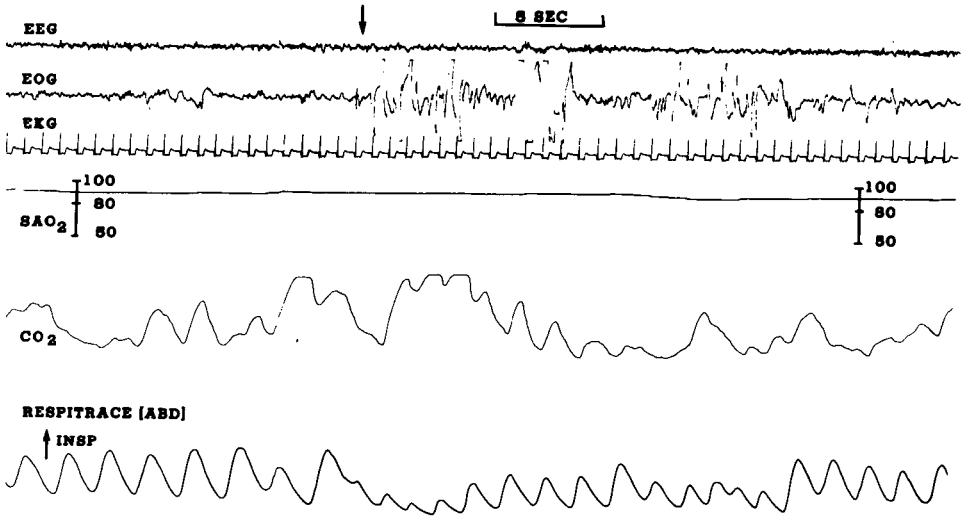

FIG. 3. Representative segment of REM sleep. At the arrow, the electrooculograph (EOG) shows tonic REM interrupted by bursts of REM with a coincident change in breathing pattern. EEG, electroencephalograph; EKG, electrocardiograph; S_aO_2, oxygen saturation.

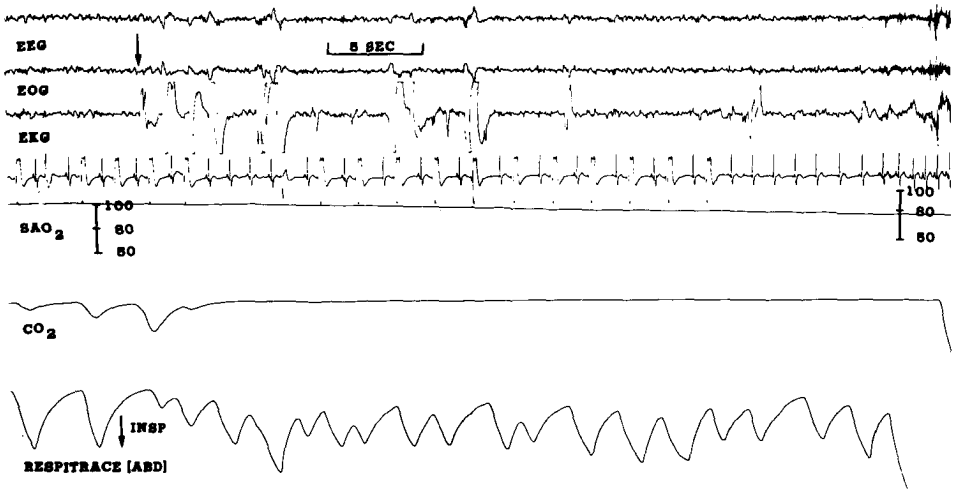

FIG. 4. Example of an obstructive apnea with the onset of phasic REM. At the arrow, phasic REM begins: Breathing becomes rapid and shallow and oronasal airflow ceases. Saturation falls to below 80% before an arousal (not shown) reestablishes airflow and regular breathing. Although breathing pattern changed frequently with onset of phasic REM, the change shown here, obstructive apnea, was rare, being present only six times in all the studies. EOG, electrooculograph; EEG, electroencephalograph; EKG, electrocardiograph; S_aO_2, oxygen saturation.

DISCUSSION

In our COPD patients, PREM made up a small proportion of the total sleep time yet was associated with most of the nocturnal desaturations. Not surprisingly, the mean S_aO_2 in PREM was lower than in TREM or NREM. As well, breathing pattern (as reflected by abdominal motion) changed with the onset of PREM in 72.5% of instances, with most often a decrease in amplitude.

There are few available data on oxygenation and breathing pattern in PREM and TREM in COPD. Skatrud and co-workers (13) reported on ventilation and oxygenation during REM in three patients with severe COPD and CO_2 retention. Data for PS_aO_2 and TS_aO_2 were compared with wakefulness and were decreased 11 ± 3 and 7 ± 11%, respectively. Minute ventilation and tidal volume were decreased relative to wakefulness, with values being least in PREM. However, it is important to note that these results are based on a very small number of data points taken from only three 20-s episodes of TREM and PREM for each of the patients. Johnson and Remmers (14) found similar results for PS_aO_2 and TS_aO_2 in a group of six severe COPD patients also with CO_2 retention. The difference in PS_aO_2–TS_aO_2 in their subjects was similar to our finding (2%), but they found this difference not to be significant, citing a lack of correction of circulation time as the likely explanation. The magnitude of the difference in S_aO_2 from awake to either PREM or TREM was larger in both groups than our findings and can be explained mostly by CO_2 retention in the former groups.

The mechanism of oxygen desaturation in REM is mostly likely the result of hypoventilation but can also be due to ventilation perfusion imbalance. Hudgel and coworkers (10) have shown that minute ventilation decreases during REM and that this hypoventilation is a major factor in the REM desaturation. However, functional residual capacity also decreased and this likely produced a ventilation perfusion imbal-

ance, which in itself may produce desaturation. Johnson and Remmers (14) have shown subsequently that there is an inhibition of accessory muscle activity during REM as a contributing factor to hypoventilation. These authors suggest that as a result of the inhibition, end expiratory lung volume falls, leading to ventilation perfusion imbalance and further oxygen desaturation (15). They found no change in abdominal excursion for PREM or TREM compared with NREM, suggesting that diaphragmatic activity was maintained. In contrast, Hudgel et al. (10) found that when comparing REM with wakefulness, diaphragmatic activity was decreased in most but not all of their patients. However, they did not compare REM with NREM or subdivide REM into PREM and TREM. Catterall et al. (16) measured changes in rib cage excursion, arterial and venous gas tensions, and cardiac output in five COPD patients. They concluded that hypoventilation was a major cause of nocturnal desaturation during REM as they could simulate the nocturnal changes in rib cage excursion, P_aO_2, and P_aCO_2 in normals during awake voluntary hypoventilation. They emphasized the point that the importance of changes in ventilation–perfusion distribution could not be quantitated by currently available techniques.

There are potential problems in interpreting qualitative changes in breathing pattern based only on abdominal excursions. It can be argued that rib cage excursion could be simultaneously increased when the abdominal excursion decreased, thus giving no net change in tidal volume. If this were the case, then there should be no change in oxygenation, contrary to what we found. Equally, the rib cage excursion could be decreased when the abdominal excursion was decreased. Johnson and Remmers (14) and Skatrud et al. (13) have shown a net decrease in rib cage excursion from TREM to PREM. If this occurred with each tonic-phasic segment, it would serve to magnify the change we observed. As well, rib cage excursion could be partially or completely out of phase with abdominal excursion (as in obstructive sleep apnea). We monitored oronasal airflow and could document only 19 apneas, 11 of which were obstructive. Six apneas began with the onset of PREM, while seven were noted in TREM.

Had we not observed any change in oxygenation with the changes in breathing pattern noted, then we would be left to wonder about coincident changes in rib cage excursion. Schmidt-Nowara and Snyder (9) did not measure changes in oxygenation in PREM and TREM, but did find that both rib cage and abdominal contributions to tidal volume were decreased with the onset of PREM. We might have been better able to describe breathing patterns by also measuring rib cage excursions, but that would not have changed the finding that oxygenation was significantly lower in PREM than in TREM. We chose not to use the rib cage belt because of previously published data, but also because there are still problems in interpreting breathing pattern based on two Respitrace belts (abdominal and rib cage) since the calibration factors may be quite unreliable as the abdominal–rib cage relationship changes with posture (17).

There are no direct neurophysiological studies in humans to explain why PREM processes cause changes in respiration. Studies in cats by Orem (18) have shown the effect of PREM and TREM on respiratory medullary neuron activity. He recorded activity in both ventral and dorsal medullary respiratory neurons and PGO wave activity. PGO waves are the most elemental PREM event being generated in the pons and propagated rostrally to the geniculate bodies and cortex. Each PGO wave is associated with activation of extraocular musculature, and sufficient summation of PGO activity produces the REMs of REM sleep (PREM). Orem concluded that PREM influences were uniformly excitatory for respiratory neurons, whereas TREM influences were

either excitatory or inhibitory. This applied to inspiratory and expiratory neurons of both dorsal and ventral groups.

Orem also examined the behavior of diaphragmatic motor neuron discharges in relation to PGO waves and found that some PREM influences transiently inhibit diaphragmatic motor neuron activity, while others excite diaphragmatic activity or have no net effect (19). This can explain some of the relative changes we saw in the abdominal excursion coincident with bursts of eye movements and together with the mechanisms proposed above likely accounts for the $PS_aO_2-TS_aO_2$ difference.

Arousal in response to these desaturations was variable, and this was consistent with previous studies involving COPD patients, normals, and animals (20–23). It is interesting to note that two of the patients aroused with each desaturation in PREM. These two were no different from the others in terms of airflow obstruction, but they did have the greatest $PS_aO_2-TS_aO_2$ difference.

We conclude that PREM is a period of perturbation of breathing. Although it makes up <5% of the night, it is associated with most of the desaturations of >5%. Changes in breathing pattern with the onset of PREM are in part responsible for these changes, and while these may secondarily produce alteration in ventilation and perfusion matching, it is not possible to quantitate such changes with current technology.

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