The Impact of Autonomic Nervous System Dysfunction on Breathing During Sleep

*Christian Guilleminault, †Jonathan G. Briskin, ‡Michael S. Greenfield, and *Rosalia Silvestri

*Sleep Disorders Clinic, †Division of Cardiology, and ‡Division of Endocrinology and Metabolism, Stanford University School of Medicine, Stanford, California

Summary: Ten patients with autonomic nervous system dysfunction (familial dysautonomia, juvenile diabetes, or Shy-Drager syndrome) were studied to assess the impact of their impairment on breathing during sleep. Several types of breathing dysfunction during sleep were identified independent of the patients' primary complaints. Obstructive sleep apnea syndrome was the most common; central sleep apnea and disturbances of the respiratory oscillator also were seen. Esophageal reflux was found to be the cause of some sleep-related problems. The observed respiratory irregularities were not associated with the usual cardiac response; a "decoupling" of heart rate from the respiratory cycle was noted during sleep in these patients. Key Words: Breathing during sleep—Autonomic nervous system dysfunction—Juvenile diabetes—Familial dysautonomia—Shy-Drager syndrome—Sleep apnea—Esophageal reflux.

In mammals, sleep and sleep states have a substantial impact on the functioning of the autonomic nervous system. Baust and Bohnert (1969) showed that, in the cat, an increase in parasympathetic tone occurs; this peaks during rapid eye movement (REM) sleep and is associated with a decrease in sympathetic activity. Considering the major involvement of the autonomic nervous system in the control of breathing, we thought it interesting to evaluate the impact of autonomic dysfunction in humans on breathing during sleep.

Patients with Shy-Drager syndrome have been shown to present obstructive sleep apnea (Castaigne et al., 1977; Guilleminault et al., 1977; Chokroverty et al., 1978). However, in our own studies, the population previously reported was elderly. We have since had the opportunity to study young subjects presenting juvenile diabetes or familial dysautonomia during wakefulness and sleep, and to evaluate their breathing patterns during sleep. This report presents an analysis of
the different abnormal, sleep-related breathing patterns noted in each of three patient groups. Subjects ranged in age from adolescence to the early sixties.

METHODS

Patient Population

A total of 10 patients, subdivided into 3 groups, was studied. Four patients had received a diagnosis of Shy-Drager syndrome (mean age = 60.1 years). Four patients were diagnosed with juvenile diabetes and autonomic neuropathy (mean age = 25 years). Two adolescent girls presented with familial dysautonomia (mean age = 13.5 years). These patients were selected specifically because of abnormal breathing patterns monitored objectively during sleep, independently of their clinical symptoms. Table I summarizes some of their clinical data.

The four Shy-Drager patients presented neurological symptoms (essentially extrapyramidal symptoms), cardiovascular problems with orthostatic hypotension and, in two patients, repetitive syncope during the daytime. All presented sexual problems; three were completely impotent and one had significant difficulty with erection and ejaculation. Three of the four complained of disabling daytime somnolence. All patients were receiving medications on a chronic basis to control extrapyramidal symptoms and orthostatic hypotension. Chronically prescribed dopaminergic medication was not discontinued during the sleep-related investigations.

The 4 diabetic patients all had been receiving subcutaneous insulin injections for at least 7 years on a daily basis. At the time of the study, all were considered as presenting controlled diabetes. None of them was receiving any other medication. One of them had an advanced diabetic retinopathy, two had symptoms of diabetic nephropathy, two were impotent, one had difficulty with ejaculation but not erection, one had obvious orthostatic hypotension with clinical symptoms (the other three had a drop of systolic pressure of 15 mmHg and of diastolic pressure of 10 mmHg upon standing up after lying relaxed on a bed for 15 minutes; however, they were without clinical complaints). None of them complained of daytime sleepiness, but one of them reported intermittent “heartburn” during sleep and consulted for a frightening episode of “choking during sleep.”

The two adolescent girls with familial dysautonomia presented a relative insensitivity to pain; moderate postural hypotension without clinical complaint was noted at examination. Both complained of cold hands and feet, had poor motor coordination, and presented hypoactive deep tendon reflexes on all four limbs. One displayed important emotional lability and was receiving psychiatric care (psychotherapy); she also presented repetitive cyclical vomiting and frequent pneumonia. The other one had unexplained bursts of rectal temperature increases and had a history of moderate breath-holding spells when near 18 months of age, which resolved spontaneously when she was about 2½ years of age. Both presented substantial body growth retardation, but had developed some secondary sexual characteristics [Tanner Stages 2 and 3 (Tanner, 1962)]. All medications had been interrupted for a minimum of one week prior to the sleep studies in both cases.

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TABLE 1. Clinical data on 10 patients with autonomic nervous system dysfunction

<table>
<thead>
<tr>
<th>Case # and primary problem</th>
<th>Age</th>
<th>Sex</th>
<th>EDS(^a)</th>
<th>Snoring</th>
<th>Impotence</th>
<th>Vomiting or heartburn</th>
<th>Retinopathy</th>
<th>Orthostatic hypotension</th>
<th>Abnormal cardiac response when tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shy-Drager syndrome</td>
<td></td>
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<td></td>
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<tr>
<td>Case #1</td>
<td>59</td>
<td>M</td>
<td>+++(^b)</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Case #2</td>
<td>61</td>
<td>M</td>
<td>+++</td>
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<td>+++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Case #3</td>
<td>59</td>
<td>M</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Case #4</td>
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<td>M</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<tr>
<td>Juvenile diabetes</td>
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<td></td>
<td></td>
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<tr>
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<td>18</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>+</td>
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<td>0</td>
<td>+</td>
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</tr>
<tr>
<td>Case #2</td>
<td>21</td>
<td>M</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Familial dysautonomia</td>
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<td></td>
<td></td>
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<tr>
<td>Case #1</td>
<td>13</td>
<td>F</td>
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<td>Not known</td>
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<td>+</td>
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<tr>
<td>Case #2</td>
<td>14</td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>Not known</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) EDS, Excessive Daytime Somnolence.
\(^b\) Symbols: +, mild; ++, moderate; ++++, severe.
None of the patients was overweight, nor did they present otolaryngologic or facial structural abnormalities.

Daytime Testing

Pulmonary function tests were obtained for all Shy-Drager and familial dysautonomia patients and for 2 of the 4 juvenile diabetics. Hypoxic and hypercapnic response curves were performed in 3 of the 4 Shy-Drager patients, one (nonvomiting) adolescent familial dysautonomia case, and 2 juvenile diabetics (Read, 1967; Rebuck and Campbell, 1974).

Night-Time Testing

Each subject was monitored polygraphically for at least 2 nights; some subjects were monitored for up to 6 nights over a period of time (the mean number of monitored nights was 3). In each case, the variables recorded depended on the patient's group and original findings; however, all subjects underwent a standard monitoring procedure on the first night.

Testing Before Lights Out

Each subject was submitted to the following standardized series of tests, which was repeated twice. (1) Investigation of respiratory influence on heart rate [the "Bennet Test" (Bennet et al., 1978)]. The patient was requested to lie relaxed on a couch for 10 min, and then to perform maximal deep-breathing maneuvers for one min. (2) Investigation of Valsalva maneuver on heart rate. (3) Investigation of a cold stress on heart rate (Khurana et al., 1980).

For maneuvers 2 and 3, patients were seated comfortably on a bed (with the upper part of the bed at a set angle of 75°). During the cold stress test, 2 plastic bags filled with ice were applied to the patient's cheeks, chin, and forehead for 1 min.

During each test, which included baseline recordings pre- and postmanipulation, heart rate (electrocardiogram lead II) and respiration (monitored by means of thoracic and abdominal strain gauges) were recorded on a Grass Model 7 Polygraph with paper speed at 10 mm/sec for the first run and 25 mm/sec for the second. (See Fig. 1 for example). Heart rate also was monitored on a 24-hour Holter ambulatory electrocardiogram in 6 out of 10 subjects.

Nocturnal Monitoring

The following variables were monitored systematically: electroencephalogram (EEG), using $C_3/A_2 - C_4/A_1$ of the 10-20 international placement system; electrooculogram (EOG); chin electromyogram (EMG); electrocardiogram (ECG) lead II; respiration (respiratory effort monitored by thoracic and abdominal strain gauges; airflow monitored by thermistors placed in front of each nostril and the mouth with results integrated to give a one-signal output); and continuous oxygen saturation (Hewlett-Packard ear oxymeter).

Several other variables were monitored simultaneously, depending on the re-

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FIG. 1. Example of recording during cold stress test while awake in a juvenile diabetic patient (case #2). ECG = lead II (speed 10 mm/sec). Note the absence of heart rate change during the test.
cording night and the patient's group. Endoesophageal pH was monitored for one night in the familial dysautonomia patients and in 2 of the 4 diabetics. Nocturnal penile tumescence (NPT) was monitored in all diabetics and two Shy-Drager patients during 3 successive nights; during these recordings, blood pressure was monitored using an external Doppler system blood pressure recorder every 10 to 15 min. Two Shy-Drager patients and one diabetic patient who presented clinical evidence of severe cardiovascular problems underwent more complex hemodynamic study during wakefulness and sleep. A right heart and femoral artery catheterization was performed, by placing a Swan-Ganz thermodilution catheter and a femoral arterial catheter. Pulmonary and femoral arterial pressures were recorded continuously during wakefulness to evaluate autonomic reflexes; interventions were used to test baroreceptors and afferent nerve pathways (tilt table, Valsalva maneuver, amyl nitrite, and carotid massage), central integrative centers (Valsalva maneuver and mental arithmetic), sympathetic outflow (Valsalva maneuver and cold pressor test), organic responsiveness (norepinephrine and angiotensin infusion), and presence of functioning nerve endings (metaraminol). During sleep, pressures and blood gases were obtained.

All monitored variables were recorded on a Grass Polygraph at a paper speed of 10 mm/sec. Hemodynamic variables were monitored simultaneously on a Hewlett-Packard recorder, and NPT was monitored on an independent recorder.

Analysis of Data and Control Values

Sleep and wakefulness were scored in 30-sec epochs following the Rechtschaffen and Kales (1968) criteria. Apnea and hypopnea were scored following standard international criteria (Tassinari et al., 1972) and each apnea was further scored as central, obstructive, or mixed. Esophageal reflux was scored when esophageal pH dropped to under 4. (Calibration of the pH probe was performed before and after recording, and evaluation of proper gastric acidity was performed prior to monitoring.)

We use the term respiratory abnormality in this report to cover any abnormality of breathing during sleep lasting for less than 10 sec (usually only one or two breaths) and consisting of the following: absence of one breath as marked by absence of normally expected inspiration; reduction of inspiration time (ti), defined as the time spent from the polygraphically recorded "trough" seen at the end of expiration to the "peak" seen at the end of inspiration; reduction, by at least 50%, of the amplitude of movements monitored by strain gauges and airflow monitored by thermistors.

Respiratory irregularities are seen in stage 1 non-REM (NREM) and in REM sleep in normal subjects; therefore, we did not score them when they occurred during these sleep states. On the other hand, in normal control adolescents and young adults monitored in our laboratory, respiratory irregularities are uncommon in stages 2, 3, and 4 NREM sleep. We used data already published by Carskadon et al. (1978), obtained on normal controls aged 9 to 14, as control values for the dysautonomia patients. (Normally, the fewest longer-than-five-sec pauses per min of sleep are seen during stages 2, 3, and 4 NREM sleep, averaging less than

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half the number seen during REM sleep. The number of short abnormal respiratory events seen in control girls during sleep was 0.017 per min of stage 3–4 NREM sleep [Carskadon et al., 1978].)

RESULTS

The results presented here focus on abnormalities of breathing seen during sleep.

Daytime Testing

The "Bennet Test," cold stress test, and Valsalva maneuver were abnormal in all Shy-Drager patients and in 3 of 4 of the diabetics. In case #2 of the familial dysautonomia group, no response was seen to the "Bennet Test" and Valsalva maneuver, but mild response to the cold stress test was noted. The last 2 patients (1 diabetic, 1 familial dysautonomia) responded to all 3 tests.

The hemodynamic tests confirmed the existence of severe cardiovascular dysfunction secondary to autonomic nervous system disturbances in the 2 Shy-Drager patients and 1 of the juvenile diabetics investigated (Briskin et al., 1978). Figure 2 presents a tracing obtained on case #3 of the diabetic group.

Nocturnal (Sleep) Monitoring

All patients presented some type of breathing abnormality during sleep, as per the above-given definitions. However, several different types of abnormality were seen.

Type 1—Obstructive Sleep Apnea Syndrome

Six of the 10 patients presented predominantly obstructive sleep apnea syndromes as shown in Table 2. It is interesting to note that there was no correlation between hypoxic and hypercapnic responses while patients were awake, and the presence or degree of sleep apnea syndrome. As can be seen in Figs. 3 and 4, a similar absence of heart rate response to obstruction during sleep was noted in the 59-year-old Shy-Drager patient and the 30-year-old juvenile diabetic. In Fig. 3, use of an endoesophageal pressure balloon allowed better appreciation of the 2 components of the apneic events recorded; there is a short diaphragmatic inhibition and then, after this initial component, a progressive increase in diaphragmatic effort against an obstructed airway. In both examples shown, termination of the apnea is associated with an "arousal," defined as a "lightening" of sleep with a change in sleep stage, but not necessarily a return to alpha EEG activity. The arousal response also is indicated by the appearance of fast or slow eye movements, as is seen in Fig. 4.

In all patients with predominantly obstructive sleep apnea and autonomic dysfunction, a clear dissociation between heart rate and respiratory response was noted. The duration of each apneic event varied within the same sleep state, when intermittent apneas were monitored, as can be seen in Fig. 4. Patterns of sudden bursts of periodically repetitive obstructive apnea could be noted (as shown in

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FIG. 2. Example of testing performed to evaluate autonomic dysfunction and results observed in juvenile diabetic case #3. No change in heart rate was noted during any of the daytime tests, and no change in nocturnal penile tumescence was monitored. The subject presented a severe autonomic nervous system dysfunction.
TABLE 2. Obstructive sleep apnea syndrome

<table>
<thead>
<tr>
<th>Case # and primary problem</th>
<th>Apnea/hypopnea index(^{a})</th>
<th>Lowest (O_2) saturation during sleep(^{b}) (%)</th>
<th>Sleep state in which lowest (O_2) values were seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shy-Drager syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case #1</td>
<td>62</td>
<td>25</td>
<td>REM sleep</td>
</tr>
<tr>
<td>Case #2</td>
<td>58</td>
<td>32</td>
<td>REM sleep</td>
</tr>
<tr>
<td>Case #3</td>
<td>59</td>
<td>26</td>
<td>REM sleep</td>
</tr>
<tr>
<td>Case #4</td>
<td>12</td>
<td>68</td>
<td>REM sleep</td>
</tr>
<tr>
<td>Juvenile diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case #2</td>
<td>9</td>
<td>81</td>
<td>REM sleep</td>
</tr>
<tr>
<td>Case #3</td>
<td>11</td>
<td>77</td>
<td>Stage 2</td>
</tr>
</tbody>
</table>

\(\text{a} \) [Total number of apneas/Total sleep time (min)] \times 60.

\(\text{b} \) Accuracy of equipment was limited to values above approximately 35% (Hewlett-Packard ear oximeter).

Fig. 4), or abrupt isolated obstructive apnea might appear. In cases where a low apnea index was monitored, very few apneic episodes were recorded in stage 3–4 NREM sleep.

Type 2—Central Sleep Apnea Syndrome

The juvenile diabetic case #4 presented bursts of central sleep apneic events, seen predominantly during stages 1 and 2 NREM sleep and REM sleep. His apnea index was 6 and his longest apneic event was 52 sec, recorded during REM sleep with an associated oxygen saturation of 84%.

Type 3—Respiratory Irregularities During Sleep Associated with Abnormal Drops in Esophageal \(pH\)

The familial dysautonomia case #1 and juvenile diabetic case #1 presented clinical symptoms pointing to esophageal reflux, with the mention of sleep-related “heart burn.” The familial dysautonomia patient presented frequent cyclical vomiting, and the juvenile diabetic reported intermittent (2–4 months apart) episodes of abrupt awakenings during the night with a feeling of choking and inability to breathe after awakening, associated with a panicked feeling of near death due to complete airway obstruction. The latter patient’s symptoms had appeared 18 months prior to recording. Monitoring during sleep, when we performed it, did not demonstrate any vomiting or laryngospasm in either of the 2 cases. However, we did note repetitive long drops in endoesophageal \(pH\) to between 3.8 and 1.9. The mean duration of the \(pH\) drop episodes was 21 min (range 1–105 min). They were seen during all stages of sleep, including stage 3–4 NREM sleep, as is seen in Fig. 5. The episodes frequently were associated with respiratory irregularities such as short hypopnea, skipped breaths, pauses, or abrupt termination of inspiration with resulting reduction in inspiration time. These respiratory irregularities seen during lowered \(pH\) were associated frequently with sleep.
FIG. 3. Example of nocturnal polygraphic monitoring performed on a 59-year-old Shy-Drager patient (see text). Note the progressive increase in endocophagel pressure during the obstructive sleep apnea and the complete absence of heart rate response to the obstructive event. EEG alpha arousal can be noted clearly at the end of each apneic event. Note also the diaphragmatic inhibition at the beginning of the apnea.
FIG. 4. Example of nocturnal polygraphic recording obtained in a 30-year-old juvenile diabetic patient (case #3). Note the repetitive obstructive sleep apnea of varying duration during stage 2 NREM sleep. Note the dissociation of heart rate and respiration, as seen also in Fig. 3 (Shy-Drager patient). No clear alpha EEG arousal can be noted at the end of the apnea; however, eye movements are seen indicating an arousal response.
FIG. 5. Example of esophageal reflux during slow wave (stage 3–4 NREM) sleep in a 13-year-old girl with familial dysautonomia.
stage changes, and sometimes led eventually to EEG alpha arousal. Compared to normative data published by DeMeester et al. (1980), these results are indicative of a pathological esophageal reflux being responsible for the respiratory irregularities.

Type 4—Respiratory Irregularities During Sleep Without Drops in Esophageal pH

This type of breathing abnormality was seen in one patient only (familial dysautonomia, case #2). It has not been described previously. When respiratory irregularities were tabulated in stage 2 and stage 3–4 (slow wave) sleep, we noted 0.25 respiratory irregularities per min during stage 2 (irrespective of type) and 0.20 during stage 3–4 (compared with 0.022 and 0.017, respectively, for normal controls; Carskadon et al., 1978).

Figure 6 shows examples of the respiratory irregularities; we have presented those seen during stage 3–4 (slow wave) sleep, as this is the sleep stage known to be associated with the most regular respiratory pattern. These respiratory irregularities were not associated with any changes in esophageal pH or heart rate. Although sleep state changes were noted in association with the respiratory irregularities at times, no systematic pattern emerged. No complete alpha EEG arousal was noted at the end of any of these irregularities in respiratory rhythm.

DISCUSSION

The autonomic nervous system is known to link peripheral receptors and central commands involved in the control of breathing. It is not surprising that patients who present impairment of the autonomic nervous system are found to have abnormal breathing patterns during sleep. Shy-Drager patients already have been singled out several times in the recent past for their abnormal respiration during sleep (Castaigne et al., 1977; Guilleminault et al., 1977; Chokroverty et al., 1978; Lehrman et al., 1978). Juvenile diabetics with autonomic neuropathy and patients with familial dysautonomia have received much less attention. However, our study demonstrates that breathing problems during sleep could endanger the lives of many patients with autonomic neuropathies, independent of the patients’ ages and the causes of the autonomic lesions.

Our studies also demonstrate that several factors may be responsible for abnormal breathing patterns noted during sleep. Multivariable monitoring must be performed, including not only respiratory but also cardiac and esophageal indices, when a patient with autonomic nervous system dysfunction is investigated. The same respiratory irregularity may be secondary to different insults to the autonomic nervous system.

It is interesting to note that there does not seem to be any correlation between waking hypercarbic and hypoxic response and obstructive sleep apnea syndrome in patients with autonomic dysfunction; the same already has been reported for patients without autonomic lesions. In our patient population, heart rate and respiration are "decoupled" during both wakefulness and sleep. One of our juvenile diabetics (case #3) presented a nearly complete cardiac denervation, with
FIG. 6. Examples of respiratory irregularities seen in a 14-year-old girl with familial dysautonomia. Note the absence of esophageal reflux and heart rate changes. These irregularities reoccurred throughout the night, and were seen often during stage 3-4 NREM (slow wave) sleep.
very abnormal cardiovascular responses; there was, however, a complete dissociation between his hemodynamic findings and the moderate obstructive sleep apnea syndrome that he presented. Although he did present sleep stage changes at the termination of apneic events, few of these were alpha EEG arousal. The relationship between hemodynamic changes and the EEG alpha arousal needs to be investigated further, and the role of baroreceptor stimulation in the arousal response in obstructive sleep apnea must be evaluated.

One of the interesting findings of this study was obtained on the familial dysautonomia case #2 patient. This adolescent girl had normal hypercarbic responses while awake, and did not present any major respiratory or clinical problems when awake or asleep. However, she did present continuous respiratory irregularities with frequent interruption of inspiration, or absence of initiation of inspiration and lack of one breath, while in stage 3–4 NREM (slow wave) sleep, the state known to be associated with the most regular respiratory pattern, particularly in the young. During slow wave sleep (stage 3–4 NREM sleep), chemical control of ventilation supposedly is at its best. Can a subject with respiratory irregularities as seen in this young woman eventually develop a more pronounced respiratory problem, as seen in the subject with a very moderate central sleep apnea syndrome [borderline abnormal, with an apnea index of 6 where 5 is considered normal (Guilleminault et al., 1978)]? What are the reasons for the continuous abortion of inspiration and the irregular breathing with decrease of diaphragmatic output (hypopnea) or absence of continuous function of the respiratory oscillator? Further studies of these borderline cases may give us more insight into the multifaceted components of the control of breathing during sleep.

Note: Since writing and orally presenting this paper, we have read the article of Rees et al. (1981) reporting a study of diabetic patients with autonomic neuropathy. They also noted the presence of central and obstructive sleep-related apneas in their patient population.

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C. Guilleminault et al.


