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Authors

Sands, Scott A
Owens, Robert L
Malhotra, Atul

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New Approaches to Diagnosing Sleep-Disordered Breathing

Scott A. Sands, PhD[a,b,*], Robert L. Owens, MD[c], Atul Malhotra, MD[c]

KEYWORDS

• Apnea • Screening • Phenotyping • Technology

KEY POINTS

- Home sleep testing is now widely used.
- Advanced analysis of respiratory sounds, electrocardiogram, and body movements will likely enable widespread screening for sleep-disordered breathing.
- Semi-automated scoring algorithms will reduce the resources required and improve consistency of diagnoses.
- Personalized sleep medicine will approach actuality as noninvasive methods reveal sleep apnea mechanisms, allowing clinicians to determine what options are best suited for individual patients.

DETECTING THE PRESENCE OF EVENTS: DIAGNOSTIC AND SCREENING TECHNOLOGY

In-laboratory diagnostic polysomnography has traditionally been the gold standard for obstructive sleep apnea (OSA) diagnosis, but the high prevalence of disease and the massive number of patients at risk of disease cannot reasonably be diagnosed at in-laboratory facilities. Peppard and colleagues[1] conservatively estimated that 10% of the US population has clinically important OSA, suggesting more than 30 million people afflicted with OSA in the United States alone. Clearly, many more are at risk of OSA or have more mild disease. Heinzer and colleagues[2] used gold-standard techniques in Switzerland and estimated up to 50% of men had some degree of clinically important apnea. Thus, the use of new technology to detect respiratory events (without the need for cumbersome and expensive in-laboratory testing) is an important step forward. Home sleep testing (HST) provides acceptable diagnostic sensitivity and specificity, although most technologies cannot distinguish wake from sleep, non-rapid eye movement (NREM) from rapid eye movement (REM) sleep, or supine from lateral posture. As a result, clinicians get only partial information when determining therapy.

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[a] Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham & Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA; [b] Department of Allergy, Immunology and Respiratory Medicine and Central Clinical School, The Alfred and Monash University, 55 Commercial Road, Prahran, Victoria 3181, Australia; [c] Division of Pulmonary and Critical Care Medicine, University of California San Diego, 9500 Gilman Dr La Jolla, CA 92093, USA

* Corresponding author. Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham & Women's Hospital and Harvard Medical School, Boston, MA.

E-mail address: sasands@partners.org

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Home Sleep Testing

HST has been used widely around the world and has recently increased in popularity in the United States. The factors driving home testing are primarily financial given the realization of the massive numbers of patients who may need to undergo testing and the data suggesting a satisfactory clinical result can be obtained using a HST approach. Several randomized trials were completed that compared the results of HST plus in home auto-titration positive airway pressure (PAP) therapy versus usual care via in-laboratory polysomnography or split night testing.[3–9] Although still the topic of debate,[10,11] the data in aggregate support a home testing approach suggesting equal if not better outcomes using home testing as compared with the traditional approach. An important caveat, however, is that most studies have carefully screened for patients at risk for moderate to severe OSA and studied patients without comorbid medical disorders (eg, chronic obstructive pulmonary disease, heart failure, obesity-hypoventilation, opioids for chronic pain).

A variety of devices are available for HST, each with potential strengths and weaknesses. In general, simple equipment provides fewer channels and potentially less data to interpret, whereas more complex equipment can record multiple channels but can be more cumbersome to use and interpret. The authors think that the number of channels on a given device is less relevant than the sensitivity and specificity of the device and the clinical outcomes that a given device can achieve. Thus, the classification system based on number of channels, for example, level 2 versus level 3, is not particularly helpful.

Given the appropriate reliance on home testing, many subtleties are worth mentioning:

a. Given that home testing rarely monitors body position in a robust manner, positional therapy becomes hard to implement in the HST era. Positional therapy can be useful for patients who are intolerant of continuous positive airway pressure (CPAP) or as an adjunctive therapy in patients with partial response to therapies such as weight loss or oral appliance therapy. Thus, in-laboratory testing or other methods of position monitoring may have a role for select patients.
b. Respiratory events may have varying impact depending on whether they occur during REM sleep versus NREM sleep. Because REM sleep is characterized by physiologic variability, some have argued that respiratory fluctuations during REM sleep may not have major consequences. On the other hand, some recent data do support clinically important impact of respiratory events during REM sleep.[12,13] Moreover, some patients experience profound desaturations during REM sleep, presumably as a result of skeletal muscle atonia in accessory respiratory muscles. These profound desaturations are unlikely to be physiologic and thus likely require therapy. As a result, CPAP therapy is often prescribed for both REM and NREM events, making the distinction during diagnostic testing between these 2 states less important clinically.
c. Because most HST devices do not monitor sleep, the devices work on the assumption that the total recording time is actually the total sleep time, that is, that the patient sleeps 100% of the night. As a result, the apnea hypopnea index (AHI) as judged by HST can underestimate the actual AHI, particularly among patients with reduced sleep efficiency. For example, a patient with 50% sleep efficiency who has an AHI of 4/h may actually have an AHI = 8/h if the impact of poor sleep quality was addressed. Thus, the interpretation of HST must be made cautiously in patients with comorbid insomnia or in patients who report poor sleep quality during the recording.
d. When sleep is not monitored, the HST-reported AHI may underestimate hypopneas that terminate as arousals from sleep. In particular, younger and leaner patients who have normal cardiopulmonary function (ie, normal lung volume, alveolar-arterial gradient), and thus less prone to oxygen desaturation for any given reduction in airflow, may not exhibit frequent (eg, >3%) desaturation events but may still have sleep fragmentation. These events may not meet criteria because arousals cannot be scored on most home devices. Home devices that do assess sleep stages and arousals may thus have additional value over those that ignore sleep staging.

Novel Approaches to Screening and Monitoring Sleep Apnea

For the large-scale screening for sleep apnea, even the most accurate HST is limited because of the availability of equipment. For longer-term monitoring of sleep apnea, in the era of patient-directed health management, the requirement for sensors to be placed on the body is an additional limitation. Novel screening approaches typically do not measure directly the key features of sleep apnea (airflow, oxygen

levels, electroencephalogram [EEG] arousal) but instead rely on surrogate measurements with a reduction in accuracy as a tradeoff for broader applicability.

Snoring and breathing sounds

Many patients with OSA present initially with witnessed abnormal breathing sounds such as snoring and gasping at night. On the basis that OSA is audible, researchers suspect that sleep apnea might be identifiable by listening to at-risk patients breathe during sleep. Evidence to date suggests that indeed sleep apnea may be distinguished from nonapneic snoring by variations in snoring sound intensity with cyclic apneas and hypopneas. Harnessing this information with the recording and advanced analysis of respiratory sounds is arguably the most promising approach to large-scale screening for sleep apnea. Given the broad availability of mobile telephone devices with sufficient computational power and microphones, the current challenge lies in the development, implementation, and validation of robust tools to screen for sleep apnea that are applicable in the home and effective across device platforms. Although no such validated approach currently exists, investigators are enthusiastically developing this technology.

A popular approach has been to examine several candidate features of snoring/respiratory sounds across the night and use these in statistical models to select the most useful features to predict (yes or no) whether a patient has sleep apnea (based on concurrent gold-standard polysomnography recordings).[14] A potential limitation of this approach is that apneas/hypopneas are not identified on an event-by-event basis, but by global features that correlate with OSA. A more powerful approach may be to identify which features specifically relate to individual respiratory events. In this context, a relatively simple approach to event detection, used by Nakano and colleagues,[15] made use of the concept that apneas/hypopneas are generally accompanied by relative dips and surges in sound power. Using a mobile smartphone placed on the chest, the frequency of 3-dB dips in time-averaged sound power (50–2000 Hz, 20-second averaging time) were counted and compared with the frequency of OSA events, yielding a relatively accurate means to screen patients for sleep apnea ($r = 0.94$, receiver operating characteristic area = 0.92). Importantly, this accuracy was achieved in a sleep laboratory, without the influence of sounds from a bed partner or the home environment. Although the challenges of unsupervised use outside the laboratory setting have not yet been overcome, the use of snoring sounds as a screening tool has tremendous potential. Central apneas are likely to represent a separate challenge because their sound characteristics are presumably quite different from those of OSA. Future methods may use multiple sound features to identify individual respiratory events more accurately.

Electrocardiogram

The recording of electrocardiograms (EKG) via Holter monitors or implantable cardiac devices is used extensively in the diagnosis and monitoring of cardiovascular diseases. Given that sleep apnea promotes cardiovascular disease, and vice versa, screening for sleep apnea in this at-risk population is of major interest. Fifteen years ago, Physionet and Computers in Cardiology proposed a challenge to the field to develop techniques to detect sleep apnea on an epoch-by-epoch basis, and to classify individuals as apneic or nonapneic using EKG alone.[16] The resulting methods, and those developed thereafter, have illustrated that the EKG provides a rich source of information for the identification of individuals with likely sleep apnea.

The EKG signal varies with respiration in 2 primary ways. Tidal respiration increases lung volume and the increased thoracic gas volume, thereby raising the thoracic electrical impedance, and in turn, reducing the amplitude of the EKG signal; alterations in the axis of the heart relative to the electrodes may play a further role. Thus, tracking the amplitude of the QRS complex across breaths (EKG-derived respiration) provides a means to observe the cyclic changes in tidal volume that characterize sleep apnea.[17] Heart rate also varies in a cyclic manner in concert with the sleep apnea cycle and provides additional information that can be used for sleep apnea screening[18,19]; day-night differences in heart rate variability may also be of utility.[20] Combined fluctuations in heart rate and EKG amplitude can yield surprisingly accurate classification of sleep apnea.[17,19,21,22] Further research is required, however, because it remains uncertain whether the available methods have utility across patients with a variety of cardiovascular comorbidities and accompanying differences in cardiac rhythm (eg, ectopic beats), heart rate variability, or the presence of paced beats (eg, in heart failure).[23]

Motion detection

The use of accelerometers to quantify motion has become widespread in the last decade across multiple fields. Since the 1990s, motion detection in the form of an actigraph worn most commonly on the wrist has been used to assess rest periods

(presumed sleep) in the field of sleep.[24] For the purpose of sleep apnea diagnosis, however, actigraph determination of sleep duration may not provide much additional accuracy when coupled with HST devices (number of events per hour of sleep),[25,26] possibly given difficulties detecting arousals or wakefulness within an extended sleep period.[27] Nevertheless, motion detection may be applied to assess the dynamic respiratory movements and screen for sleep-disordered breathing.[28,29]

AUTOMATED AND COMPUTER-ASSISTED SCORING TECHNOLOGY

Sleep technicians have generally scored in-laboratory polysomnographic recordings manually. With the move toward home testing, there is less of a need for sleep technicians to perform manual scoring of sleep. Home testing devices have automated algorithms in some cases that are reasonably accurate, although review of raw data can often be revealing in the context of artifacts. Efforts to make in-laboratory polysomnography more useful have included attempts to garner more information than just the AHI and have involved efforts to automate or partially automate scoring of the data.

The automated versus manual approaches have associated risks and benefits. Proponents of the automated approach cite data regarding reproducibility of computer algorithms versus human judgment. In addition, human fatigue during scoring is not an issue with automated approaches. Moreover, automated systems can be considerably faster and cheaper than human technicians, allowing scalable approaches to be applied to large numbers of patients. Proponents of manual approaches point to the existing gold standards, which have been used to develop current guidelines. In addition, human experience can be valuable because artifacts that can be identified easily by inspection may "fool" computer algorithms if not adequately trained. Some have also argued that loss of employment for sleep technicians may have a major detrimental effect on the field, even though their efforts could perhaps be redirected to assisting with follow-up and PAP adherence. As the automated algorithms improve, they are being gradually adopted clinically, although the utility of human judgment and experience is still valued. Thus, semi-automated or computer-assisted techniques for scoring sleep studies are likely to become the standard in the future.

Sleep State and Arousals

Computational measurement of EEG has long been used to stage sleep and detect arousals. Most commonly, methods have used EEG spectral analysis. Here two papers are briefly highlighted. In a small number of participants, Asyali and colleagues[30] demonstrated that arousals from sleep could be detected automatically using absolute beta power (16–25 Hz), an EEG frequency range that was preferable in comparison to lower frequency bands (delta, theta, alpha). Recently, Younes and colleagues[31] quantified EEG power in 3-second epochs and assigned each epoch 4 values based on the delta, theta, alpha, and beta powers (in deciles). For each combination of EEG power deciles (from [0, 0, 0, 0] to [9, 9, 9, 9], lookup tables are proprietary, not provided), the likelihood of occurring during technician-scored wake was calculated. These values have been validated to predict sleep or wake with high accuracy versus traditional 30-second technician-scored epochs. The method has been incorporated into a system to both stage polysomnographic studies and score respiratory events.[32] A potential weakness of both approaches is the reliance on absolute EEG power, such that a smaller amplitude signal, for example, due to electrical properties of the scalp or lead impedances, will reduce the EEG power in all bands and thereby affect the estimated sleep stage. The authors expect further development of proprietary and publicly available techniques to robustly quantify sleep using computational analysis of the EEG in the coming years.

Respiratory Events

Compared with the detection of sleep stage, automated assessment of respiratory events appears relatively straightforward. However, several major impediments remain. First, apneas and hypopneas are defined typically as a 30% and 90% reduction in airflow from a preceding baseline level (noting that signal amplitude may drift overnight if airflow sensors are not maintained precisely in place). Nevertheless, during cyclic breathing, there is no clear baseline level. Thus, manual scorers and automated systems will vary simply because of the use of different definitions of baseline respiration. Novel approaches are needed to ascertain what baseline eupneic ventilation is (eg, the ventilation that maintains normal arterial blood gases). Second, respiratory events are usually assessed using nasal pressure rather than true airflow via a pneumotachograph and full face mask (or nasal mask with the mouth confirmed to be closed). Nasal pressure (Pnasal) is related to true ventilation (Vflow) via an approximately square relationship ($Pnasal \approx k.Vflow^2$) with different coefficients for inspiration and expiration.[33]

Some systems use a square-root transform of nasal pressure to approximately linearize the signal to better relate to the relative changes in Vflow. This approach, however, may overestimate the flow signal at small amplitudes such that further improvement is warranted. Third, the classification of apneas and hypopneas as either obstructive (flow is reduced due primarily to upper airway narrowing) or central (due to reduced neural drive) remains a major challenge. In the absence of measures of diaphragm electromyogram or esophageal/epiglottic pressure, manual scorers rely on nuances in nasal pressure flow morphology (flattening, scooping, flutter, increase in inspiratory time), or phase shifts or paradox seen between the thoracic and abdominal belts, to determine whether a hypopnea is obstructive rather than central. Automation of these methods is still in its infancy.[34]

APPROACHES TO DIAGNOSING SLEEP APNEA PATHOPHYSIOLOGY FOR GUIDING TREATMENT DECISIONS

Personalized medicine has become a major source of discussion for many diseases, including OSA. Recent evidence has supported the notion that many mechanisms underlie OSA and that identification of these underlying endotypes can help to individualize therapy for a given individual. OSA is now recognized to be a disease of anatomic compromise with variable underlying pathophysiological mechanisms, including compromised upper airway dilator muscle activity, unstable ventilatory control (elevated loop gain), and low arousal threshold, among others. At least in theory, therapies to address these underlying mechanisms may be particularly effective in resolving apnea. Some patients may have multiple underlying mechanisms, in which case combination therapies would be predicted to eliminate apnea. For example, patients that compromise primarily at the level of the velopharynx would be predicted to respond well to uvulopalatopharyngoplasty. Similarly, patients with dysfunction in the upper airway dilator muscles may be particularly good candidates for hypoglossal nerve stimulation. Currently, OSA diagnostics yield only an AHI as an imperfect measure of sleep apnea severity but make little attempt to provide pathophysiological insight.

Here the literature knowledge is summarized, relating 4 key pathophysiological phenotypes of sleep apnea to the clinical manifestation of this disease. Overall, there is considerable evidence that pathophysiological phenotypes manifest clinically in recognizable ways. Novel methods to noninvasively quantify these phenotypes are needed to enable judicious matching of patients to emerging therapies.

Upper Airway Collapsibility: Severity

The gold-standard functional assessment of upper airway collapsibility is the critical collapsing pressure (Pcrit) measured in the anesthetized state, or during sleep when the upper airway dilator muscles are minimally active. Pcrit is defined as the level of nasal (upstream) pressure at which the upper airway collapses and is the X-intercept of a peak-flow versus nasal pressure plot. Alternatively, collapsibility can be assessed by calculating the Y-intercept of such a plot, providing the level of peak flow (or ventilation, Vpassive) at atmospheric pressure under maximally passive conditions.

Several investigators have attempted to estimate collapsibility using simpler and more clinically relevant measures, generally during wakefulness. These measures include, but are not limited to, measures of body habitus (neck circumference, body mass index), visual assessment of the upper airway (Mallampati/Friedman scores), and measures of patency/collapsibility during wakefulness (acoustic pharyngometry,[35] negative pressure pulses during expiration[36]).

The potential utility of several polysomnographic indicators of a more collapsible *passive* upper airway are highlighted:

- In comparison to NREM sleep, upper airway dilator muscles are less active during REM sleep.[37] The severity of REM sleep apnea (AHI) is more closely related to passive collapsibility than the severity of sleep apnea during NREM.[38–40] Likewise, at the other end of the spectrum, patients with primarily central sleep apnea (and presumably minimal collapsibility) typically exhibit a low AHI in REM. REM AHI may therefore be a marker of passive collapsibility.
- A greater therapeutic CPAP requirement is also expected to indicate a more collapsible upper airway. On CPAP, upper airway muscle activity is minimal. The therapeutic CPAP therefore reflects the level that slightly exceeds the value on the passive pressure flow curve that yields flow limitation.
- Patients whose sleep apnea resolves with lateral positioning (supine predominant) have a less collapsible upper airway than those with sleep apnea in both the supine and the lateral positions.[41] Indeed, supine predominance, as an indicator of milder collapsibility, is modestly predictive of successful oral appliance therapy.

A severely compromised passive collapsibility has been found previously to explain the failures of nonanatomical therapies targeting loop gain.[42]

Upper Airway Muscle Compensation

During sleep, increased upper airway resistance leads to an increase in ventilatory drive, which stimulates the upper airway dilator muscles to respond. In some individuals, these muscles effectively yield collapsibility (*active* collapsibility vs passive collapsibility) seen as an improvement in ventilation. The active collapsibility is actually a complex variable that is determined not only by the passive collapsibility but also by (1) the increase in muscle activity for a given increase in neural ventilatory drive (muscle responsiveness); (2) the ability of muscle activity to stiffen the airway and improve ventilation; and finally, (3) the ventilatory drive stimulus that can be provided without arousal from sleep (arousal threshold). Also, if the airway is not maximally activated (ie, just before arousal), the measurement may also be affected by loop gain (higher loop gain will yield more drive and thus more activation for any given drop in airflow).

Putative measures of active collapsibility or muscle compensation include the following:

- Apneas versus hypopneas. Compared with patients exhibiting hypopneas, those who consistently exhibit apneas (zero airflow at atmospheric pressure), even when the upper airway dilator muscles are maximally activated (just before arousal), by definition, have a severely compromised active collapsibility (active Pcrit >0).[43] The relative proportion of obstructive apneas versus obstructive hypopneas may therefore reflect the active collapsibility.
- REM predominant sleep apnea, where sleep apnea is more severe in REM versus NREM, is likely to be an indicator of effective upper airway compensation.[40]
- Rather than an a compensatory improvement in ventilation, some individuals exhibit a paradoxic reduction in airflow when ventilatory drive is increased, presumably a combined result of insufficient dilator muscle activation and a highly compliant upper airway. This behavior is referred to as *negative effort dependence*[44–47] (more effort yields less airflow), and this tendency may be detected within-breaths as a substantial reduction in airflow at mid-inspiration versus the peak flow. Therapies that increase ventilatory drive (eg, acetazolamide) are likely to be countereffective in this patient subgroup.

Evidence for the predictive utility of active collapsibility includes the recent finding that a greater active anatomy is a strong predictor of the response to nonanatomical therapy (loop gain, arousal threshold).[48] In principle, increasing the arousal threshold will have a maximally beneficial effect when the upper airway muscles are effective. Reducing loop gain will also have maximal utility in patients that are able to sustain a reasonable level of airflow.

Upper Airway Collapsibility: Site

Alongside the severity of pharyngeal collapse, there is an increasing awareness of the heterogeneity of the sites and structures involved. These structures include the velum or soft palate, the lateral walls, the base of the tongue, and the epiglottis.

Evidence is accumulating that the site of collapse is important for determining the effectiveness of non-CPAP anatomic therapies. Based on gold-standard upper airway visualization, available data indicate that oral appliances work most effectively in patients with tongue-base collapse,[49] but not those with isolated velum or epiglottic collapse.[50,51] Patients with isolated velum collapse may have better outcomes following uvulopalatopharyngoplasty.

Here 2 noninvasive approaches to detecting the site of collapse are highlighted. First, snoring sound analysis has been used to distinguish between velum and tongue-base collapse. Velum involvement exhibits a characteristic large-amplitude, low-frequency, narrow-band fluttering, whereas tongue-based collapse yields a high-frequency broad-band signal.[52,53] Second, the intrabreath flow shape may also consist of useful information on the site of collapse. For example, patients whose inspiratory flow pattern appears as a simple flat-top (Starling resistor) tend to exhibit tongue-base collapse (a larger, noncompliant structure), whereas those with a substantial reduction from peak flow to midinspiratory flow (degree of *negative effort dependence*) tend to exhibit collapse of highly compliant structures (velum, lateral wall, or epiglottis).[54]

High Loop Gain

Beyond upper airway physiology, a key trait causing sleep apnea is the sensitivity and stability of the ventilatory control system, a feedback loop that acts to maintain ventilation and arterial blood gases near an equilibrium. This sensitivity/stability is typically quantified by the loop gain, which reflects the increase in ventilatory drive that occurs due to a reduction in ventilation. In the absence of

a collapsible upper airway, an excessive loop gain results in central sleep apnea. However, increasing loop gain can cause OSA in those with a collapsible airway.[55–58]

The authors recently developed a method to measure loop gain from the overshoot-undershoot ventilatory pattern observed in routine polysomnography. In essence, the method fits a simplified ventilatory control system model to the available data. For any given patient, the best model is that which most accurately converts the reduction in ventilation during apneas/hypopneas to the observed ventilatory drive overshoot seen after each apnea/hypopnea. The method showed a promising ability to detect a high loop gain and predict responses to oxygen and acetazolamide.[59] Further work is needed to (1) more accurately define baseline ventilation, flow-limited breathing, and effects of arousals on ventilatory drive; (2) validate estimated ventilatory drive with respect to gold-standard drive measured with diaphragm muscle activity; and (3) to extend the approach to estimate the remaining traits.

There are several additional indicators of a high loop gain:

- The presence of central or mixed events[60]
- Shorter events and faster cycling between events[59]
- NREM dominant sleep apnea (NREM AHI > REM AHI)
- Relative hypocapnia[61]

In patients with central sleep apnea, the duration of central apneas as a fraction of the cycle period (time from the start of one event to the next) is a direct reflection of the underlying loop gain.[62] This approach has been used to detect those with extremely high loop gain and predict the acute failure of CPAP in patients with heart failure,[62] and the persistence of central events despite 4 weeks of therapy in OSA patients with complex sleep apnea.[63]

Arousal Threshold, Sleep State Instability

Most patients, even those with severe sleep apnea, exhibit stable breathing for some period of the night. Stable breathing often occurs in slow-wave sleep, likely due in part to an increase in the ventilatory drive that can be tolerated before arousal (increased arousal threshold compared with stage N2). In fact, there is a subset of patients with a low arousal threshold or sleep instability, whose sleep apnea may be ameliorated with hypnotics/sedatives to increase the arousal threshold.[64] In principle, raising the arousal threshold has 2 effects on sleep apnea physiology: (1) it allows a lower level of ventilation (eg, more severe collapsibility) to be tolerated, and (2) it allows a greater level of ventilatory drive to build up, providing a greater stimulus for upper airway muscle activation.[56,65] It is also likely that this treatment approach will be most successful in those with a relatively good active collapsibility. Drugs that promote slow-wave sleep may also be advantageous in these patients.

The authors recently developed a clinical score to identify patients with a low arousal threshold, which incorporates just 3 readily available parameters. One point is given for each of nadir saturation greater than 82.5%, the fraction of hypopneas (vs total respiratory events) greater than 58.3%, and AHI less than 30 events per hour; a score of 2 or greater correctly predicted a low- or high-arousal threshold in 84% of patients.[66] Further investigation is needed to test whether this approach helps to explain responses to therapies that increase the arousal threshold and stabilize sleep in patients with sleep apnea.

SUMMARY

A host of new ideas and advances in technology has the potential to reshape the way clinical sleep medicine is practiced. Advances in analysis of respiratory sounds and EKG will likely enable widespread screening for sleep-disordered breathing. The use of automated scoring algorithms seeks to improve the resources required and consistency of diagnoses. Personalized medicine is one step closer: methods are rapidly being developed to determine the mechanisms of sleep apnea and determine what options are best suited for individual patients.

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