Chapter
127

Snoring and Pathologic Upper Airway Resistance Syndromes

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Chapter Highlights

- Over the past 2 decades, knowledge of pathologic pharyngeal collapse during sleep has expanded from apnea and hypopnea to include even the mildest, silent inspiratory airflow limitation (IFL) during sleep. Both the clinical researcher and the sleep medicine practitioner of today must be able to recognize the mildest IFL on a polysomnogram and its clinical implications.
- Although habitual snoring is very common, the prevalence of isolated snoring (snoring in the absence of apnea and hypopnea, oxygen desaturations, arousals from sleep, and symptoms of obstructive sleep apnea) is unknown. Recent clinical investigation has led to uncertainty about whether such snoring can be considered benign.
- The paradigm of IFL during sleep leading to recurrent respiratory effort–related arousals is inadequate to explain the varied signs and symptoms of upper airway resistance syndrome (UARS) or to distinguish between patients with UARS and asymptomatic, healthy individuals whose polysomnograms are remarkably similar.

Snoring and upper airway resistance syndrome (UARS) represent obstructed breathing during sleep that is too mild to cause more than slight sleep fragmentation but with potential pathologic significance. There is growing evidence that mild inspiratory airflow limitation (IFL) during sleep, even in the absence of audible snoring or increased sleep fragmentation, may have a causative role in a variety of disabling somatic and affective disorders.

BACKGROUND

Glossary of Terms Central to This Chapter

The terms defined in the following are described in detail and in context in this chapter:

Inspiratory airflow limitation. IFL describes a state of the upper airway (UA, the pharynx) during sleep in which inspiratory airflow plateaus at a maximal level despite a continued increase in the pressure gradient between the nostrils and the hypopharynx. The failure of inspiratory airflow to increase despite the continued increase in the pressure gradient across the UA is caused by fluttering of the UA that prevents further increase in airflow. IFL can be divided into two subgroups based on whether it is *audible:* (1) *snoring* and (2) *silent IFL.*

Snoring or inspiratory snoring. Audible inspiratory fluttering of the UA. It can occur during obstructive hypopnea when hypopnea is associated with a decrease in inspiratory airflow by 30% lasting at least 10 seconds, accompanied by either an arousal from sleep or a 3% decrease in oxygen saturation. Alternatively, it can occur in the absence of the earlier criteria for hypopnea with higher levels of airflow or with shorter duration or absence of arousals or oxygen desaturation. The presence of inspiratory snoring *always indicates the presence of IFL.* Although expiratory snoring exists, and will be discussed later in this chapter, the term *snoring* used without a modifier in this chapter refers to inspiratory snoring. *Snoring* is further divided into two subgroups: (a) *habitual snoring* and (b) *isolated snoring.*

Habitual snoring: This term describes an observation (often a complaint) by a bed partner or roommate that a person consistently snores when asleep.

Isolated snoring: After polysomnography (PSG), if an otherwise healthy, asymptomatic, habitual snorer does not meet the current *International Classification of Sleep Disorders*, third edition[1] (ICSD-3) criteria for obstructive sleep apnea (OSA), the patient is described as having *isolated snoring.* Specific criteria for being "otherwise healthy" in the context of being a habitual snorer are described later in this chapter.

Silent inspiratory airflow limitation. Silent IFL is defined and characterized by the same *fluttering* of the UA that characterizes snoring; however, the frequency of the fluttering during silent IFL is, by definition, inaudible by humans.

Respiratory effort–related arousal (RERA): RERAs are transient arousals from sleep that follow a period of nonhypopneic IFL (either snoring or silent IFL) and are presumed to be caused by the inspiratory effort required to move air across a fluttering airway. Whether an arousal after a period of IFL is in fact caused by the IFL cannot be definitively

ascertained during clinical PSG; it is a presumption. To label an arousal a RERA, the ICSD-3 requires 10 seconds of recognizable IFL preceding the arousal. A standard time requirement for IFL preceding a RERA, however, is not a consistent feature of RERAs in research; a single flow-limited inspiration before arousal is the definition in some research.

Respiratory disturbance index (RDI): ICSD-3 has replaced the apnea-hypopnea index (AHI) as a measure of the severity of OSA with the frequency of apneas, hypopneas, and RERAs. In this chapter this new measure of the severity of OSA will be termed the *RDI*.

Upper airway resistance syndrome: The UARS does not exist in the ICSD-3. It should be thought of as a syndrome described by Dr. Christian Guilleminault and used by researchers who have broken away from the paradigm that hypersomnolence in patients with sleep-disordered breathing requires the presence of sleep fragmentation by apneas and hypopneas.[2] In this chapter, UARS is defined as the symptom of either hypersomnolence or fatigue, together with the presence of IFL during sleep adjudicated by PSG and an AHI of less than 5 per hour; the latter is the threshold of an OSA diagnosis in the ICSD-3.

Upper Airway Resistance Versus Pharyngeal Collapse

Two terms used to describe the behavior of the UA (or pharynx) during sleep among snorers and patients with UARS are increased *UA resistance* and *UA collapse*. Many sleep researchers consider IFL during sleep to result from narrowing of the pharyngeal airway and increased resistance caused by the relaxation of pharyngeal dilator muscles, together with subatmospheric UA pressures during inspiration. As they measure increasingly negative esophageal or supraglottic pressures during inspiratory snoring, they think of *UA resistance* increasing. From this reasoning the clinical term *UARS* was derived (as discussed later).

In contrast to this intuitive model of increasing upper airway resistance during sleep is the experimentally validated Starling resistor model of IFL[3] (see Chapter 24). The Starling resistor model postulates that the pharyngeal airway during sleep is a collapsible tube that will collapse whenever the pressure within falls below a critical level, the pharyngeal "critical pressure" (Pcrit). It has been shown experimentally that as the severity of sleep-disordered breathing increases from isolated snoring to severe OSA, the pharyngeal Pcrit progressively increases from negative (subatmospheric) levels to positive levels.[4,5] Collapse of the pharynx, however, is not synonymous with apnea. When the pharynx collapses during sleep, one might experience either apnea (no inspiratory airflow) or IFL (inspiratory airflow that has reached its maximum). When the pressure at the *upstream* end of the pharynx (the nares during inspiration) falls below Pcrit, the pharynx collapses, with resulting apnea. When the pressure at the nares is above Pcrit, but the pressure at the downstream end of the pharynx (supraglottic pressure during inspiration) falls below Pcrit, as in a snorer, the pharynx also collapses. Because pharyngeal collapse leads to cessation of inspiratory airflow, pharyngeal pressure immediately equilibrates with nasal pressure opening the airway, with resumption of inspiratory airflow. The result is cyclical collapse and opening (fluttering) of the pharyngeal airway *limiting* inspiratory airflow to a fixed, maximal level, with the driving pressure fixed at nasal pressure minus Pcrit, no matter how low supraglottic pressure descends. Therefore, according to the Starling resistor model, the UA does not experience *increased resistance* during sleep, but a *fixed driving pressure* that limits airflow to a maximal level.

The language subsuming UA resistance and UA collapse therefore is derived from two different models of IFL. In this chapter we will allude to *pharyngeal collapse* in the section that follows, describing the polysomnographic appearance of IFL, but use the term *UA resistance* for the remainder of this chapter, which does not require modeling of IFL.

Upper Airway Resistance Syndrome

As introduced in the glossary, we use the term *UARS* in this chapter, and it is still found as a diagnosis in the medical literature. However, the ICSD-3 does not include UARS in its classification of sleep-related breathing disorders, but rather incorporates the polysomnographic manifestations of UARS into OSA. A brief discussion of the history of UARS will help the reader understand this dichotomy.

UARS came to public attention after the publication of a case series in 1993 by Dr. Christian Guilleminault and associates.[2] From among 48 patients with a diagnosis of idiopathic hypersomnolence, they selected 15 with the following characteristics: intermittent or continuous snoring with an AHI below 5 per hour, more than 10 arousals per hour of sleep (a threshold they chose), and arousals associated with *UA resistive events* identified using a pneumotachograph measurement of airflow and esophageal manometry to quantify effort.

Treatment of these 15 patients with nasal continuous positive airway pressure (CPAP) relieved the patients' hypersomnolence (measured objectively by the Multiple Sleep Latency Test). Because the patients did not meet diagnostic criteria for OSA, the investigators designated a new syndrome—UARS. They hypothesized that the hypersomnolence was related to sleep fragmentation by UA resistive events too mild to meet the diagnostic criteria of hypopnea. They further hypothesized that patients with UARS have increased sensitivity to the respiratory effort related to these resistive events, giving rise to repetitive arousals, compared with patients with OSA who typically arouse in response to higher degrees of obstruction, that is, apneas and hypopneas. The hypothesis that patients with UARS exhibit increased sensitivity to respiratory effort during sleep led to their arousals being termed *RERAs*.

Almost from the start, the establishment of a new syndrome of sleep-disordered breathing based on sleep fragmentation by RERAs created controversy.[6,7] To eliminate the need for an additional syndrome of sleep-disordered breathing based on sleep fragmentation by RERAs, the authors of ICSD-3 incorporated RERAs into the diagnostic criteria for OSA, creating diagnostic thresholds for OSA based on the combined frequency of obstructive events: apneas, hypopneas, and RERAs—the RDI. Therefore, by the clinical criteria of ICSD-3, UARS has been "absorbed" into OSA.

Investigators have since observed that the sleep of patients with UARS is characterized not only by the presence of RERAs but also by electroencephalographic differences and differences in sleep architecture that distinguish it from the sleep of healthy individuals. These *qualitative* differences in the sleep of patients with UARS resolve with treatments that eliminate IFL during sleep and the hypersomnolence of patients with UARS. Therefore, although the ICSD-3 clinical criteria for OSA will result in many patients being treated for OSA who previously were diagnosed with UARS, it is not established that these former patients with UARS are

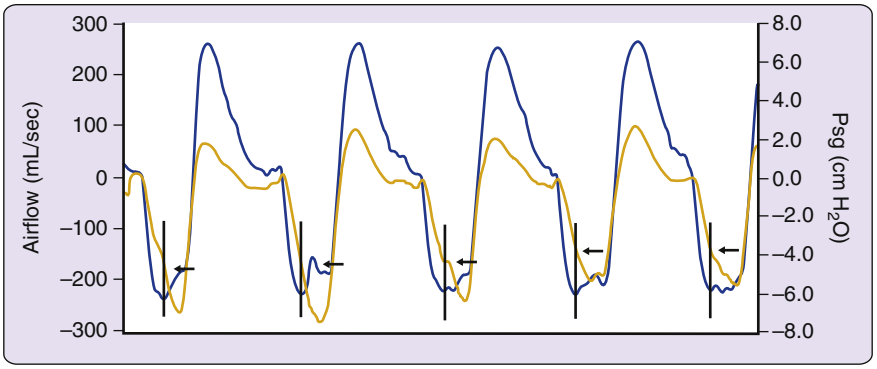

Figure 127.1 This figure illustrates inspiratory airflow limitation (IFL) in a sleeping research participant wearing a nasal mask attached to a pneumotachograph measuring airflow, with a pressure catheter placed through her nose to just above her vocal cords to measure supraglottic pressure (Psg). Airflow is the *blue tracing* with the units indicated on the left axis (inspiration is downgoing). Effort, represented by the Psg, is the *yellow tracing* with the units indicated on the right axis. For each inspiration, a plateau in airflow during early inspiration is intersected by a *vertical line*. Beyond the line, there is no further increase in inspiratory airflow despite the continued decrease in Psg and a continued increase in the inspiratory pressure gradient Patm—Psg. Indeed, not only does the inspiratory airflow not increase, but also, in the first four breaths it appears to decrease, a phenomenon known as *negative effort dependence* of airflow. IFL occurs when Psg decreases below this participant's pharyngeal critical pressure (Pcrit). The *horizontal arrows* mark the Psg at the onset of maximal flow (intersected by the *vertical line*) and suggest that this participant's pharyngeal Pcrit is approximately –4 cm H_2O, a common value for primary snorers or individuals who have upper airway resistance syndrome.[4]

hypersomnolent because of sleep fragmentation by RERAs. In consequence, UARS continues as a syndrome being studied by researchers examining alternatives to the OSA pathophysiologic paradigm of sleep fragmentation by apneas, hypopneas, and RERAs.

Inspiratory Airflow Limitation

Classically, the term *snoring*, the audible fluttering of the pharynx during inspiration, has been used to describe IFL during sleep. The term *snoring*, however, implies that pharyngeal fluttering is present only when it can be heard by a listener; the word *snore* itself resembles the sound of snoring. Hearing, however, is an insensitive means of detecting inspiratory fluttering of the pharyngeal airway during sleep. Because using the term *snoring* may lead one to believe that IFL is only present when audible, we have chosen to describe the characteristic inspiratory airflow through a fluttering UA during sleep as a state of *inspiratory airflow limitation* (as defined in the glossary earlier). The term *IFL* was first used by Schwartz and associates[8] in their study of pharyngeal collapsibility during sleep in healthy humans[8] and was derived from the parallel term *expiratory airflow limitation*, used to describe expiratory airflow from the lungs of patients with asthma, chronic obstructive bronchitis, and emphysema whose bronchi flutter on expiration, limiting airflow.[9]

Recognizing Inspiratory Airflow Limitation with Physiologic Testing

With the incorporation of RERAs into the diagnostic criteria for OSA, recognizing the presence of IFL preceding an arousal and differentiating its appearance from that of non-flow-limited breathing during PSG is an important skill. To visually identify IFL using a digitized airflow signal, one must sample the analogue signal adequately to see rapid oscillations of inspiratory airflow caused by fluttering of the airway. A sampling frequency of at least 100 Hz should be used for this purpose.[10] Furthermore, filtering of the airflow signal with a high-frequency filter can eliminate the oscillations of inspiratory airflow and should not be used during the collection of the airflow signal. The signal should be collected unfiltered and, ideally, analyzed without either high- or low-frequency filtering.[11] The airflow and pressure tracings that appear in the figures that follow were collected unfiltered with a sampling frequency of 128 Hz, and are displayed unfiltered.

Figure 127.1 illustrates five breaths during continuous non–rapid eye movement (NREM) stage 2 (N2) sleep at atmospheric pressure, all characterized by IFL. The individual being monitored is a 24-year-old woman with a body mass index (BMI) of 19.9 kg/m^2, does not snore, and has an AHI of 0.3 per hour. Because Figure 127.1 has both an airflow tracing and a supraglottic pressure tracing, it precisely demonstrates the presence of IFL. Specifically, it shows that inspiratory airflow is limited to a maximal level (intersected by the vertical lines), despite the observation that the pressure gradient across the pharyngeal airway (atmospheric pressure minus supraglottic pressure) continues to increase (atmospheric pressure remains the same while supraglottic pressure continues to decrease beyond the vertical line). This defines IFL.

Figure 127.2 demonstrates both IFL and non-flow-limited inspiration in the same individual diagnosed with UARS during nasal CPAP titration. Although the left panel of the figure clearly demonstrates IFL at atmospheric pressure like that observed in Figure 127.1, the right panel, recorded at the therapeutic nasal CPAP level of 4 cm H_2O, presents airflow and supraglottic pressure tracings that parallel each other through four inspiratory cycles. The parallel tracings demonstrate that inspiratory airflow is continuously proportional to the driving pressure, 4 cm H_2O minus supraglottic pressure, and thus, according to the earlier definition of IFL, is not flow limited.

Figures 127.1 and 127.2 illustrate that, when one is provided with both an airflow signal and a supraglottic pressure signal, recognizing IFL is not difficult. It is emphasized that IFL is not defined by any specific decrease in inspiratory airflow (e.g., a 30% or 50% decrease in airflow) relative to *non*-flow-limited inspiration. Rather, IFL is defined by a specific relationship of airflow to driving pressure (nasal pressure minus supraglottic pressure). IFL can be more difficult to recognize in the absence of a supraglottic pressure signal because one is then missing driving pressure; indeed, the presence of IFL can only be *assumed* in the

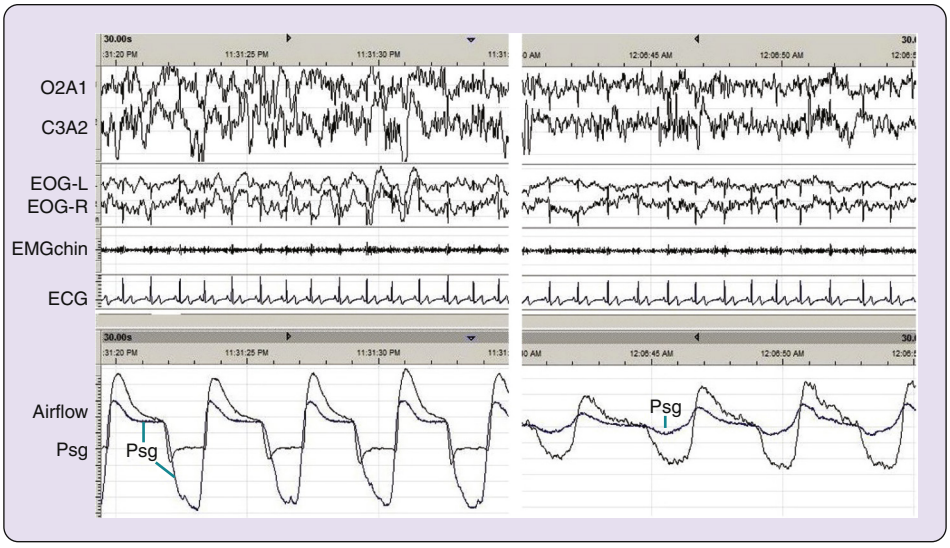

Figure 127.2 This figure demonstrates both inspiratory airflow limitation (IFL) and *non*-flow-limited inspiration in the same individual during nasal continuous positive airway pressure (CPAP) titration. The two polysomnographic tracings are obtained in stage N2 sleep, 1 hour apart. Below the sleep monitoring channels recording electroencephalograms (O2A1, C3A2), electrooculograms (EOG-L [left] and EOG-R [right]), superficial electromyograms of the chin (EMGchin), and electrocardiogram (ECG) are recordings of airflow (a pneumotachograph tracing) and supraglottic pressure (Psg). The *left panel* demonstrates four breaths at atmospheric pressure, whereas the *right panel* demonstrates four breaths with nasal CPAP at 4 cm H_2O. In each panel, airflow (*black tracing*) and Psg (*blue tracing*) are superimposed. The *left panel* demonstrates the plateau of inspiratory airflow (downgoing) at a maximal level occurring as Psg continues to decrease, which defines IFL. In the *right panel*, because pharyngeal pressure and Psg do not fall much below 4 cm H_2O (the CPAP applied to the nasal mask), Psg always remains above pharyngeal critical pressure, and the airflow and pressure tracings parallel each other (airflow is always determined by the pressure gradient: 4 minus Psg).

absence of a supraglottic pressure tracing. To enable clinicians to recognize IFL during clinical PSG without the recording of supraglottic pressure, researchers have investigated the possibility of identifying IFL from the airflow signal alone.

In 1998 two studies evaluated the utility of a plateau of inspiratory airflow measured as a nasal pressure signal (pressure transducer-generated airflow [PTAF]) to identify IFL.[12,13] One study[13] used a computer algorithm to classify each PTAF inspiration as non-flow-limited (sinusoidal in shape and resembling the airflow signal in the right panel of Figure 127.2), flow-limited (having a clear plateau and resembling the airflow signal in Figure 127.1 and the left panel of Figure 127.2), or intermediate (not sinusoidal but not fulfilling their program's criteria for an inspiratory plateau). The PTAF signal clearly separated their asymptomatic controls of patients without OSA from their patients with OSA, with the former having fewer flow-limited events. In a similar study of seven habitual snorers, Clark and associates[12] found that an inspiratory airflow plateau determined by PTAF identified flow-limited inspirations with a sensitivity and specificity of approximately 80%. Thus PTAF evidence of a clear inspiratory airflow plateau is a reasonably reliable method for identifying IFL during clinical PSG.

The ability to recognize IFL during diagnostic PSG, whether in-laboratory or during out-of-center sleep testing (OCST), can also be aided by the finding that the ratio of the inspiratory time to the time of the entire respiratory cycle (i.e., the "duty cycle") is prolonged.[14] This distinction is illustrated in Figure 127.2, where four flow-limited inspirations (left panel) take up a larger portion of the respiratory cycle time than the non-flow-limited inspirations (right panel), where expiratory time is more prolonged. During IFL, the inspiratory airflow increases rapidly and remains near maximum throughout most of inspiration (left panel), maximizing the tidal volume under the flow-limited conditions. During the *non*-flow-limited breaths (right panel), the increase in inspiratory airflow is more gradual, and airflow remains near maximum for a shorter portion of inspiration.

Figure 127.3 represents both IFL and *non*-flow-limited breathing in a single patient with UARS undergoing nasal CPAP titration. In the absence of a supraglottic pressure signal, IFL can be recognized by the change in the airflow tracing between the two left panels recorded at CPAP levels of 4 and 5 cm H_2O demonstrating IFL, and the right panel recorded at a CPAP of 6 cm H_2O illustrating non-flow-limited airflow at therapeutic CPAP. At 4 and 5 cm H_2O, the flow-limited inspiratory airflow tracing is characterized by a rapid increase in airflow to a maximum, followed by a prolonged plateau at maximal flow. At 6 cm H_2O, the non-flow-limited inspiratory airflow increases more gradually without a subsequent plateau but with a rapid decrease of airflow and a shorter ratio of inspiratory time to respiratory cycle time (exhalation is prolonged relative to flow-limited conditions). Thus, in the absence of a supraglottic pressure signal, both the shape and the relative duration of the inspiratory airflow tracing provide evidence for the presence of IFL.

In Figure 127.4, a 30-second epoch of sleep from a patient with UARS provides examples of overt IFL, more subtle IFL, and *non*-flow-limited breathing. Although several breaths in Figure 127.4 demonstrate the rapid increase in inspiratory airflow and long inspiratory airflow plateau of IFL, several (marked by an asterisk) demonstrate a less prolonged plateau of inspiratory airflow. The presence in these breaths, however, of a rapid increase in inspiratory airflow followed by a short plateau, as well as the accompanying snoring (recorded by microphone) for one of the breaths, can be used to identify all of these as examples of subtle IFL compared with the one *non*-flow-limited inspiration (marked by an arrow). Viewed from the perspective of respiratory cycle time, one can also appreciate that the non-flow-limited breath is preceded by the

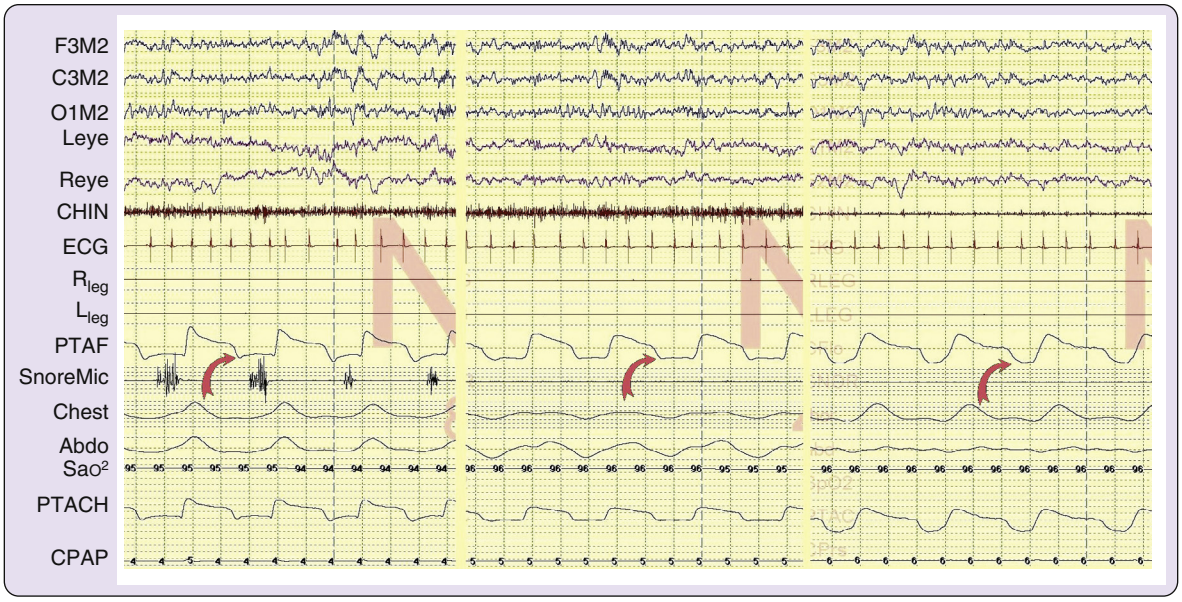

Figure 127.3 This figure's three panels, from left to right, represent three 12-second intervals at nasal continuous positive airway pressure (CPAP) levels of 4 cm H_2O, 5 cm H_2O, and 6 cm H_2O. Below the sleep monitoring channels recording electroencephalograms (F3M2, C3M2, O1M2), electrooculograms (L_{leg} and Reye), superficial electromyograms of the chin (CHIN) and right and left tibialis anterior (R_{leg} and L_{leg}), and ECG are several channels recording respiratory parameters. The respiratory channels include a pressure transducer-generated airflow (PTAF) signal, a microphone placed on the neck to record snoring (SnoreMic), impedance plethysmography of the chest and abdomen (Chest and Abdo; movement), oxyhemoglobin saturation (Sa_{O_2}), a pneumotachograph airflow signal (PTACH), and a pressure transducer-recorded CPAP level (CPAP). At 4 cm H_2O, the *left panel*, the patient's inspirations all demonstrate inspiratory airflow limitation (IFL) with audible snoring. Inspiratory airflow (downgoing) is seen to increase rapidly and then to plateau with a prolonged time spent at maximal inspiratory airflow (highlighted by the *arrow*). At 5 cm H_2O, IFL persists without snoring. Inspiratory airflow, again, increases rapidly and then demonstrates a prolonged plateau at maximal flow (highlighted by the *arrow*). At 6 cm H_2O, the airflow tracing no longer demonstrates IFL. Inspiratory airflow increases to its maximum more gradually and then immediately decreases, spending only a short time at maximal airflow. Expiratory time is prolonged relative to flow-limited conditions (the two *left panels*), and inspiration is a smaller percentage of the respiratory cycle.

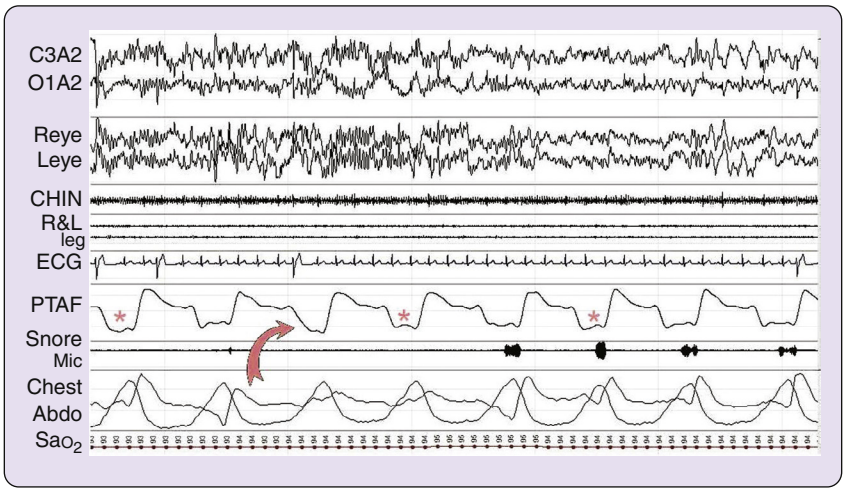

Figure 127.4 This figure demonstrates a 30-second epoch of non–rapid eye movement stage 2 (N2) sleep containing eight consecutive breaths representing both overt and subtle (*asterisks*) inspiratory airflow limitation and a *non*-flow-limited breath (*arrow*). The sleep parameters recorded include electroencephalograms (EEGs; C3A2, O1A2), electrooculograms (EOGs; Reye and Leye), superficial electromyogram of the chin (CHIN), superficial electromyograms of the right and left tibialis anterior (R_{leg} and L_{leg}), and electrocardiogram (ECG). The respiratory parameters recorded are labeled similarly to those in Figure 127.3. Refer to the text for a complete characterization of the breathing. PTAF, Pressure transducer-generated airflow.

longest exhalation, and the ratio of inspiratory time to respiratory cycle time for the breath is lower than for the flow-limited breaths in the figure.

To summarize, IFL can be recognized, using a nasal pressure signal, as a plateau in inspiratory airflow and a prolongation of inspiratory time relative to total respiratory cycle time. Inspiratory airflow can be observed to rise rapidly to a maximum and to remain there for most of inspiration. Snoring, the audible manifestation of the fluttering pharyngeal airway characterizing IFL, is not as sensitive an indicator of

IFL as the combined airflow and driving pressure criteria (Figures 127.1 and 127.2) or the airflow tracing alone. Figure 127.1, which in fact is a tracing of a lean female with no history of snoring, demonstrates definitive evidence of IFL determined by her airflow and supraglottic pressure recordings. In Figure 127.3, nasal CPAP of 5 cm H_2O resolves the patient's snoring before the airflow tracing demonstrates resolution of IFL at 6 cm H_2O. Figure 127.4 demonstrates five breaths clearly characterized by the airflow plateau associated with IFL, only four of which demonstrate snoring. For this reason, the presence of snoring should not be relied on to determine whether a patient with sleepiness or fatigue has sleep-disordered breathing. Even in the absence of apneas and hypopneas, silent IFL (defined in the glossary) associated with arousals (RERAs) may be prevalent enough to establish a diagnosis of OSA when using ICSD-3 criteria, or UARS, using the criteria of sleepiness or fatigue in the presence of IFL as presented in the glossary. Similarly, the absence of snoring should not be relied on to determine whether a nasal CPAP level is therapeutic (i.e., has eliminated IFL). Rather, the polysomnographic technologist and sleep medicine physician should differentiate IFL during sleep from non-flow-limited inspiration using an airflow signal generated by either a pneumotachograph or a PTAF signal and determine therapeutic nasal CPAP as the pressure that eliminates IFL (as demonstrated in Figures 127.2 and 127.3). A CPAP level that eliminates IFL will, of necessity, eliminate all apneas, hypopneas, and RERAs.

PATHOLOGIC UPPER AIRWAY RESISTANCE SYNDROMES: CLINICAL ASPECTS

Snoring

Habitual snoring, as described early in the glossary, can be observed in patients with OSA complaining of daytime sleepiness, fatigue, and insomnia. Habitual snoring may also occur in the absence of symptoms and signs of OSA and without an RDI (a frequency of apneas, hypopneas, and RERAs) adequate to establish a diagnosis of OSA in the absence of symptoms, that is, an RDI of 15 per hour. In the latter instance, according to the ICSD-3, it is regarded as "isolated snoring," listed in the category of sleep-related breathing disorders.

As already noted, snoring is a sleep-related sound caused by vibration of soft tissue in the UA under conditions of IFL. In most individuals with isolated snoring, the snoring is limited to inspiration, although early expiratory snoring or snoring throughout expiration can occur.[15] The presence of expiratory snoring with low mean oxygen saturation during sleep may indicate coexisting chronic obstructive pulmonary disease in patients with OSA, warranting further evaluation for pulmonary disorders.[16] Whether occurring during inspiration or expiration, snoring is generated by high-frequency opening and closing (fluttering) of UA structures, including the tongue base and soft palate, aided by the adhesive properties of mucosal secretions. Acoustic studies have shown that the major frequency content of snoring is below 2000 Hz, with peak power below 500 Hz.[17] Snorers experience increased total pulmonary resistance during sleep related to reduced UA muscle tone causing IFL and leading to increased inspiratory effort.[18]

There is considerable variation in the prevalence figures reported for habitual snoring, because of differences in subject selection and whether the snoring data is subjective (from patient or bed partner) or objective (measured or recorded) and how it was defined (isolated or habitual). In addition to differences in methodology regarding diagnoses and snoring assessment, differences in gender and obesity distribution between studies may affect snoring prevalence significantly. Both gender and obesity can affect UA resistance (alternatively, collapsibility, assessed as the pharyngeal Pcrit) either by structural changes or neuromuscular mechanisms. Thus the variability of study design is one reason for the varied prevalence figures for habitual snoring seen in the literature.

The severity of subjective snoring reported by the bed partner may not correspond with either objectively assessed snoring or the subjective assessment of the sleep technician monitoring the patient.[19] This may, in part, be due to considerable night-to-night variability of snoring intensity. The time spent snoring and snoring volume within one individual can vary from night to night, depending on factors such as sleeping position, medications, alcohol intake, and cumulative or acute sleep debt. Alternatively, the discrepancy observed between a bed partner's report of snoring severity and that observed during in-laboratory PSG could be due to allergens in the home environment altering UA pressure-flow relationships or even the bed partner's sensitivity to the noise or willingness to complain.[20]

In the 2011 Centers for Disease Control and Prevention report on unhealthy sleep behaviors, the study reports a snoring prevalence of 48% based on a telephone survey.[21] The report does not indicate how many of the snorers in this survey complained of hypersomnolence or other symptoms of OSA. Furthermore, the report does not specify the snoring severity of those individuals labeled as snorers: intermittent versus habitual. Based on data from the Sleep Heart Health Study, a sample of 5615 community-dwelling adults between the ages of 40 and 98 years, 13% of the participants had an AHI of less than 5 per hour and reported *habitual* snoring (3 to 7 nights/week).[22] These data estimate a prevalence of habitual snoring without OSA of less than 15% in a community sample. Symptom data, however, are not provided, and so one cannot determine a prevalence of isolated snoring. Of note, 29% of the 5615 men and women did not know whether they snored (perhaps because of not having a bed partner). Although the previous two examples illustrate the difficulty investigators have in determining the prevalence of habitual and isolated snoring, it remains clear that snoring is a common phenomenon that frequently prompts a referral for a sleep evaluation to establish a diagnosis of OSA.

When a habitual snorer presents for a sleep evaluation, PSG is warranted if witnessed apnea, hypersomnolence, fatigue, insomnia, somatic syndromes typically described among patients who have UARS (discussed in the next section), or comorbidities such as metabolic syndrome, cardiac dysrhythmia, or atrial fibrillation are present. In this case PSG may lead to treatment of OSA when the ICSD-3 diagnostic criteria for OSA are met. Habitual snoring in the absence of witnessed apnea, symptoms or syndromes, or comorbidities (after appropriate screening for comorbidities) does not automatically warrant a polysomnogram. Habitual snoring is a common occurrence among middle-aged, overweight men, and polysomnographic evaluations of *all* habitual snorers carries a very high cost-to-benefit ratio. A more practical approach would be to monitor asymptomatic, healthy, habitual snorers over time for the development of signs and symptoms that would support obtaining PSG. Alternatively, OCST can be used to rule out moderate to severe OSA in asymptomatic, healthy, habitual snorers in need of reassurance.

The rationale for not obtaining PSG in asymptomatic, healthy, habitual snorers extends beyond the issue of costs, to a

consideration of benefit. Specifically, even if such an individual fulfills ICSD-3 criteria for OSA, the question is whether such an asymptomatic, healthy individual is in fact in need of treatment. To the contrary, cross-sectional polysomnographic data from a study by Pavlova and associates[23] of 163 asymptomatic, nonobese individuals screened for the absence of metabolic syndrome and cardiovascular disease (25% reporting "some" snoring) demonstrate that many such individuals have RDIs above 15 per hour, fulfilling ICSD-3 criteria for OSA. Indeed, the mean RDI for individuals older than 65 years was 22 per hour in Pavlova's study. Similar data exist in three studies comparing inspiratory airflow dynamics during sleep between patients with somatic syndromes[24,25] and UARS[26] with those of rigorously screened healthy control subjects. For the three studies, 4 (11%) of 35 healthy control subjects (14 men and 21 women) met the ICSD-3 threshold for OSA that would justify their treatment without symptoms or comorbidities (RDI ≥ 15/hour). Another 4 of the healthy control subjects had values of RDI between 10 per hour and 15 per hour, approximating the threshold for treatment.

Lee and associates[27] demonstrated that the amount of time spent snoring was correlated with the extent of asymptomatic carotid artery stenosis, independent of AHI and histories of other comorbidities. These findings suggest that in individuals predisposed to atherosclerosis (by smoking, hypertension, or hyperlipidemia), habitual snoring may be an *additional* risk factor for developing carotid artery atherosclerosis. On the other hand, a study with a 17-year follow-up of 380 community-dwelling adults failed to document a significant relationship between objectively measured nocturnal time spent snoring and all-cause mortality from cardiovascular disease.[28] In the absence of certainty about the effects of habitual snoring, one should evaluate, beginning with noninvasive methods, an asymptomatic, habitual snorer without metabolic syndrome or atrial fibrillation for evidence of atherosclerosis before deciding that the patient is not in need of treatment and can be followed over time.

Asymptomatic, healthy individuals seeking treatment for habitual snoring or isolated snoring (after PSG because of reports of witnessed or patient-perceived apnea) will usually do so because they are concerned about the disruption of their bed partner's sleep. Any treatment that will lower the pharyngeal Pcrit, reducing the occurrence of IFL, will also have a beneficial effect on audible snoring. A wide variety of over-the-counter remedies are available for snoring, but they are of limited efficacy. There are limited or absent benefits of products such as nasal dilators, lubricants, oral dietary supplements, and magnetic pillows and mattresses.[29] In contrast to these ineffective treatments, any effective treatment used for OSA will be effective for asymptomatic snoring. Among these treatments, few isolated snorers choose nasal CPAP, considering it a burden to use and to maintain.

Successful or partially successful treatment of isolated snoring has been reported using lifestyle modifications. A lifestyle modification such as weight reduction (by diet or bariatric surgery, see Chapter 139) can be an effective treatment for snoring because it can substantially lower pharyngeal Pcrit.[30] There is an independent, beneficial effect of physical activity on self-reported snoring in obese women.[31] Another lifestyle alteration that can decrease the intensity of snoring is avoiding alcohol consumption before going to bed.[32] Other lifestyle modifications that can reduce snoring include avoiding sleep deprivation and the use of sedative-hypnotic medications.

Oral mandibular advancement appliances have been used successfully for the treatment of mild to moderate OSA and asymptomatic snoring in patients with a healthy dentition. Good results can be achieved with 50% to 75% of maximal voluntary protrusion.[33,34] For patients with an insufficient number of healthy teeth, a tongue-retaining device may be a good alternative. Patients should be advised that snoring may not be completely abolished, but significant reductions in the time spent snoring and snoring intensity can be obtained. They should also be aware that mandibular and maxillary incisors may procline (mandibular) or retrocline (maxillary) significantly with long-term use of an oral appliance.[33]

Surgery can be performed for isolated snoring to decrease its occurrence and intensity. Surgical targets include the nasal turbinates and septum, the nasopharynx, oropharynx, tongue base, and hypopharynx. Sleep nasendoscopy with a flexible endoscope is increasingly used to perform a preoperative assessment of possible surgical targets. For this procedure, anesthesia is used to simulate sleep. At present, the data regarding the value of nasendoscopy before surgical treatment of snoring are indeterminate. The surgical method depends on the surgeon's preference and the availability of equipment, but procedures are performed using a scalpel, radiofrequency ablation, and yttrium-aluminum garnet laser. Studies assessing the efficacy of these procedures have typically shown good immediate- and short-term results. However, many of these studies have relied only on subjective assessments of snoring. A study on the subjective versus the objective improvement of snoring after palatal surgery published in 1994 did not find any objective improvement in snoring despite a subjective improvement in greater than 75% of the participants.[35] Palatal surgery for isolated snoring improved subjectively and objectively, but the objective improvement was short lived and correlated poorly with the subjective improvement on an individual basis.[36] A long-term study evaluating patients treated with palatal surgery found a substantial rebound of snoring even in the absence of weight gain. In addition, about a third of the patients continued to experience surgical side effects (swallowing dysfunction, altered voice, and pain) that left them dissatisfied with the decision to have palatal surgery.[37] Surgery intended to relieve nasal obstruction alone does not produce a significant improvement of objectively assessed snoring intensity and snoring time, nor does it decrease the AHI, despite improvement in nasal resistance.[38]

The consequences of leaving isolated snoring untreated relate specifically to the concern of whether untreated isolated snoring progresses to OSA over time. According to a study that followed individuals with isolated snoring over 5 years with PSG, isolated snoring does not progress to OSA over 5 years in the absence of a significant change in body weight.[39] Thus, to date, there is no evidence that isolated snoring progresses to OSA in the intermediate term.

In summary, isolated snoring is a diagnosis of exclusion reserved for habitual snorers who are otherwise asymptomatic, without metabolic syndrome and cardiovascular disease, and who do not meet polysomnographic or OCST criteria for OSA. The potential for adverse long-term cardiovascular outcomes in isolated snoring remains uncertain. Treatment of isolated snoring is currently limited to attempting to improve the sleep quality of the bed partner. Available treatments include lifestyle modifications, oral appliances, and soft tissue surgery. Most available treatment options lead to short-term success but fail in the long term.

Upper Airway Resistance Syndrome

UARS is defined as the symptom of either hypersomnolence or fatigue, together with the presence of IFL during sleep by

in-laboratory PSG and an AHI of less than 5 per hour (see the glossary earlier in this chapter). ICSD-3 absorbs UARS into OSA by including RERAs into the severity assessment of sleep fragmentation in OSA. ICSD-3 criteria for OSA now classify any patient fulfilling the previously noted UARS definition with an RDI above 5 per hour as having OSA. Clearly a portion of UARS has been absorbed into OSA by the clinical criteria of ICSD-3. However, there are still patients meeting the definition of UARS elaborated in this chapter, with an RDI of less than 5 per hour who are not included within the ICSD-3 definition of OSA and are not considered, clinically, to have sleep-disordered breathing. Nevertheless, to investigators of UARS and to clinicians attempting to treat the hypersomnolence of a patient without a clear diagnosis because of too few RERAs, the recognition that sleep-disordered breathing may, in fact, exist outside the limits of the ICSD-3 is important and worthy of consideration. In this section we discuss the varied clinical presentation of UARS, its polysomnographic appearance, and its evolving paradigm. To facilitate this discussion, when we refer to OSA, we will use the ICSD-2 definition of OSA—an AHI of at least 5 per hour—to match the definition used in the research to be presented.

Anthropometric Features and Risk Factors

Compared with patients with OSA, those with UARS are younger, leaner, and more frequently female. Published studies of patients with UARS, as defined by the previous criteria, have established a mean age of 40 years, with the average BMI between 23 and 30 kg/m^2 (normal weight or overweight; less often, obese), and approximately 50% female.[40–42] Although craniofacial abnormalities, such as a narrow, elongated face characterized by a high arched palate, reduced upper and lower intermolar distances, and a narrow anterior nasal aperture (adenoid facies), have been reported in patients with UARS, these same findings are also commonly observed in patients with OSA[43] and so cannot be considered specific for UARS. The presence of these abnormalities suggests a disturbance of facial development caused by increased nasal resistance during early childhood with mouth breathing.[44]

Signs and Symptoms

The most observed polysomnographic feature of UARS patients is nonapneic, habitual snoring or silent IFL with relatively few adjudicated apneic or hypopneic events (AHI < 5/hour). In clinical practice, these patients will seek medical attention for their condition because they also suffer from nonrestorative sleep, fatigue, sleepiness, or insomnia. In fact, patients with UARS are more commonly referred to a sleep disorders center for their symptoms than for their snoring. Before referring these patients for cognitive behavior therapy (CBT) for insomnia, a careful sleep-related history revealing snoring without witnessed apnea will prompt polysomnographic investigation with documentation of IFL during sleep. It is emphasized that a report of witnessed apnea does not preclude a diagnosis of UARS because about one-third of patients with UARS are reported to have witnessed apnea but have an AHI below the threshold for OSA.[45] Similarly, the absence of audible snoring does not preclude a diagnosis of UARS because inaudible IFL is observed in about 10% of patients diagnosed with UARS.[45,46] Typically, these patients have been diagnosed with insomnia and, in the absence of a sleep-related history of habitual snoring, are referred for CBT without performing PSG. When CBT fails to improve their condition and PSG is performed to exclude an intrinsic sleep disorder, IFL in the absence of audible snoring can be demonstrated.[47]

The earliest reports of UARS emphasized the importance of hypersomnolence as a diagnostic criterion distinguishing it from isolated snoring.[2,15] Before those reports, PSG technology used a thermistor or thermocouple to generate a qualitative airflow signal that could not be used to recognize IFL. Thus the link between hypersomnolence and IFL could not be made, and patients with UARS often received a diagnosis of idiopathic hypersomnolence. The earliest reports of UARS substituted a pneumotachograph recording of airflow for the qualitative airflow signal, together with an esophageal pressure catheter measurement of inspiratory effort to establish the presence of IFL during sleep in patients with UARS.[2,15] With time and the growth of clinical experience evaluating patients with UARS, the diagnostic criteria for UARS have been expanded to include complaints of hypersomnolence or fatigue.[7,45]

Hypersomnolence indicates increased sleep pressure expressed by short sleep latency, a state that is inconsistent with a complaint of insomnia. Fatigue, on the other hand, is generally associated with longer sleep latencies, reflecting a state of hyperarousal commonly observed in patients with insomnia. About one-third of patients with UARS complains of sleep-onset insomnia, and nearly two-thirds reports sleep maintenance insomnia.[40] Characteristically, the complaints of fatigue and insomnia among patients with UARS are associated with the complaint of nonrestorative sleep.

Of interest, patients with UARS complain of more subjective sleep disturbance than patients with OSA who have much more disrupted sleep.[48] Patients with UARS can also experience a variety of parasomnias. Among these are sleep-related bruxism,[45] chronic sleepwalking in children,[49] and catathrenia.[50]

At present, there is not enough evidence to conclude that UARS is an independent cardiovascular risk factor. An increased prevalence of arterial hypertension among nonapneic snorers has been reported,[51] and borderline arterial hypertension has been lowered with nasal CPAP in a small series of patients with UARS.[52] Hypotension and orthostatic intolerance have also been documented in about 20% of patients with UARS.[53]

Psychiatric symptoms such as depression[41,42,54,55] and anxiety[54-56] have been demonstrated among patients with UARS and have responded dramatically to treatment using nasal CPAP and rapid palatal expansion in case reports.[54,55] Conversely, failure to diagnose and treat UARS is associated with a worsening of these symptoms over time.[41]

At present, there are limited data available regarding cognitive function among patients with UARS. Using a psychomotor vigilance task, Stoohs and associates[57] have reported increased reaction times among patients with UARS compared with patients who have OSA. Although those with UARS perceive themselves to have impaired cognitive function compared with healthy control subjects, objective testing fails to demonstrate such a difference.[58]

Patients with UARS also commonly present with a variety of findings characteristic of the functional somatic syndromes: headaches and functional gastrointestinal symptoms and alpha-delta sleep.[45] These functional somatic syndrome symptoms and signs (specifically, sleep-onset insomnia, headache, irritable bowel syndrome, and alpha-delta sleep) decrease in prevalence among sleep-disordered breathing patients as the

AHI increases.[45] Conversely, when patients with functional somatic syndromes undergo PSG, IFL during sleep is commonly observed (fibromyalgia, temporomandibular joint syndrome, Gulf War illness, and irritable bowel syndrome have been studied).[24,25,59,60] In this setting, nasal CPAP has been shown to relieve the symptoms of functional somatic syndrome patients by relieving their IFL during sleep[60,61] (see the section Pathophysiology and Clinical Correlates for a discussion of mechanism).

Polysomnographic Findings

Polysomnographic findings among patients with UARS can be subdivided into those characterizing breathing with associated arousals and those characterizing sleep architecture (electroencephalographic frequencies, sleep staging). Concerning sleep architecture, researchers have observed findings consistent with unstable, nonrestorative sleep among patients with UARS.

Polysomnographic Findings Characterizing Breathing. Breathing in UARS is, by definition, characterized by an AHI below 5 per hour of sleep and periods of IFL during sleep with flows greater than 50% of waking levels (exemplified in Figures 127.2 to 127.4) and terminated by arousals or changes in the background electroencephalographic rhythm associated with a return of airflow to a non-flow-limited state (i.e., RERAs).[41] In several large studies, the mean AHI for patients with UARS is consistently 2 per hour, and the frequency of RERAs is between 5 per hour and 20 per hour.[40–42] Oxyhemoglobin saturation generally remains greater than 90% throughout sleep.[40,42] One study that used a snore microphone to determine the prevalence of breaths associated with audible snoring among 424 patient with UARS observed a 21 ± 23% (mean ± standard deviation) prevalence of such breaths during sleep.[42] It is likely that if a study were performed that included both a snore microphone and a pressure transducer for airflow measurement to identify both snoring and inaudible IFL, the prevalence of such breaths would be considerably higher and not a sporadic occurrence.

The preceding description of breathing during sleep in UARS does not define the syndrome based on thresholds for IFL or RERAs. Empirically, periods of IFL during sleep in UARS may last a few breaths or be continuous for many PSG epochs. The presence of IFL has not been defined by a consensus frequency of *resistive* events, but it is a characteristic of breathing during sleep that can be described in a PSG report based on the sleep stages in which it occurs and an impression of the prevalence of flow-limited breaths in those sleep stages (e.g., continuous, intermittent, or uncommon; Figure 127.4 is one 30-second epoch of continuous IFL in a patient with UARS). Similarly, in the UARS literature, RERAs have not been defined by a consensus length of the preceding period of IFL, as has been done in the ICSD-3. Rather, the duration of IFL preceding a RERA has been undefined[2]: 10 seconds[41] or one flow-limited breath,[26] depending on the study. Because the diagnosis of UARS is not dependent on thresholds for resistive events or RERAs, UARS cannot be classified as mild, moderate, or severe based on these events. Indeed, there are no published data relating the severity of hypersomnolence among patients who have UARS to RERA frequency or prevalence of IFL. New techniques to analyze flow signals to document not only flow limitation but also recovery breaths may lead to more useful methods to characterize the abnormal breathing events.[62]

Polysomnographic Findings Characterizing Sleep Architecture. PSG of patients who have UARS demonstrates findings consistent with unstable, nonrestorative sleep. Among these findings is alpha frequency intruding into sleep, increased sleep stage shifts, and cyclic alternating pattern (CAP).

Patients with UARS experience increased alpha frequency, a frequency observed during quiet wakefulness, within their sleep electroencephalogram.[45,63] This increased alpha frequency may be seen in stage N3 sleep, where it has been termed *alpha-delta sleep*[45,64] (Figure 127.5) or in N1 and N2 sleep[55] (Figure 127.6; also observed in Figure 127.4). It is emphasized that this alpha frequency occurs during continuous sleep and is not the consequence of an electroencephalographic arousal. Resolution of this finding has been observed among adolescent patients with UARS when sleep quality improves after rapid palatal expansion[55] (Figures 127.5 and 127.6).

Patients with UARS also demonstrate sleep stage instability with frequent shifting from deeper to lighter sleep stages or to wakefulness, with decreasing depth of sleep designated as the stage sequence: REM, N3, N2, N1, and wake. The frequency of sleep stage shifting in patients who have UARS is decreased by treatment with nasal CPAP[61] (Figure 127.7) and rapid palatal expansion.[55] The mechanism by which nasal CPAP eliminates sleep stage shifts is not simply elimination of sleep fragmentation associated with RERAs. Although shifts between stages N2, N1, and wake require an intervening arousal, stage shifts between REM, N3, and N2 do not require an arousal. Indeed, the N3-to-N2 sleep stage shifts in Figure 127.7 that decrease in frequency with nasal CPAP all occur during continuous sleep, the difference between N3 and N2 being determined by the prevalence of delta waves, and do not represent the elimination of RERAs by nasal CPAP. The occurrence of frequent shifts from deeper to lighter sleep is hypothesized to be an adaptive response to a danger or *stressor*, lightening the individual's sleep and allowing a quicker response to an emergency.[65] Increased shifts from deeper to lighter sleep commonly occur in healthy people sleeping for the first night in a new location, such as a sleep laboratory.[66]

A second manifestation of sleep stage instability among patients with UARS is the occurrence of CAP, which is defined by a periodic disruption of NREM sleep by electroencephalographic events that do not meet the threshold for an arousal by conventional sleep staging criteria.[67] Among patients with UARS, increasing levels of these nonarousal electroencephalographic events correlate with increasing levels of sleepiness and fatigue.[67] Furthermore, the presence of CAP is a marker for increased sympathetic nervous system tone commonly found under conditions of stress.[68]

Pathophysiology and Clinical Correlates

Hypotheses concerning the pathophysiology of UARS continue to evolve as the manifestations of the disorder and the body systems affected increase in number. Initially it was hypothesized that the disorder as one of sleep fragmentation by RERAs associated with hypersomnolence that improved with nasal CPAP treatment.[2,15] Although this paradigm of UARS, henceforth termed the *RERA paradigm*, provided an explanation for the hypersomnolence associated with UARS, it did not provide an explanation for the somatic, cognitive, and affective complaints, such as insomnia, fatigue, body pain,

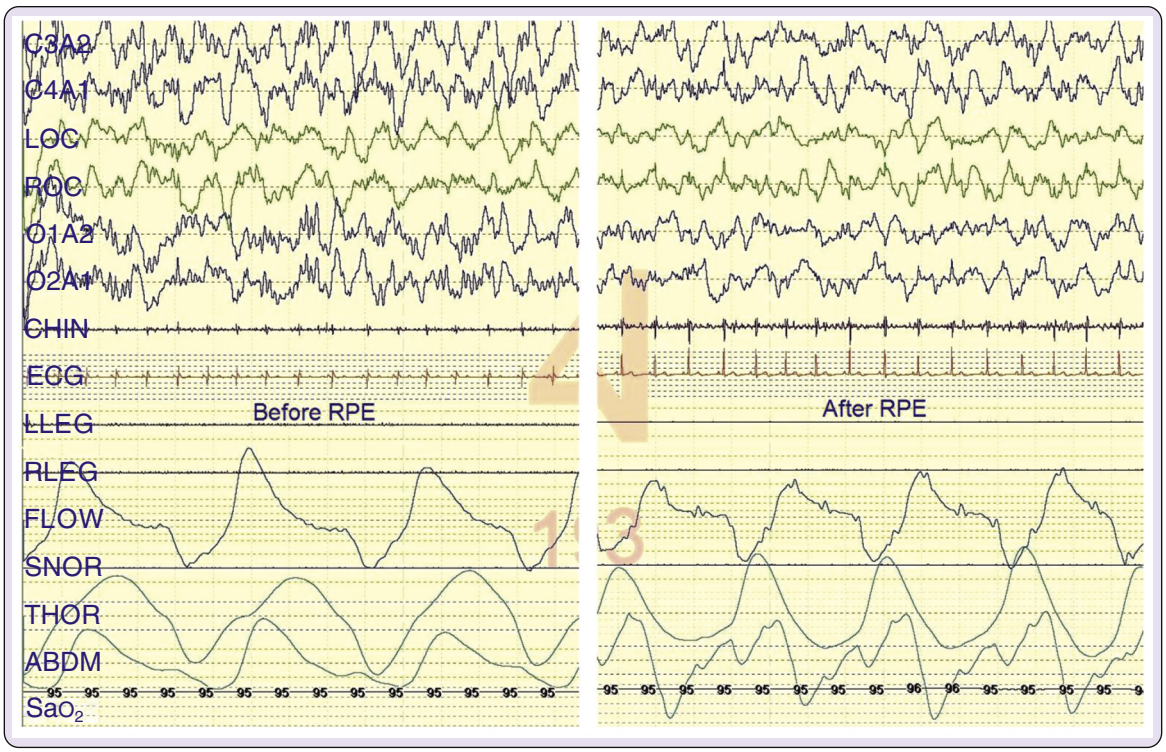

Figure 127.5 This figure demonstrates two 15-second periods of NREM stage 3 (N3) sleep recorded at the same time of night, before and after rapid palatal expansion (RPE; 13 months between studies) in a 16-year-old boy with severe chronic fatigue who was diagnosed with upper airway resistance syndrome. Recording includes four electroencephalographic channels (*purple*; C3A2, C4A1, O1A2, O2A1), left and right electrooculograms (*green*; LOC, ROC), electromyograms of the chin (CHIN) and left and right tibialis anterior muscle (LLEG, RLEG), and an electrocardiogram (ECG). Respiratory channels include pressure transducer airflow (FLOW), a snore microphone (SNOR), thoracic and abdominal wall movement (THOR, ABDM), and oxygen saturation (Sao_2). Before RPE, the patient demonstrates alpha-delta sleep characterized by low-frequency, high-amplitude delta waves with superimposed prominent 7- to 11-Hz alpha waves observed best in electroencephalographic leads C3A2 and C4A1. After RPE, the alpha frequency is greatly decreased in amplitude or gone. Associated with this change, the ECG demonstrates a decrease in heart rate between studies from 72/minute before RPE to 64/minute after RPE, suggesting decreased sympathetic nervous system tone between studies.

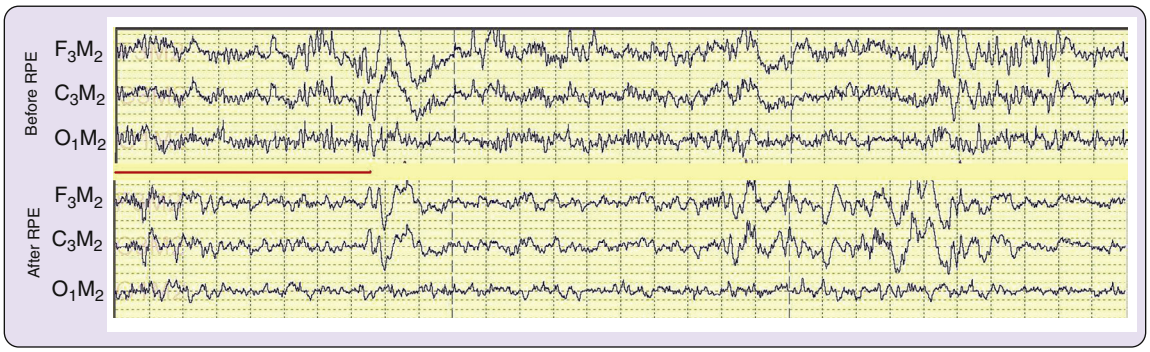

Figure 127.6 This figure demonstrates 30 seconds of stage N2 sleep recorded at the same time of night, before and after rapid palatal expansion (RPE), from an 18-year-old man with severe depression who was diagnosed with upper airway resistance syndrome. The two recordings each include three electroencephalographic channels (F_3M_2, C_3M_2, O_1M_2). As in Figure 127.5, the recording before RPE shows prominent alpha frequency (at approximately 7 Hz; seen well above the *orange line*). After RPE, the alpha frequency is greatly reduced in amplitude, and the underlying theta frequency of 3 to 5 Hz is seen more clearly. (Reproduced with permission from Miller P, Iyer M, Gold AR. Treatment resistant adolescent depression with upper airway resistance syndrome treated with rapid palatal expansion: a case report. *J Med Case Rep.* 2012;6[1]:415.)

depression, anxiety, cognitive dysfunction, and gastrointestinal dysfunction, or for the parasomnias, such as bruxism, sleepwalking, and catathrenia, that have subsequently been associated with UARS.*

As clinical experience with patients who have UARS increased, investigators came to postulate that the hypersomnolence of these patients is not simply the consequence of sleep fragmentation but also of altered sleep quality that affects its restorative properties. The alpha frequency intrusion into sleep[45,63] and the unstable sleep stages characterized by

*References 45, 49, 50, 54–56, 58, 69, 70.

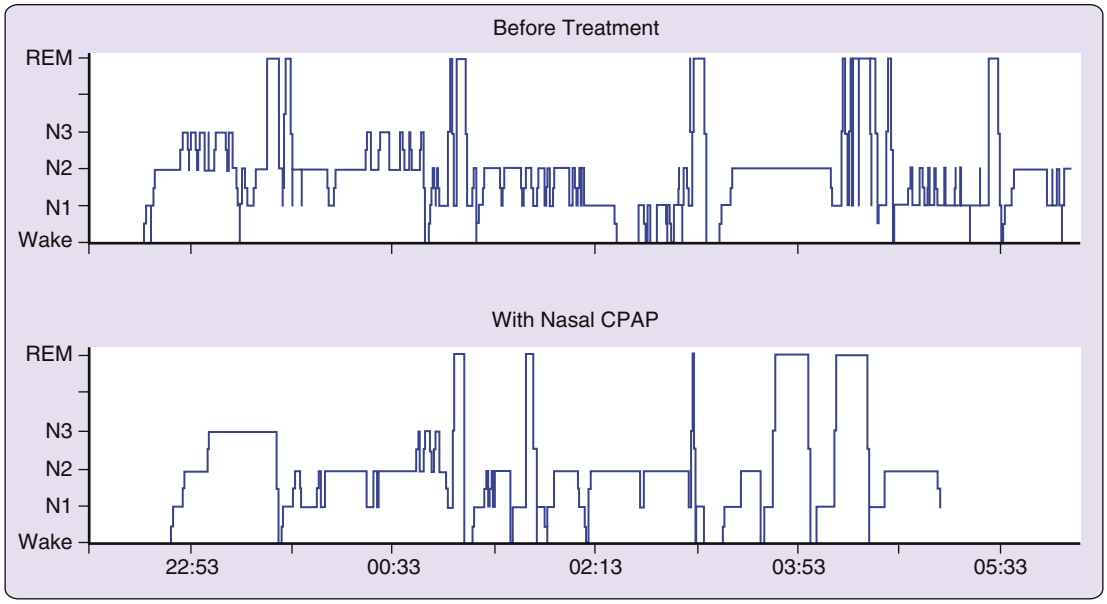

Figure 127.7 This figure demonstrates two hypnograms (plots of sleep stages against time of night, with increasing depth of sleep staged as wake, N1 [NREM stage 1], N2, N3, [REM]) from a 43-year-old veteran of the first Gulf War (1990–91) who returned with complaints of moderate fatigue and severely impaired sleep quality (symptoms of Gulf War illness) and was found to have an apnea hypopnea index of 5 per hour.[61] The upper hypnogram is derived from his polysomnogram before treatment, and the lower hypnogram was obtained from a polysomnogram performed (while sleeping with nasal continuous positive airway pressure [CPAP] at 9 cm H_2O) after the veteran slept with nasal CPAP nightly for 3 weeks and experienced improvement of his fatigue and sleep quality. The initial hypnogram demonstrates frequent shifts from deeper to lighter sleep stages throughout the night. The hypnogram obtained after symptomatic improvement demonstrates fewer sleep stage shifts. Frequent shifts from deeper to lighter sleep are thought to be an adaptive response to stress that enables the individual to respond more quickly to an emergency. NREM, Non–rapid eye movement; REM, rapid eye movement. (Reproduced with permission from Amin MM, Gold MS, Broderick JE, Gold AR. The effect of nasal continuous positive airway pressure on the symptoms of Gulf War illness. *Sleep Breath.* 2011;15[3]:579–87.)

increased shifts from deeper to lighter sleep[55,61] and CAP,[67] as described earlier, were considered alternative responses to pharyngeal collapse during sleep that maintain a more patent pharyngeal airway while maintaining sleep continuity. Bao and Guilleminault[71] have further hypothesized that UARS evolves into OSA over time because of UA trauma related to snoring. According to this hypothesis, because of the effect of snoring on the UA, patients with UARS eventually lose their increased sensitivity to pharyngeal collapse and their sleep-maintaining response. As a consequence, their sleep deepens, and their mild resistive events become hypopneas and apneas terminated by arousal. This proposed *sleep quality* paradigm of UARS provides an explanation for the alpha frequency intrusion into sleep and sleep stage instability characterizing patients who have UARS; however, it does not explain the spectrum of somatic, cognitive, and affective disorders also associated with UARS.

A third paradigm of UARS, the *chronic stress* paradigm, builds on the *sleep quality* paradigm of UARS and provides a more complete explanation for the varied symptoms associated with the syndrome.[72] The paradigm postulates that some individuals can become sensitized to UA resistance as a stimulus that activates the stress response (activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system by the brain's limbic system) as if it were an existential threat. Because UA resistance during sleep occurs for at least several hours daily, in these individuals it constitutes a chronic stress with associated symptoms, including sleep-onset and sleep-maintenance insomnia, headaches, gastrointestinal and bladder irritability, body pain, anxiety, and depression. In addition to these symptoms, so prevalent among patients with UARS, chronic stress is associated with hypertension, type 2 diabetes mellitus, gonadotrophic hormone deficiency leading to sexual dysfunction (erectile dysfunction in men and polycystic ovarian syndrome in women), and growth hormone deficiency leading to diminished growth in children. These are all prominent medical conditions associated with OSA. According to such a chronic stress paradigm, the sleep fragmentation by arousals and altered sleep quality caused by alpha frequency intrusion and sleep stage instability observed among patients with UARS is not a direct effect of UA resistance on sleep continuity but an adaptive response of the brain to the existence of a disturbance or threat. Having sleep continuously interrupted or having a state of vigilance maintained during sleep through alpha frequency intrusion and sleep stage instability theoretically enables the individual to respond more quickly to a danger, an apparent survival advantage.[65] This advantage, however, is accompanied by the disadvantages of parasomnias and daytime sleepiness resulting from the chronically altered sleep. Two recent studies that used self-report somatic arousal (the symptoms of increased sympathetic nervous system activity) to quantify stress in sleep-disordered breathing patients support the chronic stress paradigm. The studies demonstrate that as the level of somatic arousal increases among patients with UARS and with OSA, the severity of sleepiness and fatigue and the prevalence of insomnia complaints, anxiety,

and somatic syndromes increases.[73,74] The chronic stress paradigm of UARS explains not only the hypersomnolence associated with UARS, but also the somatic complaints, affective disorders, cognitive dysfunction, and parasomnias observed among patients with UARS.[72]

In summary, the pathophysiologic and associated clinical paradigm of UARS has evolved from sleep fragmentation by RERAs through altered sleep quality as a direct response to UA resistance, leading to milder resistive events than occur among patients with OSA, to recent consideration of UA resistance, provoking chronic stress with sleep-related, somatic, cognitive, and affective consequences. The pathophysiologic paradigms of UARS will continue to evolve as new data accumulate. However, the recognition that altered sleep *quality* contributes to the hypersomnolence and fatigue of patients with UARS supports the idea that UARS also exists below the RDI threshold for a diagnosis of OSA, an important possibility when one contemplates making the diagnosis of idiopathic hypersomnolence.

Treatment

The treatment of UARS uses the same treatments that have been discussed earlier for snoring. Chief among these treatments is nasal CPAP, which is highly effective and can be precisely titrated by the prescribing physician to eliminate IFL during sleep. To titrate nasal CPAP for patients with UARS, one must titrate to convert IFL during sleep into non-flow-limited breathing, as illustrated in Figures 127.2 and 127.3. The mean therapeutic level of nasal CPAP for 22 patients with UARS was found to be 7 cm H_2O with a range of 4 to 9 cm H_2O.[5] There is no published data using autotitrating positive airway pressure (PAP) in these patients. For patients unable (or unwilling) to use nasal CPAP, alternative forms of treatment, such as mandibular advancement appliances or tongue-retaining devices, weight loss, and surgical procedures, may be considered as previously described. Applying PAP through an oronasal mask may not be a reliable method for eliminating IFL during sleep[75,76] and anesthesia.[77] Among pediatric patients, rapid palatal expansion performed by an orthodontist has been used effectively to treat UARS (e.g., the patients in Figures 127.5 and 127.6[55]) and mild OSA.

Future Directions

An effort is underway to describe, more completely, the pathophysiology associated with increased UA resistance (IFL) during sleep. With the progress occurring in artificial intelligence and machine learning, an effort is underway to use technology to study the prevalence of IFL during sleep in large populations and to correlate its presence with signs and symptoms of sleep-disordered breathing. In 2017, under the auspices of the American Thoracic Society, a workshop was conducted to develop standards for the recording of airflow and the visual identification of IFL, to improve its clinical recognition and serve as a resource for technologic innovators using machine learning to quickly analyze PSG airflow signals for the presence of IFL.[11] Subsequently, studies have been published applying machine learning to IFL detection demonstrating high levels of sensitivity and specificity.[10,78] The effort appears to be underway to better define the role of IFL in isolated snoring and pathologic UARSs.

CLINICAL PEARLS

- Silent inspiratory airflow limitation (IFL) during sleep is characterized by either an inspiratory airflow plateau or an increase in the ratio of inspiratory time to the respiratory cycle time, with a prolongation of the time near maximal inspiratory airflow.
- In a patient consulting the clinician for habitual snoring that disturbs his or her bed partner, with normal alertness, no somatic or metabolic disorders, and no known cardiovascular disease, polysomnography (PSG) will likely reveal either isolated snoring or asymptomatic obstructive sleep apnea (OSA). Consider evaluating the results of a carotid ultrasound, looking for evidence of atherosclerosis, before foregoing specific OSA treatment in this setting.
- For patients with functional somatic syndromes complaining of insomnia, fatigue, headache, body pain, gastrointestinal or bladder irritability, and anxiety and depression, with or without audible snoring, consider performing PSG to diagnose upper airway resistance syndrome (OSA by ICSD-3 criteria) because prevention of IFL during sleep may be an effective treatment not only for fatigue and insomnia but also for somatic symptoms.

SUMMARY

Our understanding of pathologic pharyngeal collapse during sleep has progressed from recognizing obstructive apneas and hypopneas associated with arousal from sleep and oxygen desaturation (clinically, OSA) to recognizing the mildest IFL without audible snoring, arousal, or oxygen desaturation. At the same time, our understanding of the consequences of pathologic pharyngeal collapse during sleep has expanded from hypersomnolence and cardiovascular and metabolic disorders to include associations with somatic syndromes, affective disorders, and carotid artery atherosclerosis independent of metabolic syndrome. Underlying this evolution is a new paradigm of *sleep-related breathing disorders* (often referred to as "sleep-disordered breathing") in which pharyngeal collapse during sleep acts not only directly, causing oxygen desaturation and arousal from sleep, but also indirectly, with even the mildest IFL during sleep serving as a chronic activator of the body's stress response. In this context, one can appreciate the evolving understanding of what constitutes clinically significant sleep-related breathing disorders associated with sleep-related UA pathophysiology.

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REVIEW QUESTIONS

1. Inspiratory airflow limitation (IFL) is defined by which of the following?
   - **A.** Decrease of maximal airflow of 30%
   - **B.** Decrease of maximal airflow of 50%
   - **C.** Maximal airflow that is independent of supraglottic pressure
   - **D.** None of the above

2. To best identify inspiratory airflow limitation, the airflow signal should be:
   - **A.** Recorded unfiltered and digitized with a sampling frequency ≥100 Hz
   - **B.** Viewed unfiltered
   - **C.** Viewed with inhalation downgoing
   - **D.** A and B

3. A 36-year-old woman has been diagnosed with chronic fatigue syndrome for complaints of headache, diffuse joint pain, insomnia, and fatigue present for more than 6 months. She takes sodium oxybate (Xyrem), which provides incomplete relief of her sleep-related symptoms. The patient's bed partner claims that she snores lightly when on her back. She has not been diagnosed with hypertension, glucose intolerance, or hyperlipidemia. Polysomnography reveals intermittent snoring, with an apnea-hypoxia index of 2 per hour and a respiratory effort–related arousal (RERA) index of 10 per hour. Alpha-delta sleep is present. Which of the following is the most correct diagnosis?
   - **A.** Isolated snoring
   - **B.** Chronic fatigue syndrome
   - **C.** Upper airway resistance syndrome (UARS; obstructive sleep apnea [OSA] by the International Classification of Sleep Disorders, third edition [ICSD-3] criteria) with associated symptoms of insomnia, headache, and body pain
   - **D.** Both A and B

4. The typical polysomnographic signs of UARS include which of the following?
   - **A.** Hypopneas with oxyhemoglobin desaturation to below 90%
   - **B.** Cyclic alternating pattern (CAP)
   - **C.** Flow-limited breaths
   - **D.** Both B and C

5. A 35-year-old woman presents with problems initiating sleep, a 2-year history of occasional snoring, and fatigue. A previous referral for cognitive behavior therapy (CBT) improved her sleep to a modest degree, but the effect did not last, and she is not eager to try CBT again. She reports that her problems initiating sleep have significantly curtailed her total nightly sleep. Which of the following should be your recommendation?
   - **A.** Referral for a second attempt at CBT
   - **B.** Polysomnographic testing for IFL during sleep, followed by a trial of nasal CPAP if IFL is present
   - **C.** Prescription of a short half-life hypnotic agent
   - **D.** Referral to an otolaryngologist for surgical treatment of the snoring

6. A 43-year-old man with habitual snoring and a few witnessed apneas, but without daytime sleepiness, fatigue, or affective or somatic complaints, is brought in by his wife who asks: "Is he going to die in his sleep?" She maintains her sleep without having to leave the bedroom. The patient has no hypertension, diabetes mellitus, or hyperlipidemia. After mild reassurance fails to calm the wife's concerns, you order a polysomnogram, which excludes OSA based on a respiratory disturbance index (apneas, hypopneas, and respiratory effort–related arousals) below 15 per hour (failure to meet ICSD-3 criteria) but demonstrates snoring during more than half of the total sleep time. Which of the following should be your next step before telling the wife that there is nothing to worry about?
   - **A.** Test noninvasively for carotid artery atherosclerosis and cardiovascular disease
   - **B.** Repeat the polysomnogram
   - **C.** No further testing is necessary
   - **D.** Both A and B

7. Signs and symptoms of UARS include which of the following?
   - **A.** Obesity
   - **B.** Symptoms such as intestinal bloating, diarrhea, insomnia, and anxiety
   - **C.** Depression
   - **D.** Both B and C

ANSWERS

1. **C.** IFL is the condition in which supraglottic pressure is no longer the effective downstream pressure determining inspiratory airflow. Rather, the pharyngeal critical pressure is the effective pressure determining inspiratory airflow. Information supporting this answer can be found in the section Recognizing Inspiratory Airflow Limitation with Physiologic Testing.

2. **D.** To best observe the airway/airflow fluttering characterizing inspiratory airflow limitation, high frequency filters must be avoided because they will smooth the signal. Low-frequency filters may also decrease the amplitude of the airway fluttering, but to a lesser extent. Similarly, a high sampling frequency is needed because the oscillation of airflow is a high-frequency occurrence.

3. **C.** Airway stabilization during sleep with nasal CPAP or a mandibular advancement appliance is expected to improve the patient's fatigue, insomnia, and body pain. Information supporting this answer can be found in the section Upper Airway Resistance Syndrome (subsection, Signs and Symptoms).

4. **D.** Recurrent hypopneas and apneas with oxyhemoglobin desaturation are a typical polysomnographic finding among patients with OSA. Patients with UARS present with IFL with a decrease in airflow that does not meet the threshold for hypopnea and that can be detected by inspection of the inspiratory airflow tracing. CAP is a nonspecific polysomnographic finding associated with stress and nonrestorative sleep seen among patients with UARS. Information supporting this answer can be found in the section Upper Airway Resistance Syndrome (subsection, Polysomnographic Findings).

5. **B.** The combination of fatigue, snoring, and insomnia complaints are common among women with UARS (and with functional somatic syndromes). Before encouraging the patient to try CBT again or prescribing medication, polysomnography should be performed. The presence of IFL warrants a treatment trial with nasal CPAP. Surgical correction of snoring has a high relapse rate and is not likely to relieve the underlying IFL. Information supporting this answer can be found in the sections Upper Airway Resistance Syndrome (subsection, Signs and Symptoms) and Pathologic Upper Airway Resistance Syndromes: Clinical Aspects (subsection, Snoring).

6. **A.** This patient has isolated snoring by ICSD-3 criteria and no symptoms or metabolic signs associated with OSA. There is no reason to treat if the bed partner's sleep is not disturbed. However, if carotid artery atherosclerosis or cardiovascular disease is present, it would be prudent to treat the isolated snoring. A repeat polysomnogram is only warranted if poor sleep quality under testing conditions leads to uncertainty concerning the result. Information supporting this answer can be found in the section Pathologic Upper Airway Resistance Syndromes: Clinical Aspects (subsection, Snoring).

7. **D.** Patients with UARS are seldom obese (mean values of body mass index in several large studies range from 23 to 30 kg/m^2). They commonly present with the symptom profile of the functional somatic syndromes and affective disorders. These symptoms can include functional gastrointestinal complaints, insomnia, and anxiety. Information supporting this answer can be found the section Upper Airway Resistance Syndrome (subsections, Anthropometric Features and Risk Factors and Signs and Symptoms).