

A close-up, artistic photograph of a woman's face, tilted slightly. Her eyes are closed, and her expression is peaceful. Several autumn leaves in shades of yellow and orange are scattered around her face, some resting on her forehead and cheeks. The background is a soft, out-of-focus green, suggesting foliage.

SLEEP INTERNATIONAL

THE GLOBAL JOURNAL OF SLEEP MEDICINE

Sleep Roundtable
Executive Profiles
Sleep Apnea
Negative Expiratory Pressure
Sleep Studies

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study published in the journal SLEEP finds that people with OSA are at an increased risk of having cardiovascular disease. The study, which attributes the increased link between OSA and cardiovascular disease to heightened recognition and perhaps a rising prevalence, found mounting data suggesting a potentially important causative role of OSA in cardiovascular disease, particularly systemic hypertension, bolstered by well-described pathophysiologic responses to apnea and hypopneas. Recently published longitudinal cohort studies have strengthened previously recognized associations with stroke and mortality from cardiac events. According to the researchers, there is abundant physiologic evidence implicating OSA in perpetuating, if not enticing, heart failure. In addition to their association with systemic hypertension, OSA-related stressors, including hypoxemia, increased sympathetic drive, acute surges in blood pressure, and mechanical effects of intrathoracic pressure swings, have varying effects on myocardial oxygen supply and demand, particularly in the already compromised heart..

ON YOUR MARKERS

Recent research shows sleep disruptions as potential markers of prothrombotic cardiovascular risks. In a study from the University of California San Diego, researchers performed full-night polysomnography in 135 unmedicated patients, who had no history of sleep disorders. Three different types of antigens, morning fasting plasma levels of von Willebrand Factor (VWF), soluble tissue factor (sTF), and plasminogen activator inhibitor (PAI-1), and D-dimer were gathered and determined. Also, statistical analyses were adjusted for age, gender, ethnicity, body mass index, blood pressure, and smoking history. Results showed that measures of sleep fragmentation and sleep efficiency were related to VWF and sTF, and apnea-related measures were related to PAI-1. Researchers conclude that sleep disruptions, even in a relatively healthy population, are associated with prothrombotic changes. This study appears in the March issue of CHEST, the peer-reviewed journal of the American College of Chest Physicians.

KEEPS ON TICKING

Researchers have gained new insight into the workings of biological clocks, according to Medical News Today, citing a recent study at the University of Georgia. A UGA research team discovered how three genes in *Neurospora crassa* - bread mold - make such a clock tick at the molecular level. The research describes how to identify genetic networks and show how the tools of systems biology can yield insights into what makes the clock tick. The discovery also has broad implications for understanding biochemical signaling and other regulatory processes in cells. Before this research, there has been little experimental support for any of the many existing models of the biological clock. The UGA team studied actions of three genes in *Neurospora*: white-collar-1, white-collar-2 and frequency. The team found that the products of these three genes constitute the building blocks of a biological clock. The discovery crosses species boundaries, since human beings have a gene analogous to white-collar-1.

SIT UP STRAIGHT

When a person lies down, a small amount of fluid displaced from the legs to the base of the neck can narrow soft tissue around the throat and increase airflow resistance in the pharynx by more than 100 percent, predisposing the person to obstructive sleep apnea. So says a report published in the American Journal of Respiratory and Critical Care Medicine.

News

□ June-July 2007

INFLAMED

Patients with moderate to severe sleep apnea who have significantly higher serum levels of inflammatory markers that serve as precursors to coronary artery disease, as well as lesions associated with silent brain infarction, have an elevated risk of stroke, according to a group of Japanese medical researchers, reported Medical News Today. Researchers at Showa University School of Medicine in Tokyo studied silent brain infarction, brain tissue death from lack of blood supply, in 50 male patients with obstructive sleep apnea. The researchers also examined the effects of three months of treatment with nasal continuous positive airway pressure (nCPAP) on serum inflammatory marker levels in 24 male patients who had moderate to severe OSA. Research results showed that occurrence of stroke in patients with OSA is likely preceded by subclinical cerebrovascular disease, or silent brain infarction, which is detectable with brain magnetic resonance imaging (MRI). The lesions identified as silent brain infarction were either wedge-shaped or round and showed up in brain white matter on MRI scans. The investigators noted that cardiovascular disease is commonly characterized by ongoing inflammatory responses that can enhance platelet activation and increase the prevalence of silent brain infarction. They found that use of nCPAP, a treatment designed to reduce the number of episodes of breathing stoppage associated with sleep apnea, significantly lowered serum levels of C-reactive protein and the levels of the two platelet-activating proteins, all associated with cerebrovascular disease. As such, nCPAP may be an important treatment intervention for decreasing the cerebrovascular risk in this susceptible population of obstructive sleep apnea patients.

EAT YOUR HEART OUT

Cardiovascular disease can pose a threat to both men and women. While a diet rich in fat and high in cholesterol as well as lack of exercise can contribute to cardiovascular disease, a

Researchers measured leg fluid volume, neck circumference and airflow resistance in the throats (pharynx) of 11 healthy, non-obese subjects while they lay on their backs. Next, the researchers applied a lower body positive pressure device (anti-shock trousers) for five minutes to displace fluid from the legs to the neck area. The study pointed out that a factor not ordinarily considered when dealing with apnea is fluid accumulation at the nape of the neck and around pharyngeal soft tissue. Obstructive sleep apnea is very common in fluid-retaining states such as heart failure, renal failure and peripheral edema of unknown cause. Research data showed that displacement of a small amount of fluid such as 340 ml, about 12 ounces, from the legs is sufficient to cause a 102% increase in airflow resistance of the pharynx in healthy, non-obese subjects. According to the authors, when the pharynx narrows in obstructive sleep apnea and in healthy subjects, airflow resistance increases as the person transits from wakefulness to sleep. Consequently, an even greater degree of fluid shift into the neck during sleep would cause further pharyngeal airflow obstruction. The authors noted that further studies would be required to determine whether fluid displacement increases pharyngeal obstruction as a person moves from upright to a recumbent position, especially when the person does not have a predisposing condition.

REMEMBER

Patients with obstructive sleep apnea may improve their memory by using CPAP, according to a recent study in CHEST. The study showed that the majority of patients with OSA who were memory-impaired prior to treatment demonstrated normal memory performance after 3 months of optimal CPAP use. The study also showed that memory improvement varied based on CPAP adherence. Patients who used CPAP for at least 6 hours a night were nearly eight times as likely to demonstrate normal memory abilities compared with patients who used CPAP for 2 or fewer hours a night. Researchers examined the degree to which varying levels of CPAP adherence improved memory in 58 memory-impaired patients with clinically diagnosed OSA. All patients underwent cognitive evaluation involving verbal memory testing prior to initiation of CPAP and at a 3-month follow-up visit. Patients were prescribed CPAP machines, and adherence was covertly monitored using internal microprocessors within each device. At baseline, all patients were found equally impaired in verbal memory, with the average verbal memory score being approximately 2 SD below the mean for all participants. Following 3 months of CPAP treatment, 21 percent of poor users, 44 percent of moderate users, and 68 percent of optimal users demonstrated normal memory performance. Compared with poor users, optimal users of CPAP were nearly eight times as likely to demonstrate normal memory abilities. Overall, the average verbal memory score for all patients improved approximately 1 SD.

ZAP THE ZZZs

Prescription sleep aids may do little to improve the use of continuous positive airway pressure among patients with obstructive sleep apnea. A recent study by researchers at the Naval Medical Center in San Diego, CA found that patients with OSA who were given prescription sleep aids were no more likely to use their CPAP machines than patients with OSA taking a placebo. Researchers noted that CPAP treatment improves daytime alertness and quality of life for most patients with OSA and may prevent some of the long-term complications of this disorder, including heart attacks and strokes, but that many

people find CPAP difficult to use. People with a good initial experience are more likely to use CPAP regularly. As such, the research team hypothesized that a sleeping pill might help new CPAP users adjust to sleeping with the equipment and promote long-term usage. To determine the effect prescription sleep medications have on CPAP compliance, researchers compared CPAP use among 72 newly diagnosed male patients who were referred for CPAP treatment. All patients participated in standardized CPAP training and were randomized to receive zolpidem, a placebo pill, or standard care with no sleeping pill or placebo. Patients taking zolpidem or placebo were instructed to take one pill each night, 30 minutes prior to bedtime for the first 14 days of treatment. During the four-week trial, CPAP use was recorded by an internal data chip. Compared with the placebo pill and standard care groups, the zolpidem group did not show greater CPAP usage in terms of total days used or average time used per night over the course of four weeks. When the initial 14 days of CPAP treatment were analyzed separately, there was also no difference in number of days used or average nightly use. Despite results, researchers believe prescription sleep medications, when used correctly, may prove helpful for a subset of patients with OSA. Upon completion of the trial, all patients showed significant symptom improvement on the Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire. Baseline demographics revealed no difference in age, body mass index, ESS, FOSQ, nadir oxygen saturation, or CPAP pressure setting among the three groups. Despite randomization, the standard care group had a higher apnea/hypopnea index than the other two groups.

SLEEP PRODUCTS

TAKING LICENSE

Respironics, Inc announced that the FDA granted 510(k) clearance of the BiPAP autoSV device, which is intended to provide noninvasive ventilatory support to treat adult patients with OSA and respiratory insufficiency caused by central and/or mixed apneas and periodic breathing. The BiPAP autoSV device was previously launched in Europe and Canada and to date the market acceptance of this product has been very positive. This product is designed for managing complicated sleep-disordered breathing patients and combines a number of Respironics' core technologies to recognize and respond to patients' changing pressure needs. The BiPAP autoSV device delivers optimal therapy for these complicated sleep-disordered breathing patients utilizing a multi-level algorithm. On a breath-by-breath basis, the revolutionary algorithm utilizes Respironics' core technologies to adjust pressure support upon detecting a sleep event, such as an apnea, hypopnea or periodic breathing, to stabilize the patient's breathing pattern. This algorithm also calculates the patient's spontaneous breathing rate and will automatically trigger a breath for the patient should a sleep event occur. This device also combines Respironics' proven BiPAP technology, Encore Pro Data Management Software, Digital Auto-Trak Sensitivity, integrated alarms and optional integrated heated humidification. Contact respironics.com.

PHONE HOME

Cleveland Medical Devices Inc (CleveMed) announced that it recently conducted the first virtually attended sleep study using mobile phone broadband internet service from a subject's home. The study was performed using CleveMed's proprietary wireless

technology and medical communication system to provide real-time transmission of polysomnography data. This new technology combined with CleveMed's established wireless PSG systems can now allow a technologist to perform virtually attended sleep studies from almost anywhere in the world. The Crystal Monitor 20-B is a wireless 14 channel PSG system for diagnosing sleep-disordered breathing. Unlike sleep screeners that only collect a limited number of physiological signals, the Crystal Monitor 20-B is a complete PSG system that collects all of the relevant data needed for proper sleep diagnosis including EEG, ECG, EMG, EOG, airflow, snore, thoracic and abdominal respiratory efforts, body position and pulse oximetry. Because a large number of homes in the United States and around the world still are without high speed internet access, CleveMed's system utilizing the mobile phone broadband network allows for virtually attended studies to be performed in almost any setting, regardless of the patient's personal access to the internet. During the virtually attended study, a sleep technologist monitored the PSG signals and video in real-time from several miles away. Because the data is monitored in real-time, the sleep technician was able to view the data in a supervised manner that is comparable to a study done in the sleep lab where the sleep technologist monitors the patient in the next room. "The diagnostic power of in-lab evaluation, combined with the convenience and cost effectiveness offered by the home environment, would benefit millions of patients who suffer from sleep disordered breathing, their doctors and the insurance companies," said Hani Kayyali, CleveMed President. Potential applications include pediatric studies, pharmaceutical research for drug development, and studies for patients who are unable to go to sleep labs.

SLEEP ROUNDTABLE

Actigraph

John G. Schneider

John Schneider is with ActiGraph.

What products do you offer for diagnostics?

We have two diagnostic products right now, both activity monitors. Our main product is the ActiGraph GT1M for sleep monitoring. The other is our brand new ActiTrainer, which incorporates heart rate data from world renowned Polar® with the ActiGraph's physical activity data.

What are the latest trends for such products?

The trends for using the ActiGraph are for doctors to use them for screening patients who complain about sleep problems, pain management, exercise compliance, and rehabilitation efficacy.

How has technology changed in the past several years?

The changing technology has helped us in making our instruments much easier to use, reducing their size and cost, as well as making them more reliable.

Please discuss your company's current R&D efforts.

We are presently pursuing wireless technology for our ActiGraph products. We see many more uses and opportunities for a wider market by developing this capability and our main R & D efforts are in that area.

How does your product deal with electronic records management?

From the very start ActiGraph's products have been electronically downloadable using the standard ASCII (text) format. This allowed the Centers for Disease Control & Prevention to provide over 2 gigabytes of data for public release on the first two years of its national research program (NHANES) while using our ActiGraph physical activity monitor.

What clinical trials have been performed on your device?

We have had numerous trials and validation on the ActiGraph. Presently the University of South Carolina is investigating the ActiGraph's ability to accurately score sleep while being worn on the waist. Though the study is not yet finished, it appears that the finding will be favorable to actigraphy. This could allow physicians to study both daily activity and sleeping without having the patient move the ActiGraph from waist to wrist.

What is the level of clinical evidence supporting the use of your device?

The AASM has presented many papers and articles over the last 3 to 4 years indicating the wider use and acceptance of actigraphy in sleep clinic settings. We are also seeing a rapid increase in sleep clinics and general doctor's offices requesting information and purchasing the GT1M ActiGraph.

Does your product have portable monitoring capability?

Actigraphy is the ultimate in portability for sleep monitoring. The ActiGraph can be worn similar to a watch on the wrist or to a pager on the waist – free of any cords. The unit can be initialized and simply given to a patient to be worn overnight. The device is then returned and the data downloaded by either a clinician or physician.

How can your product improve patient compliance?

The ActiGraph acts as an impartial jury. It measures movement, so if you prescribe an exercise regimen, the data will show what movement was made during the wear of the device. If it is either not worn, or the patient is not compliant, the data will show the lack of activity, both with number charts and pictorial graphs.

How can your product improve patient outcomes?

A patient who knows they are being monitored will more than likely do as prescribed, and thus improve their outcome and/or comply with doctor orders. In sleep analysis, the ActiGraph will clearly tell whether the patient has a sleeping problem or not. This will prevent longer analysis periods which will, in turn, benefit both patient and sleep clinics.

Please discuss cost-savings/benefits for both purchasers and patients using your products.

The use of actigraphy has been granted a temporary billing code of 0089T. This would provide the purchasers a means of billing insurance for reimbursement, which would save patients from having to pay for the ActiGraph out of their own pocket. Another cost saving benefit to the patient would be if the sleep scoring from the ActiGraph (used as a precursor to more invasive sleep diagnostics) shows the patient does not have a sleep problem they would not have to pay for a night in the sleep clinic. With wider use the ActiGraph could eventually become a screening device for the general public, possibly increasing the need for full sleep clinic analysis and weeding out those without sleep problems.

Viasys Healthcare, Inc.

Steve Birch

Steve Birch is Director of Marketing, Sleep Diagnostics and Therapeutics, Viasys Healthcare, Inc.

What products do you offer for diagnostics? What are the latest trends for such products?

VIASYS's SomnoStar Pro sleep diagnostics system is a global leader in sleep disorders center based data acquisition and analysis systems. The SomnoStar Pro is a very capable and flexible system that allows clinicians to configure the system and its output to their needs. The SomnoStar Pro system incorporates respiratory inductive plethysmography (RIP) technology that gives the clinician a uniquely detailed perspective into the patient's respiratory efforts. Calibrated signals help to assess the degree of obstruction and the Flow Volume Loops that are displayed provide a graphical reduction of complex information and allow the clinician to more easily titrate therapy.

One of the trends in polysomnography is focused on improved assessment of upper airway obstruction with the intent to provide improved therapy. Calibrated RIP is one of the more significant advances and there is an interest in volumetric calibration to provide an even better assessment. A second trend is developing in the areas of data management, data transfer and process management. This trend is becoming increasingly important as sleep disorders centers continue to grow and become more networked.

What products do you offer for therapy? What are the latest trends for such products?

VIASYS is currently expanding and developing a complete line of new therapy devices ranging from patient interfaces to CPAP devices and beyond. With the acquisition of Tiara Medical Systems VIASYS can now offer a complete range of patient interfaces, including nasal and full faces masks as well as a direct nasal interface and accessories. The acquisition of Hoffman Laboratories BreatheX CPAP technologies provide us with a platform off which we can launch new compact, quiet and efficient therapy devices. These technologies position us to establish new trends in OSA therapy that allow patients to integrate treatment into their lifestyles. Clearly, the small size of therapy devices is an ongoing trend as are reduced sound level. Compact battery power that affords true portability is another trend that helps patients to use their therapy systems where they are needed.

How has technology changed in the past several years?

Clearly, CPAP systems are getting smaller and the integration of humidification is now expected. Improved comfort of the delivery of pressure has also been seen in some areas, but this has not yet become the standard as it should be.

Please discuss your company's current R&D efforts.

VIASYS has research and development efforts focused on all areas of sleep diagnostics and therapy. Sleep diagnostic development is a continual process that is periodically punctuated with new product releases. A large portion of this R&D effort is invested in evolving the diagnostic software to provide the best product for all of our customers. Multiple teams are working on various efforts in the sleep therapy from

the evolution of our patient interfaces to the development of new therapy devices.

How does your product deal with electronic records management?

The SomnoStar Pro system interfaces to our Lab Manager software for the management and transfer of PSG records. This software allows access to the numerous people that are involved in the collection, scoring, over-reading if needed and report generation and final reporting. Lab Manager also has a DME function that allows the tracking of therapy devices and the management of patients in an on-going fashion.

Please discuss your assistance programs and training programs for purchasers and/or patients.

VIASYS has recently released the V-Care program and it is now available on our VMAX PFT system and the SomnoStar Pro PSG system. This tool allows for remote access to the system for troubleshooting and assistance. This provides the user with real time support that has been otherwise unavailable for PSG systems. Additionally, the VIASYS Clinical Support staff, staffed extensively by registered sleep technicians, is available 24/7 for direct access to address any technical problems that may arise.

Our training programs are extensive and provide for in-house and classroom training on the SomnoStar Pro system. Additionally, we offer mask fitting workshops that qualify for AARC continuing education credit.

The RIP technology that is central to the respiratory monitoring function of the SomnoStar Pro system has been widely tested regarding both the calibration process and the on-going monitoring of breathing patterns. The use of Flow Volume Loops for the monitoring of breathing pattern changes has also been widely studied in the clinical setting.

All of our systems and software releases are tested in the clinical environment prior to release. These tests are conducted with experienced sleep clinicians and are documented to assure the optimal performance of every product.

What is the level of clinical evidence supporting the use of your device?

The RIP technology has been widely studied and level one and two research has demonstrated the function and utility of this aspect of the SomnoStar system. We look forward to working with researchers as our new systems are released to conduct additional research.

Does your product have portable monitoring capability? If so, please discuss.

VIASYS does have two portable sleep monitoring systems in addition to a portable version of the SomnoStar. Additionally we are engaged in the development of new portable sleep monitors to address the growing demand for these systems with technology that interfaces with our existing PSG devices. These systems are compact and possess a feature set that addresses the global need for portable monitoring.

How can your product improve patient compliance?

VIASYS designs all of our therapy products with the patient in mind. We appreciate the challenges associated with regular use of CPAP and strive to find ways to reduce these challenges for the patient. Whether it's a quieter CPAP system or one that can

be powered by a battery, we're designing our product to address the issues that give rise to non-compliance. The BreatheX is one of the quietest CPAP systems on the market. The battery power feature means that you can use your CPAP system in almost any setting.

How can your product improve patient outcomes?

Improved patient outcomes are vitally important to the future of sleep medicine and to our continued ability to provide therapy to patients. The impact of non-treatment or inadequate treatment is that the co-morbidities that appear to arise from OSA will develop into a costly problem for global healthcare delivery. These problems, including heart disease, diabetes and metabolic disorder represent a growing healthcare expense. We believe that CPAP technologies that are easily integrated into patient lifestyles and that provide comfortable treatment are most likely to be complied with. The BreatheX technology is quiet, comfortable to breathe on and is highly efficient such that it can be used for up to 12 hours on a small battery pack. This allows patients to continue to utilize CPAP when they are traveling or are in remote locations. This will help promote continued utilization.

VIASYS provides technologies that deliver a high value to the clinicians and providers as well as patients. Our reliable PSG platform and extensive support system provides maximum up time which reduces cancellations and rescheduling which does result in costs to both provider and patient. On the therapy side VIASYS is continually looking for ways to reduce manufacturing costs while producing a high quality and innovative product. Our R&D efforts are continually looking for ways to provide high levels of functionality at the lowest possible cost. As the adoption of CPAP therapy continues to grow this approach will be increasingly important since the total cost will become a target for payors.

Compumedics

Tom Lorick

Tom Lorick is with Compumedics

What products do you offer for diagnostics? What are the latest trends for such products?

Compumedics offers one of the widest ranges of PSG diagnostic tools in the market. Compumedics has a unique approach to delivering comprehensive solutions by offering a 3 step approach to purchasing the perfect system for each lab. First, choose the fixed, wireless or ambulatory amplifier system that best suits your needs. Second, choose the optimum mix of acquisition, analysis and review packages from our all new Profusion 3 software suite. Third, choose from data handling options including NeXus Lab Management System, Nexus secured remote access, and the level of HIS interface or HL7 connectivity you require. It really is a "pick and choose" solution to scale the right solution from a single bed lab up to a multiple bed, multiple facility installation with worldwide remote review capabilities and full data interface with the Hospital Information System (HIS). And with the continuing interest in home-based PSG diagnostics, Compumedics is established as a market leader from development of our P-Series system used for the Sleep Heart Health Study, to the Somté limited 8 and 5-channel recorders to the all-new 16-

channel SomtéPSG system recently released in Australia and pending FDA market clearance in the USA.

What products do you offer for therapy? What are the latest trends for such products?

Currently Compumedics does not offer therapy products, though we support a variety of data integration options from many existing manufacturers.

How has technology changed in the past several years?

Primarily everything has been driven by two factors, ever increasing computing requirements and the need for paperless, comprehensive data integration. At Compumedics we are working diligently to develop software that takes full advantage of increased computing power, and by developing tools to streamline labs and make the use of our systems easier. Sleep studies are simultaneously becoming simpler (in ease of use) and more complex (in data handling requirements and flexibility). The recent resurgence of interest in automatic scoring processes is another area that Compumedics has anticipated with its current products and ongoing R&D efforts.

Please discuss these R&D efforts.

As stated above, we are constantly evolving our products to meet market needs. For instance, our just released ProFusion3 software extends on the popularity of our renowned diagnostic software by adding features that streamline the workflow in the lab, automate more mundane tasks and add tools that help with the latest lab accreditation requirements. Other projects in the works focus on our presence as a world wide market innovator and the needs of the different healthcare environments in different countries. For instance, while unattended studies are currently not reimbursed in the USA, we have several products in other markets that address this niche in unique ways that allow us to leverage work that has originally been tailored to the USA marketplace.

How does your product deal with electronic records management?

Compumedics introduced our extremely powerful NeXus Lab Management System in 2004. NeXus is a patient-centric product; it allows all data associated with any one patient to be kept in a single record. NeXus is our key to integrating with Hospital HIS systems and for complete paperless lab operation. Through NeXus we offer a complete HL7 connectivity solution that allows us to interface with many of the established hospital systems on the market such as EPIC and Cerner to name only two; in fact Compumedics is one of only two manufacturers currently certified to operate with the US Government VA and VISTA worldwide data records systems.

Please discuss your assistance programs and training programs for purchasers and/or patients.

At Compumedics we believe that the systems can only reach their true potential excellence if the people using them feel comfortable and well trained on all aspects of the system. We provide a variety of solutions including on-site, custom tailored training courses per facility, regional courses and corporate office based training options. Recently we have added a full range of online training for our users so that they can work one-on-one with our trainers in the comfort of their own lab. We don't believe in simply "dropping a system and letting the customer fend for themselves." We offer continuing education opportunities throughout the year. These cost-effective regional

opportunities bring the training closer to our customers and are tailored to meet the needs of the individual attendees.

What clinical trials have been performed on your device?

Compumedics is most proud to have been chosen as the vendor for the Sleep Heart Health Study, with over 20,000 studies recorded; plus many follow-up research trials also selected the Compumedics systems. We are currently working with several facilities on trials that, due to various agreements, cannot be discussed in any detail at this time. Compumedics systems have always been developed to provide the critical data required by researchers' worldwide, and offer flexible software tools such as MATLAB compatibility, Software Developer Kits and data export in a variety of formats.

What is the level of clinical evidence supporting the use of your device?

As we are celebrating our 20th anniversary, and over 10,000 systems installed I think that we have some pretty impressive credentials! However, I'd again point to the Sleep Heart Health Study, as well as our development institutions in Australia and the USA to clearly demonstrate our clinical acceptance.

Does your product have portable monitoring capability? If so, please discuss.

Compumedics offers several models that address portable or ambulatory requirements. Our Siesta802 series allow a lab to be set up virtually anywhere as its Wi-Fi connection eliminates the need for most cabling requirements. Our Safiro is an exceptional ambulatory EEG monitor and finally we have the unique Somte which offers respiratory sleep recording capabilities as well as a complete cardiac analysis package.

How can your product improve patient compliance?

The best way to garner patient compliance in PSG studies is to make the set-up, calibration and data collection routines as unobtrusive and fast as possible, thus allowing the patient to rest for the study. We have designed our software to streamline the patient set-up and in addition offer tools like our exclusive QuikCap PSG. The QuikCap PSG provides faster set-up, faster clean-up and several measures of quality control that can get the patient set-up, and cleaned up faster for a better overall sleep lab experience.

How can your product improve patient outcomes?

Because we are in the diagnostic side of the sleep market, the best thing we can do is provide the highest quality of data, along with the analysis tools to help make an accurate and comprehensive diagnosis. Our NeXus Lab Management System provides many tools to help in tracking and reporting patient outcomes.

Please discuss cost-savings/benefits for both purchasers and patients using your products.

Compumedics has taken the approach that good diagnostics make for good medicine. Therefore we focus on quality data. We offer cost-effective solutions that are scalable. We do not just focus on the cost of the amplifiers but look at time savings, infrastructure reduction, and data integration tools that reduce or eliminate a lot of labor intensive tasks. In order to realize the true value to any lab the goals and desired outcomes have to be evaluated, and the systems and solutions need to be scalable to the specific lab in question. Compumedics has taken the total approach to offer every required diagnostic product from a

single source. Therefore Compumedics is one of the only manufacturers that develops, builds, sells, installs, trains and services everything required for a successful diagnostic lab. We manufacture everything in house from our sensors and amplifiers to our QuikCaps, we write our own software code, and we provide the extensive network and data integration services required in today's modern and increasingly paperless lab. It is our goal to be the one-stop value provider for everything in sleep diagnostics from the home to the research focused lab.

XLTEK

John Mumford

John Mumford is President and CEO of XLTEK.

What products do you offer for diagnostics?

XLTEK currently offers a complete line of polysomnography equipment including fixed, portable, and ambulatory systems. We also provide diagnostic testing equipment for EMG, EEG, epilepsy monitoring, and intra-operative monitoring.

Please discuss current R&D efforts.

One project we're working on right now is to combine our diagnostic knowledge and experience with PAP therapy to improve compliance and outcomes for patients with OSA. The problem we see with PAP therapy today is that there is no way to objectively determine the effectiveness of therapy with respect to sleep quality despite the fact that many patients will still have poor sleep due to comfort issues, co-morbidities, pressure settings, or other reasons. Currently it's left up to the patient to seek help if they feel the therapy isn't working but unfortunately people are more likely to just stop using the device when that happens. That leads to poor compliance and outcomes. We've spoken to many clinicians who would love to be able to monitor their OSA patients' breathing and sleep quality once on therapy so they can intervene promptly – before the therapy is rejected - when necessary. Measuring sleep quality is especially important because the patient's perception is based on their sleep, not breathing. If a patient is breathing well with PAP but not sleeping well then they'll still feel tired and decide that PAP isn't worth the effort because it doesn't make them feel any better even though their long-term cardiovascular risks may be reduced. There is nothing on the market that can provide this information to the clinician in a cost, time, and effort efficient manner but we'd like to change that soon.

How are you going to do this?

We've adopted a strategy similar to Aspect Medical System's level of consciousness monitoring technology. We have designed a proprietary forehead electrode array along with signal processing and analysis that allows us to determine the patient's sleep state using the same electrophysiological criteria as traditional polysomnography. These electrodes are designed to be embedded in the PAP mask system so the patient can apply them with no extra effort. We are very focused on making this technology available directly and through OEM partnerships with PAP manufacturers and vendors.

What clinical trials have been performed?

We've been developing the recording and analysis technology

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for some time including an informal trial with 75 patients. An independent research team at a local university teaching hospital is now in the data processing phase of a formal 100 patient study to validate the accuracy of this system. Future trials will focus on the effect of this technology on compliance and patient outcomes.

What are the benefits to the patient and physician?

The benefit to the patient is better therapy. If they have not received effective treatment there will be objective evidence to allow their physician to modify or supplement the therapy. The physician benefits by being able to provide real treatment, instead of just a prescription, which improves the quality of care they can offer. The patient will also have that feedback so they can be proactive about their treatment instead of just feeling guilty if it isn't working.

What are the benefits to the purchaser?

The purchaser has made a significant investment in a PAP system as well as the diagnostic testing to get them to that point. That's a worthwhile investment for the reduced long-term risks and improved alertness but only if the therapy is working. This system will ensure efficacy and improve compliance which is precisely the goal of the purchaser to begin with. We're especially interested in the savings of lives and dollars that will be achieved by reducing residual sleepiness which is known to lead to traffic accidents, lost productivity, and the like.

Embla

Kassandra Keller

Kassandra Keller is Director of Marketing for Embla.

What products do you offer for diagnostics? What are the latest trends for such products?

Embla is unique in that we offer the broadest range of sleep diagnostic products; from two channel screening devices to research level polysomnography and EEG amplifiers. All of these systems are integrated into our sophisticated, yet easy to use, sleep software platforms, Rembrandt and Somnologica.

The latest trends are efficiency and integration. We provide our customers with tools that assist them in streamlining their operation and helping them become more efficient. We do this with our Embla Enterprise software which integrates to the customers' HIS or laboratory management system. Enterprise facilitates electronic management of patient records, provides efficiency statistics, referral patterns and assists with Accreditation procedures.

What products do you offer for therapy? What are the latest trends for such products?

While Embla is focused solely on diagnostics, we appreciate that many of our customers are seeking both diagnostic and therapeutic solutions from a single vendor. We are proud to offer ResMed therapy products as part of our portfolio. Additionally, our systems are compatible with other manufacturers' therapeutic devices. The latest trends are related to treating Central Sleep Apnea in all its forms such as Complex Sleep Apnea or mixed sleep apnea. A unique approach is required to diagnose and treat these patients and we are excited to be part of the solution.

How has technology changed in the past several years?

Technology and the science of medicine are dynamic and exciting. These advances enable us to develop superior products with increased features. The devices continue to get smaller and smarter as we use innovation to combine unique tools for diagnosing and treating sleep disorders with lower cost manufacturing techniques.

Please discuss your company's current R&D efforts.

Embla is the global leader in sleep diagnostics. We are focused on our customers, asking them how we can continually improve our product lines to meet the changing needs of the marketplace. We are currently involved in software and hardware development that will give our customers new products to improve their operation and treat their patients. These efforts include the strategic integration and enhancement of our current sleep software platforms, a new wireless ambulatory PSG amplifier, and expansions to our Embletta product line.

How does your product deal with electronic records management?

Our Embla Enterprise system is an integrated business management solution designed to efficiently maintain and manage comprehensive patient records. Document management features facilitate electronic management of history & physical, patient questionnaires, patient data, follow up activities and more. Enterprise also interfaces to HIS or laboratory management systems via HL7 making electronic record management easy to achieve.

Please discuss your assistance programs and training programs for purchasers and/or patients.

Embla provides installation and training packages with all our systems to assure our customers are fully trained in its use. We also offer additional training tools that are excellent for continuing education and staff turnover.

What clinical trials have been performed on your device?

Embla has a rigorous quality system that includes both internal testing and verification, as well as, controlled releases that involve patients. Our systems have been utilized in numerous clinical trials in the US and across Europe many of which have been published.

What is the level of clinical evidence supporting the use of your device?

Embla devices are all CE & FDA approved for use in identifying and diagnosing sleep disorders. Many of our products, such as the Embletta for polygraphy are considered to be the gold standard.

Does your product have portable monitoring capability? If so, please discuss.

Many of our products are designed specifically for portable monitoring in a variety of settings. We offer screening devices to full portable polysomnography.

How can your product improve patient compliance?

From the diagnostic perspective, we provide clinicians with tools to easily show a patient the severity of their disorder and the clinical benefit of treatment. ResMed therapeutic products can provide reports on compliance and efficacy data. Clinicians can use this information to analyze usage trends and treatment efficacy.

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MediPalm® • 22 Channels
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- Two products developed by an industry leader in portable recording technology.

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How can your product improve patient outcomes?

The Embla Enterprise system allows clinicians to manage their patients from referral to follow up. This provides the tools needed to manage the patient outcomes.

Please discuss cost-savings/benefits for both purchasers and patients using your products.

We are dedicated to developing high quality products using the latest technologies. This allows us to provide our customers with a greater selection of products that in turn allow them to diagnose and treat more patients in a cost effective manner.

Braebon

Michael Clark

Michael Clark is Director of Marketing and Sales for Braebon.

What products do you offer for diagnostics?

Braebon offers a complete diagnostic line of products that include sensors, MediByte snoring and apnea screener, MediPalm full PSG system, and Pursuit Outcomes management software.

What are the latest trends for such products?

We believe the sleep testing market is moving towards more portable type recording environments. This could be testing in the home, hotels, nursing homes, hospital wards (ie, inpatients), truck drivers and other areas where more compact or portable equipment would be a benefit. Our MediByte screener and MediPalm PSG system are two products ideally suited for portable recording.

How has technology changed in the past several years?

Well, things are smaller and faster. What I mean is advances in electronic technology have allowed us to develop smart PSG recording amplifiers that include powerful microprocessors and lots of memory. This provides the opportunity to program these devices to operate in a number of configurations with or without a computer. As an example, our 10 channel MediByte screener weighs less than 3 ounces including battery and can be programmed a week in advance to record two back to back night studies. The MediPalm can be set up to record up to 22 channels for full PSG testing in either portable or stationary configurations. Both these products use advanced technology which provides the user with a high level of recording flexibility.

Please discuss your company's current R&D efforts.

Braebon invests a significant amount of revenue back into carefully selected R&D projects each year. In addition, as part of our ISO 13485 process all four product lines are constantly being improved to increase reliability and meet customer expectations. We are unique in that all products are developed and manufactured under one roof allowing us to ensure top quality control.

How does your product deal with electronic records management?

Our Pursuit Outcomes database software handles this requirement exceptionally well. This is effectively core management software that controls and tracks many aspects of a busy sleep testing facility. The centerpiece of this SQL database is the patient's electronic record with 22 sections of

information in a variety of formats. This includes demographics, insurance, physicians, questionnaires, sleep study results, scanned documents and images, diagnostic codes, patient history, medications and a number of other areas.

Please discuss your assistance programs and training programs for purchasers and/or patients.

Braebon has a variety of training programs for purchasers that include on-site or over the internet. Both the MediByte and MediPalm systems were designed to be so easy to learn and easy to use that in most cases all the configuration and training can be done over the web.

What clinical trials have been performed on your device?

The MediPalm and MediByte have been used in a number of hospital and private lab clinical trials. The most recent study was done by a large hospital based sleep lab that simultaneously compared the MediByte to the "gold standard" overnight PSG test. The results, to be published soon, clearly show our multi-channel screening device is an effective tool for detecting obstructive sleep apnea.

Does your product have portable monitoring capability?

Yes, both the 10 channel MediByte screener and 22 channel MediPalm have the best *performance per size ratio* on the market today. This means they have the most number of channels per square inch of enclosure size and are ideal for portable monitoring applications.

How can your product improve patient outcomes?

Our Pursuit Outcomes database tracks patients' outcomes in a variety of ways. In addition to CPAP compliance, a number of other important patient parameters such as medical history, sleep study results, therapy options and follow-up procedures are all tracked to ensure patients are able to receive the best treatment and service available.

Please discuss the cost-savings/benefits for both purchasers and patients using your products.

Braebon provides many of the most cost effective and extended warranted products available. As an example the MediPalm PSG system has a complete 3 year warranty. Our company mission is to provide quality, innovative alternatives in the field of sleep medicine.

Resmed

Michael Farrell

Michael Farrell is ResMed Vice President of Marketing, Americas.

What products do you offer for diagnostics? What are the latest trends for such products?

ResMed offers the first step in quality sleep patient management with the ApneaLink screening tool. The ApneaLink is a simple yet accurate way to screen potential OSA patients, guaranteeing that patients can be identified, triaged and diagnosed in the most efficient manner possible. A versatile tool, the ApneaLink can be used in the patient's home or any ambulatory setting: it simplifies and streamlines the sleep-screening process. The latest advance for ApneaLink is an integrated oximetry capability, adding pulse and pulse oximetry to AHI, flow limitation and snoring on its reports.



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ResMed's Adapt SV technology has successfully treated thousands of patients suffering from complicated sleep-disordered breathing. To learn more about the only device that effectively treats complex sleep apnea and periodic breathing, visit www.resmed.com/simplyamazing.

"We've had patients continue to have high AHI with central events, despite our best efforts to titrate with CPAP and bilevel. With these complex patients, VPAP Adapt SV effectively normalizes breathing where the other therapies have failed. It makes our lives easier because our patients' lives are improved. I'm very impressed with it."

— **Dr. Bruce Corser, Sleep Management Institute**

RESMED

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What products do you offer for therapy? What are the latest trends for such products?

We offer a wide range of products for the screening, treatment and management of sleep-disordered breathing. Our award-winning product line covers all aspects of the SDB treatment spectrum, including continuous positive airway pressure (CPAP), automatic positive airway pressure (APAP) and bilevel positive airway pressure. We also offer a range of humidification products, nasal interface systems and accessories, screening tools and clinical systems. Positive airway pressure (PAP) treatment has come a long way since its invention in 1981, with a shift toward consumer-friendly products packed with more features to ensure comfortable therapy for patients as well as adherence and outcome data for clinicians. Even the size of therapy products has changed over the past couple of years, with the introduction of more compact and lightweight devices, like ResMed's S8 series of flow generators and our Mirage Swift™ II nasal pillows system. Now more than ever, these lifestyle-oriented products are designed with the patient in mind to improve comfort and increase compliance.

How has technology changed in the past several years?

Advances in technology have allowed us to treat a broader range of patients more comfortably and effectively than ever before. Our masks and flow generators are designed for every type of sleeper and every type of nocturnal breathing disorder. For example, the adaptive servo-ventilation algorithm in ResMed's VPAP Adapt SV device treats patients with complex sleep apnea where other technologies have failed. ResMed's EPR technology provides a way to improve patient compliance without compromising therapy effectiveness by lowering pressure upon exhalation so that breathing feels more natural. EPR offers three comfort settings in addition to other built-in controls so clinicians can reliably manage expiratory pressure relief therapy.

Please discuss your company's current R&D efforts.

We invest approximately 6-7% of revenues in research and development efforts, which is a growing dollar figure every year. ResMed's team is focused on developing innovative therapies for SDB that enhance patient comfort and convenience while improving health. We interact directly with customers on a daily basis through our field clinical and sales force, and our marketing team ensures that the customer's voice actively drives our product development process. ResMed is constantly looking for ways to improve our products to benefit both our customers who distribute them and our patients who use them. Our products for the pediatric sleep apnea market, the Mirage Kidsta and VPAP III ST-A, are an example of ResMed putting the needs of children and their parents at the top of our development list.

How does your product deal with electronic records management?

With Boomerang Access, ResMed offers a comprehensive tool that is effective for efficiently managing a few patients to a few thousand patients. Boomerang Access helps users manage compliance and replacement schedules with multiple patient reminders, auto-generated notes and forms and management reports. Boomerang Access is a powerful, efficient and user-friendly data management system designed specifically for organizations that dispense equipment and supplies for the treatment of SDB.

Please discuss your assistance programs and training programs for purchasers and/or patients.

ResMed's Clinical Education team is made up of a dedicated group of respiratory technicians and registered sleep technologists with extensive backgrounds in both cardiopulmonary and sleep medicine. The team works with our sales representatives to assist hospitals, sleep centers and sleep

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¹ Todd Elken, RPSGT- Sleep Review™ Sept. 2003
² Richard Berry, MD- CHEST Sept. 2003
³ William Orr, PhD- APSS 2003

labs with their educational needs. We offer specific training in ventilation, titration techniques and diagnostic procedures, with the opportunity for providing continuing education units (CEUs) to respiratory therapists, nurses, registered sleep technicians and case managers. We also have a team of technical experts as part of our Customer Service team who assist our customers with day-to-day queries, from product support to clinical questions. Our Reimbursement Hotline is also available for customers who have questions regarding insurance guidelines and procedures. In addition, we offer multiple online resources, including therapy tips for CPAP patients at MyResMed.com, information for undiagnosed sleep apnea patients at HealthySleep.com, and information for clinicians regarding the VPAP Adapt SV at www.resmed.com/SimplyAmazing.

What clinical trials have been performed on your device?

Clinical trials comparing the adaptive servo-ventilation algorithm of the VPAP Adapt SV to other treatment modalities have been performed in regions around the world, including the United States, Europe and Asia. These studies have compared the effectiveness of the Adapt SV technology versus continuous positive airway pressure (CPAP), bilevel and oxygen therapy in treating central sleep apnea. These studies show that the Adapt SV technology outperforms other modes of treatment in resolving a range of obstructive and central apneic events, restoring slow-wave sleep and reducing arousals. A study conducted by Philippe also showed improvement in quality of life measures and left ventricular ejection fraction in patients with heart failure on Adapt SV therapy. The following studies reference the effectiveness of the adaptive servo-ventilation algorithm:

- 1 Philippe et al. Compliance with and effectiveness of adaptive servo-ventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart* 2006;92:337-342
- 2 Teschler et al. Adaptive pressure support servo-ventilation: A novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001;164:614-619.
- 3 Banno K, Okamura K, Kryger MH. Adaptive servo-ventilation in patients with idiopathic Cheyne-Stokes breathing. *J Clin Sleep Med* 2006;2(2):181-186.
- 4 Pepperell et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003;168:1109-1114.
- 5 Zhang et al. Efficacy of adaptive servo-ventilation in patients with congestive heart failure and Cheyne-Stokes respiration. *Chin Med J* 2006;119(8):622-627.
- 6 Hanly PJ and Zuberi-Khokhar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med* 1996;153:272-276.

What is the level of clinical evidence supporting the use of your device?

Peer-reviewed literature published over the last seven years shows that the algorithm in ResMed's VPAP Adapt SV normalizes breathing, completely suppressing central sleep apnea and/or Cheyne-Stokes respiration in heart failure patients.^{1,2} It also improves sleep architecture¹ (increases the amount of time the patient spends in slow-wave and REM sleep) and enhances quality of life.^{2,3} In addition to the clinical trials listed above, ResMed's adaptive servo-ventilation therapy has been used successfully on thousands of patients around the world for millions of treatment hours. The clinical results with the Adapt SV have been consistently and overwhelmingly positive.

Does your product have portable monitoring capability? If so, please discuss.

Data stored on the VPAP Adapt SV can be viewed on a PC via ResScan software, which allows users to view, assess and report therapy information. In addition, the ResLink module with oximetry captures in-depth data and monitors oxygen saturation. In addition, ResMed's S8 AutoSet Vantage, S8 Elite, VPAP III and VPAP III ST have wireless, internet-enabled monitoring systems for remote monitoring. ResTraxx technology will work in a truck, at a hotel or in the home – it moves with the patient, allowing tracking of adherence and efficacy data.


How can your product improve patient compliance?

VPAP Adapt SV ensures that pressure support is synchronized to the patient's own recent breathing rate and flow pattern. It provides constant, low pressure support to maximize patient comfort and compliance. And, unlike traditional bilevel therapy, VPAP Adapt SV delivers a smooth pressure waveform, which is similar to natural breathing. Additionally, the optional integrated humidifier improves comfort by relieving the symptoms that are associated with CPAP therapy.

How can your product improve patient outcomes?

The VPAP Adapt SV is the first and only device cleared for the treatment of central sleep apnea (CSA), mixed sleep apnea and periodic breathing such as Cheyne-Stokes respiration (CSR) in both hospital and homecare environments. By providing this

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revolutionary therapy, the VPAP Adapt SV is able to deliver amazing results and superior patient outcomes where other therapies have failed.

Please discuss cost-savings/benefits for both purchasers and patients using your products.

Unlike conventional SDB therapies such as CPAP, the VPAP Adapt SV device treats central sleep apnea in all its forms to provide the right therapy the first time. Patients with complex sleep apnea cannot be adequately treated with CPAP, but the proven track record of the VPAP Adapt SV ensures a simple and effective solution for these complex breathing disorders. Clinicians benefit from this revolutionary device that treats these patients where other technologies have failed. The default settings on the VPAP Adapt SV are suitable for most patients, so titrating patients is a simple process for sleep lab technicians. Most importantly, patients benefit from the effective therapy that the VPAP Adapt SV delivers. As a result their lives are improved and they can finally get a good night's sleep. Visit resmed.com/SimplyAmazing for further information.

Clevemed

Hani Kayyali

Hani Kayyali is President of CleveMed (Cleveland Medical).

What products do you offer for diagnostics?

Crystal Monitor 20-S and Crystal Monitor 20-B are small, handheld, 14-channel wireless PSG systems that come with two different data transmission frequencies. With different frequency options, sleep labs are able to choose the system best suited for their environment.

Sapphire PSG is a 22-channel wireless PSG system that offers full PSG diagnostic capabilities in a small and flexible package. With multiple wireless data transmission frequency options built into the hardware and software, the Sapphire PSG offers the flexibility to be used in hospitals, even in critical care areas, as well as sleep labs, patient homes and international markets. SleepScout is a small and compact 9-channel screener for sleep-disordered breathing or restless leg syndrome. Unlike other sleep screeners, SleepScout is designed with an onboard wireless data transmitter that can communicate with a PDA or laptop computer to confirm proper electrode placement. In addition to the 7 dedicated channels, SleepScout's flexible design offers an additional 2 channels that are fully programmable in which the technician can acquire any combination of EEG, EOG, ECG and EMG. Data is stored on a removable memory card for later retrieval. Each system includes a sophisticated PSG software package and a flexible, wireless design that allows for attended, virtually attended, and unattended studies in almost any setting.

What are the latest trends for such products?

The latest trend in diagnostic products is Wireless. Sleep disorders, especially sleep disordered breathing (SDB), is no longer an isolated disorder. It is strongly linked and can impact the management of care of many life threatening diseases like cardiovascular and pulmonary diseases. Undiagnosed SDB can also complicate surgeries and can play a role in caring for the elderly. It is not reasonable to ask all these patients to come to the sleep lab for diagnosis; labs are overcrowded as it is. In

order to properly diagnose these patients, we must go to them, whether it is in the hospital room, surgical suite, nursing home or their own home. This is where wireless comes in. Just like the way cell phones changed the communication industry, wireless PSG will change the sleep diagnosis market by quickly reaching those patients wherever they are and when they most need it.

What products do you offer for therapy? What are the latest trends for such products?

We are currently working on a new CPAP device that has vastly improved diagnostic capability. We can not say much about our new technology at this point because it is confidential, but we believe that new applications will fuel CPAP's growth. Whether using CPAP postoperatively to reduce surgical complications, or whether it monitors subtle and serious changes in the patient's disease state over time, CPAP technology must step up to meet these new needs. One example is Complex Sleep Apnea. Research is finding that up to 15% of the current CPAP users may in fact be developing Central Sleep Apnea, which will likely need different treatment. Current CPAP machines can not detect those changes, and therefore cannot properly report on the progress of potentially thousands of patients! Who knows what new disease states we will find in the near future that demand careful therapy management. Therefore, future therapeutic products are those that are smarter with capabilities to offer effective therapy for the complicated patient who is becoming the norm and not the exception. As importantly, these technologies must be developed for home use since pressures to shift diagnosis and treatment from the lab to the home continue to mount.

How has technology changed in the past several years?

While advancements in oral appliance technologies and surgeries have improved, CPAP continues to be the most effective and popular sleep apnea therapy. However, as mentioned earlier, traditional CPAP is no longer sufficient. I believe the traditional CPAP market will slowly but surely be replaced with smarter CPAP technologies. Indeed, several benchmark studies have shown improvement in Auto-Adjust CPAP technologies over the past couple of years. There is a lot more work to do in this area, especially since SDB is a relatively young disease with new clinical manifestations and comorbidities that continue to be uncovered regularly.

Please discuss your company's current R&D efforts.

CleveMed's R&D efforts have been focused on finding new and innovative technologies for both the diagnosis and treatment of sleep disorders. Our current product offerings include the Crystal Monitor 20-S and Crystal Monitor 20-B, complete wireless 14 channel PSG systems and SleepScout, a 9 channel sleep disorders screener. To help physicians find the system best suited for their environment, CleveMed will be releasing Sapphire, a 22 channel wireless PSG system, in June of this year. All four systems include Crystal PSG software, a sophisticated software package for data acquisition, scoring and reporting. Later this year, the software will be expanded to include scoring for neonatal sleep studies. CleveMed's R&D for sleep disorders diagnosis has been focused on expanding the reach of the sleep lab to include other settings such as hospital patient rooms, outpatient pre-surgical centers, nursing homes, "sleep hotels" and patients' homes. In doing so, physicians and technologists who need flexibility because of different service contracts benefit from our systems, as do patients that are better suited to

testing outside of the sleep lab, such as pre-surgical patients, children and those that are less mobile. To complement our products in these settings, CleveMed will be releasing two new proprietary medical communication systems for the hospital inpatient setting and the patient's home. These systems will allow for attended, virtually attended, and unattended studies. In addition to the up and coming line of diagnostic products currently under development, CleveMed is heavily involved in R&D for a new line of CPAP products.

How does your product deal with electronic records management?

We work directly with customer sites and offer HL7 integration. In addition, our systems include a built-in patient database and record storage and archival capabilities. To help organizations comply with HIPAA regulations, our systems offer security features such as data encryption and access control.

Please discuss your assistance programs and training programs for purchasers and/or patients.

We offer on-site technologist training, additional web-based training, 24/7 technical support and on-staff clinical specialists. Loaner units are provided at no cost during the warranty period as needed to eliminate downtime.

What clinical trials have been performed on your device?

Our PSG systems have been validated in clinical trials against other commercial sleep systems, resulting in similar diagnostic outcomes on both systems. Currently clinical trials are taking place using our sleep systems for testing hospital inpatients and home testing. Our wireless systems combined with intranet or internet connections allow for testing to be virtually attended from nearly anywhere.

What is the level of clinical evidence supporting the use of your device?

Clinical evidence has been well established for diagnostic sleep testing. Our products make sleep testing more convenient for the patient and sleep technologist by allowing the study to take place anywhere. This is particularly important for patient populations that may be difficult to test in a lab such as pediatrics, inpatients and the elderly.

Does your product have portable monitoring capability? If so, please discuss.

Our Crystal Monitor PSG Series and upcoming Sapphire PSG integrate the headbox, amplifiers, transducers and data telemetry into one small, handheld patient unit that transmits the data wirelessly to a computer unit attached to a PC up to 100 feet away. Because of the systems' wireless design, time consuming and costly hard-wiring is eliminated, allowing for fast, simple and cost-effective system setup and rearrangement in any setting. Additional technology options for these products include the ability to perform virtually attended PSG studies, in which the sleep technician can monitor the patient's PSG signals and video live from almost any location, regardless of distance from the patient. Multiple wireless operating frequency options also help to make the systems suitable for almost any setting, including Bluetooth based radios, hospital specific frequencies (WMTS) and more.

CleveMed also offers SleepScout, a 9-channel wireless sleep screener with a removable memory card. The simple and compact design allows for preliminary assessment of sleep

disordered breathing to be made outside of the traditional sleep lab, such as in a patient's home or in a hospital setting.

How can your product improve patient outcomes?

Our products can help a sleep lab test patients sooner. By testing patients sooner to correctly diagnose the patient they can begin treatment sooner, which will improve outcome.

Please discuss cost-savings/benefits for both purchasers and patients using your products.

Both patients and purchasers benefit from our products' flexibility, wireless design and competitive pricing. Our suite of products range from a 22 channel full PSG system to 14 channel PSG systems to a sleep screener, and we offer proprietary technology to allow the lab to perform attended, virtually attended or unattended studies. In other words, patients can be tested in the setting most suitable to their personal situation, and sleep labs are able to select from a variety of products and setting options, giving them the ability to readily expand their reach to non-traditional settings and fulfill new needs. Patients also benefit from the systems' wireless design in increased comfort and mobility. In addition, CleveMed's pricing is extremely competitive considering the high quality proprietary technologies, patented wireless design, high reliability, and compact size.

EXECUTIVE PROFILE

Teleflex Medical

Christianna Vance

Christianna Vance is Sleep Therapy Product manager, Teleflex Medical.

Teleflex Medical is a global organization dedicated to supporting healthcare providers with a broad range of medical solutions. With a history of providing quality products, our brands have a reputation for excellence that spans nearly two hundred years. With our entry into the Sleep Therapy Market, Teleflex Medical is focused on providing breakthrough CPAP interfaces that help clinicians overcome the challenges presented by traditional masks: patient comfort and oral leaks.

By offering cutting edge, innovative solutions to meet the needs of the sleep apnea patient, we are proud to introduce the Hybrid CPAP Mask. The Hybrid is a unique fusion of technologies, designed to be a universal interface for patients and clinicians. The Hybrid is a dual-airway interface that consists of an oral cushion that covers the mouth and two nasal pillows that fit into the patients nostrils.

The Hybrid technology is ideal for patients who experience claustrophobia during therapy by minimizing the multiple points of contact on the face. The Hybrid eliminates the problems commonly associated with full face masks: skin breakdown on the nose and forehead, patient comfort and claustrophobia. The Hybrid promotes superior patient care by providing a more comfortable fit for the patient while allowing them to wear glasses as needed.

Teleflex Medical utilizes the Voice of Customer Process to truly

understand the needs of patients and clinicians. In market surveys we found that both clinicians and patients identified oral leaks as one of the most difficult side effects encountered during CPAP therapy. Because the Hybrid is the only dual-airway design that addresses oral leaks, while at the same time increasing patient comfort, this is the mask of choice for a wide range of CPAP patients.

We stay close to the CPAP community through organizations like Talk About Sleep and cpaptalk.com. Through these chat forums we are able identify our customers' needs and make appropriate design changes. This was extremely effective in the redesign of the Hybrid Headgear. We made the headgear more robust with 6 points of adjustability providing the patient a more comfortable, custom fit.

Teleflex Medical views the clinician as a vital part of the product design process. We look to clinicians to provide feedback in order to make changes and improvements to our entire respiratory line. We are dedicated to supporting healthcare providers by developing innovative solutions that truly make a difference today, tomorrow and for years to come. Contact teleflexmedical.com.

- 1 Teschler H et al. Am J Respir Crit Care Med. 2001; 164: 614–19
- 2 Philippe C. Heart. 2005; Published online Jun 20
- 3 Töpfer V et al. Pneumologie. 2004; 58(i): 28–32

Depression and Obstructive Sleep Apnea

Carmen M. Schröder, Ruth O'Hara

Abstract

For over two decades clinical studies have been conducted which suggest the existence of a relationship between depression and Obstructive Sleep Apnea (OSA). Recently, Ohayon underscored the evidence for a link between these two disorders in the general population, showing that 800 out of 100,000 individuals had both, a breathing-related sleep disorder and a major depressive disorder, with up to 20% of the subjects presenting with one of these disorders also having the other. In some populations, depending on age, gender and other demographic and health characteristics, the prevalence of both disorders may be even higher: OSA may affect more than 50% of individuals over the age of 65, and significant depressive symptoms may be present in as many as 26% of a community-dwelling population of older adults.

In clinical practice, the presence of depressive symptomatology is often considered in patients with OSA, and may be accounted for and followed-up when considering treatment approaches and response to treatment. On the other hand, sleep problems and specifically OSA are rarely assessed on a regular basis in patients with a depressive disorder. However, OSA might not only be associated with a depressive syndrome, but its presence may also be responsible for failure to respond to appropriate pharmacological treatment. Furthermore, an undiagnosed OSA might be exacerbated by adjunct treatments to antidepressant medications, such as benzodiazepines.

Increased awareness of the relationship between depression and OSA might significantly improve diagnostic accuracy as well as treatment outcome for both disorders. In this review, we will summarize important findings in the current literature regarding the association between depression and OSA, and the

possible mechanisms by which both disorders interact. Implications for clinical practice will be discussed.

Depression in OSA

Definition and prevalence of OSA: OSA is by far the most common form of sleep disordered breathing and is defined by frequent episodes of obstructed breathing during sleep. Specifically, it is characterized by sleep-related decreases (hypopneas) or pauses (apneas) in respiration. An obstructive apnea is defined as at least 10 seconds interruption of oronasal airflow, corresponding to a complete obstruction of the upper airways, despite continuous chest and abdominal movements, and associated with a decrease in oxygen saturation and/or arousals from sleep. An obstructive hypopnea is defined as at least 10 seconds of partial obstruction of the upper airways, resulting in an at least 50% decrease in oronasal airflow.

Clinically OSA is suspected when a patient presents with both snoring and excessive daytime sleepiness (EDS).^{1,2} The diagnosis of OSA is confirmed when a polysomnography recording determines an Apnea-Hypopnea-Index (AHI) of > 5 per hour of sleep.³ Even if cutoff points have never been clearly defined, an AHI of less than 5 is generally considered being normal, 5–15 mild, 15–30 moderate and over 30 severe OSA.

The prevalence of OSA is higher in men than in women. OSA is found in all age groups but its prevalence increases with age. In children, the prevalence of OSA is less well defined and has been estimated to be 2–8%.⁴ In subjects between the ages of 30 to 65 years, 24% of men and 9% of women had OSA.⁵ Among subjects over 55 years of age, 30–60% fulfill the criterion of an AHI > 5 .^{6–8} In a population of community-dwelling older adults, 70% of men and 56% of women between the ages of 65 to 99 years have evidence of OSA with a criterion of AHI > 10 .⁹

The abnormal respiratory events which are the hallmark of OSA are generally accompanied by heart rate variability and arousals from sleep, with frequent arousals being the most important factor resulting in EDS. With regards to sleep architecture, we find a significant increase in light sleep stage (mainly stage 1) at

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the expense of deep slow wave sleep (stages 3 and 4) and REM sleep. Slow wave sleep is sometimes even completely abolished. However clinically, patients are often not aware of this repetitive sleep interruption (with sometimes hundreds of arousals during one night), but simply do not feel restored in the morning. Other nocturnal symptoms can include restlessness, nocturia, excessive salivation and sweating, gastroesophageal reflux, as well as headache and dry mouth or throat in the morning on awakening.

The extent to which daytime functioning is affected generally depends on the severity of OSA. Symptoms other than EDS which greatly impact daytime functioning are neuropsychological symptoms such as irritability, difficulty concentrating, cognitive impairment, depressive symptoms, and other psychological disturbances. Thus, OSA can easily mimic symptoms of a major depressive episode.

Correlation studies of OSA and depression

Among the first studies investigating the relation between OSA and depression, Guilleminault et al.¹⁰ reported that 24% of 25 male patients with OSA had previously seen a psychiatrist for anxiety or depression, and Reynolds et al.¹¹ showed that around 40% of 25 male OSA patients met the research diagnostic criteria for an affective disorder, with a higher risk of depression in those patients who were sleepier during the day. Similarly, Millmann et al. observed that 45% of his 55 OSA patients had depressive symptoms on the Zung Self-Rating Depression Scale, with the group scoring higher for depression also having a significantly higher AHI.¹² Whereas only 26% of OSA patients described themselves as currently depressed, 58% fulfilled DSM-III criteria for major depression of four or more depressive symptoms.¹³ Others observed increased depression scores on the Minnesota Multiphasic Personality Inventory (MMPI) in patients with OSA.^{14,15} Indeed, Ramos Platon et al. found elevations in several MMPI scales in 23 OSA patients (moderate to high severity) compared to 17 controls.¹⁶ Aikens et al.¹⁷ showed that 32% of their OSA patients had elevated depression scores on the MMPI and in the same series of studies, there were twice as many OSA patients with elevated depression scores than age and sex matched primary snorers.¹⁸ However, the percentage of depressive symptoms was not significantly different when compared to patients with other primary sleep disorders, such as periodic limb movements during sleep (PLMS).¹⁹ Most recently, in an epidemiological study of 18,980 subjects representative of the general population in their respective countries (UK, Germany, Italy, Portugal, and Spain) and assessed by cross-sectional telephone survey, Ohayon determined that 17.6% of subjects with a DSM-IV breathing-related sleep disorder diagnosis also presented with a major depressive disorder diagnosis, and vice versa.²⁰ This correlation persisted after controlling for obesity and hypertension.

In contrast to the numerous studies observing a positive correlation between OSA and depression, some investigations found no association between both disorders. In a 5-year longitudinal study, Phillips et al. did not find any significant depressive symptoms in elderly patients with a relatively mild OSA (AHI > 5/h), when compared to a control group without OSA (AHI < 5/h).²¹ However, there are multiple limitations to this study, besides a relatively small sample size for group comparisons and a non-representative study population. OSA was only assessed at baseline, but not repeated at the five-year follow-up, i.e. neuropsychological data were compared between

two groups based on OSA status five years earlier. Second, OSA severity was mild even in the OSA group. Third, the groups differed significantly by age, with the OSA group being older than the control group. Finally, the attrition rate over the five years was very high with only 42 out of the initial 95 subjects completing the follow-up assessment. In another large-scale study, Pillar and Lavie did not observe any association between respiratory disturbances and Symptom Check List 90 in 2,271 predominantly male patients assessed for OSA.²² However, the SCL-90 questionnaire was developed as a screening tool for psychiatric patients, and not for a normal study population. Therefore, it might be a less sensitive tool with regards to milder forms of mood disturbances than other scales. Interestingly, Pillar and Lavie observed that among the minority of women in this study, those with severe OSA had higher depression scores than those with mild OSA. Bardwell found that other factors such as age, body mass index (BMI) and hypertension accounted for the correlation between sleep parameters and total mood disturbances in 72 OSA patients when compared to 40 controls.²³ However, the chosen cutoff point to distinguish between OSA and the control group in this study was relatively high (AHI of 15/h), thus subjects with a mild OSA were probably included in the control group.

In sum, the majority of studies to date report an association between depression and OSA, but methodological considerations render the comparison between investigations difficult. Some of the mixed findings among studies can be explained by differences in sample size, study population, gender distribution, age and AHI cut-off in relation to age, as well as variability in terms of the questionnaires and scales used to assess depressive symptomatology. Given the heterogeneity of these data and considering the numerous confounding factors, future longitudinal studies of patient populations are required to better understand the relation between both disorders.

Treatment studies for OSA: reversibility of depressive symptoms?

The gold standard treatment for moderate to severe cases of OSA is continuous or bilevel positive airway pressure (CPAP/BiPAP) which mechanically maintains the upper airways space open during sleep via the administration of ambient air with a certain pressure. The minimum necessary pressure level has to be titrated individually for each patient.²⁴ Other treatments, especially for mild cases of OSA, include weight loss, dental devices (which advance the tongue or mandible to increase posterior airway space) or upper airway surgery (e.g. combined tonsillectomy/adenoidectomy, nasal reconstruction, and uvulopalatopharyngoplasty). Different upper airway surgical procedures can be used for particular cases with craniofacial abnormalities.²⁵

Overall, CPAP treatment studies for OSA and its effect on depressive symptoms have yielded controversial findings. Derderian et al.²⁶ compared results on the Profile of Moods Questionnaire before and after 2 months of CPAP treatment in an OSA group (n = 7) and showed a significant drop in Total Mood Disturbance. This improvement was correlated with an increase in slow-wave sleep. Those patients in the study of Millmann et al. who received CPAP displayed a significant decrease in their Zung Depression Scale scores.¹² Similarly, Engleman et al. reported an improvement in a comprehensive battery of mood and cognitive assessment scales after 4 weeks

of CPAP treatment in 32 patients with moderate OSA²⁷ as well as in 16 patients with a mild OSA.²⁸ Means et al.²⁹ showed an improvement on Beck Depression Inventory (BDI) depression scores after 3 months of treatment in 39 OSA patients, and Sanchez et al.³⁰ confirmed lower BDI scores after 1 and 3 months of CPAP therapy in 51 OSA patients. Ramos Platon et al.¹⁶ underscored the progressive improvement in depression scores on the MMPI scale over the first year of treatment. A systematic review on the influence of CPAP on neurobehavioral performance of patients with OSA also supported the clinical perspective that typically depressive symptoms remit together with EDS under CPAP therapy.³¹

Among the negative studies on CPAP therapy and its effect on depression, Borak et al.³² did not observe any improvement in emotional status after 3 and 12 months of CPAP therapy in 20 patients with severe OSA, similar to Munoz et al.³³ who also did not show improvement of BDI scores in 80 subjects with severe OSA after 12 months of CPAP. Using subtherapeutic CPAP as the placebo control, Yu et al.³⁴ and Henke et al.³⁵ found no difference in improvement on depression scores between the treatment and the control group, over a short treatment duration (1–3 weeks). However, whereas Borak, Munoz and Henke do not find any effect of CPAP therapy on mood, Yu observed a positive effect on mood of both CPAP therapy and the subtherapeutic CPAP control group.

Intriguingly, there are no systematic differences with regards to the sample size, the initial severity of OSA or the duration of CPAP therapy which might explain the differences between studies observing an improvement after CPAP therapy and those who did not. Several issues have to be considered: First, it is difficult to design a good control (“placebo”) condition for CPAP treatment. “Sham-CPAP” which uses insufficient positive airway pressure as a placebo condition (1–2 cm H₂O), is now used more frequently. Two of the negative studies employed this method for their control group, which raises the possibility that the previously observed positive effects of CPAP on mood may have been a placebo effect. Second, compliance to CPAP treatment is problematic, because patients have to wear a nasal or even an oranasal device during the entire night. The compliance may even be particularly decreased in depressed patients. Indeed, Edinger et al.³⁶ reported a positive correlation between lower depression scores on the MMPI prior to treatment and CPAP compliance at 6 months of treatment in 28 patients. However, Lewis et al.³⁷ did not find any association between baseline depression scores and subsequent CPAP use for the first month of treatment. The most important factor to explain the differences among these studies may be the variability in the severity of initial depressive symptoms. Whereas the severity of OSA itself does not seem to have a differential impact on mood improvement after CPAP therapy, the severity of depressive symptoms associated with OSA may impact response to CPAP treatment. As Millmann indicates, OSA patients with more severe mood symptoms responded better to CPAP treatment, whereas patients with less severe or no mood symptoms actually had less benefit from CPAP therapy.¹² However, all negative treatment studies either excluded subjects suffering from a major depressive disorder, or their depression scores were even at baseline in a normal range (baseline values: mean BDI of 7.5 in,³² mean depression score on POMS scale of 12.5 in,³⁴ mean BDI of 8 in,³³ and no information given on assessed GDS scores in³⁵). Future studies should seek to include OSA patients with a broader range of depressive

symptoms in treatment studies, to investigate whether CPAP might have a better effect on mood in more depressed OSA patients.

OSA in depression

Compared to the large number of studies investigating depressive symptomatology in OSA patients, far fewer studies have focused on the screening for OSA in a primarily depressed study population. In one of the few investigations of the prevalence of OSA in a depressed cohort, Reynolds et al. found, in a small sample of 17 older patients with major depression, that 17.6% also had an OSA syndrome, compared to 4.3% of 23 healthy elderly controls.³⁸ This suggests that OSA might be an important confounding factor for studies on mood disorders in general, as its presence is not routinely determined in either research studies examining mood or clinical settings. However, many more studies are required to assess the prevalence of OSA in primarily depressed patients, particularly as it can be suspected from existing studies that OSA is greatly underdiagnosed in this patient population.

Clinically, this is of particular concern, as sedative antidepressants and adjunct treatments for depression may actually exacerbate OSA. Notably hypnotics prescribed to treat depression-related insomnia might further decrease the muscle tone in the already functionally impaired upper airway dilator muscles, blunt the arousal response to hypoxia and hypercapnia as well as increase the arousal threshold for the apneic event, therefore increasing the number and duration of apneas.^{39,40} These effects might differ depending on the patient population and the severity of OSA. Older depressive subjects are of primary concern: both, frequency of OSA and depressive symptoms increase with age, as do prescription and consumption of sedative psychotropic medication. Pharmacologic treatment of depression and depression-related insomnia in this age group should therefore routinely consider the potential presence of a concomitant OSA.

Finally, as Baran and Richert point out, the diagnosis of a mood disorder in the presence of OSA has its very own challenges.⁴¹ Considering the DSM-IV definitions,⁴² it could either be viewed as a mood disorder due to a general medical condition, or classified as an adjustment disorder with depressed mood, due in particular to EDS and its debilitating consequences on the patients’ daytime functioning. The identification of pathophysiological features that allow distinction between OSA and depression might assist with such diagnostic issues.

Sleep architecture in depression and OSA

Both depression and OSA have been well characterized with regards to their sleep architecture. Typically, for major depression, polysomnography (PSG) findings confirm the patients’ complaints of insomnia, notably difficulties falling asleep (PSG: increase in sleep latency), frequent awakenings during the night and early morning awakenings (PSG: idem) as well as non-refreshing sleep (PSG: decrease in slow wave sleep). PSG furthermore reveals a shortened REM latency, i.e. the first episode of REM sleep appears earlier than usual, with an increase in total percentage of REM sleep during the night, as well as in its eye movement density (referred to as REM sleep disinhibition).⁴³ On the other hand, the sleep of patients with OSA is fragmented, and contains a lot of transitional sleep stages (stage 1) at the expense of REM sleep and particularly of slow wave sleep (stages 3 and 4).^{44,45} At least two studies have

investigated sleep architecture at the interplay of OSA and depression or depressive symptoms. Reynolds et al. stated that, in contrast to the sleep EEG of depressed patients which characteristically shows a shorter latency of REM sleep, sleep apnea patients with depression displayed an increase in REM latency.¹¹ Bardwell et al. compared a group of 106 patients with and without OSA with regards to their sleep architecture. Depressed patients who also had OSA displayed a decrease in sleep latency when compared to the depressed group without OSA; and OSA subjects with depressive symptoms had a higher percentage of REM sleep than OSA subjects without depression.⁴⁶ Rather than distinguishing a primary depressive illness from an organic affective syndrome related to OSA,¹¹ however, the aforementioned polysomnographic results underscore how both disorders interplay, thus confounding EEG findings characteristic for each disorder.

Possible mechanisms underlying the association between depression and OSA

Sleep fragmentation and hypoxemia: The two main factors suspected to be responsible for depressive symptoms in OSA are sleep fragmentation and oxygen desaturation during sleep. Sleep fragmentation is a direct consequence of the recurrent microarousals associated with the apneas and hypopneas, and the nocturnal hypoxemia is due to the intermittent drops in oxygen saturation caused by the respiratory events.⁴⁷ Sleep fragmentation is the primary cause of EDS in OSA patients, and is suggested to result in the depressive symptomatology in OSA. This last perspective gains support from the finding that EDS as measured by the Epworth Sleepiness Scale (ESS) and the Maintenance of Wakefulness Test (MWT) was found to be correlated with higher depression scores on the Hospital Depression Scale (HAD-D) in 44 patients with OSA.⁴⁸

Furthermore, a Canadian study on 30 OSA patients showed a significant correlation between the severity of psychological symptoms on SCL-90 and less total sleep time, as well as percentage of wake time after sleep onset and ESS scores.⁴⁹ With respect to hypoxemia, Engleman et al noted in a recent review that the effect size of cognitive impairment in OSA correlated highly with severity of hypoxic events, ranging from .3 standard deviations for milder levels of AHI to 2–3 standard deviations for higher levels of AHI.⁵⁰ Recently, preliminary imaging data suggests that hypoxemia related to OSA might also play a role in impacting mood. Cerebral metabolic impairment resulting from recurrent nocturnal hypoxemia in OSA have previously been observed in several imaging investigations on OSA,^{51–53} independently, white matter hyperintensities (WMH) have been linked to depressive symptomatology in studies on affective disorders.^{54–58} Aloia et al. reported in a small sample of older patients with OSA more subcortical WMH in the brain MRI of patients with a severe OSA as compared to those with minimal OSA, and a tendency for a positive correlation between these subcortical hyperintensities and depression scores on the Hamilton Depression Scale.⁵⁹

Neurobiology of depression and upper airway control in OSA: the role of serotonin

The high comorbidity of OSA and depression also suggests that both disorders may share a common neurobiological risk factor. On the neurotransmitter level, the serotonergic system has a central role as a neurobiological substrate underlying impairments in the regulations of mood, sleep-wakefulness cycle, and upper airway muscle tone control during sleep. Depression is associated with a functional decrease of

serotonergic neurotransmission, and is mostly responsible for the alterations in sleep as outlined above.⁶⁰

The physiopathology of OSA involves numerous factors, among whose the abnormal pharyngeal collapsibility during sleep is one of the most compelling. Serotonin delivery to upper airway dilator motor neurons has been shown to be reduced in dependency of the vigilance state.⁶¹ This leads to reductions in dilator muscle activity specifically during sleep, which may contribute to sleep apnea. However, whereas the role of serotonin in mood disorders has been largely documented, its involvement in the pathophysiology of sleep apnea remains to be clarified. Interestingly, molecules increasing 5-HT neurotransmission such as the Serotonin reuptake inhibitors (SSRI) are widely prescribed antidepressant molecules that are suggested to similarly improve the apnea hypopnea index in OSA. Serotonergic drugs such as fluoxetine, protryptiline and paroxetine have already been tested for OSA, with limited success and numerous adverse effects.⁶¹ Several 5-HT receptor ligands and bi-functional molecules are under development, which may in the future be able to target both, the depressive syndrome and OSA.

Shared risk factors: OSA and depression share common risk factors, which may partly explain their high comorbidity in the general population. Very frequently in studies of the impact of OSA on cognitive and psychological functioning, a conglomerate of disorders is shown to contribute to the overall neuropsychological outcome. Therefore, the presence of a polypathology often associated with OSA, such as obesity, cardiovascular disease, hypertension and diabetes, should increase the suspicion of an underlying or coexisting OSA in a depressed patient.

Both, depression and OSA, have independently been shown to be associated with metabolic syndrome, and also with the development of cardiovascular disease.^{62,63} The association between depression and metabolic syndrome has been suggested to be reciprocal,⁶⁴ and a priori not attributable to genetic factors as twin studies revealed.⁶⁵ In particular, insulin resistance (IR) has been suggested to contribute to the pathophysiology of depressive disorder and has been proposed to subserve the association between depression and cardiovascular disease.⁶⁶ Similarly, OSA has been observed to be independently associated with the cardiovascular risk factors comprising metabolic syndrome,⁶⁷ in particular IR.⁶⁸ The magnitude of this association has even led researchers to suggest that metabolic syndrome should encompass OSA.⁶⁹

Although OSA and depression share these common risk factors, there are currently no studies available which have investigated the issue of antecedent or consequence in the relationship between depression, OSA and metabolic syndrome, and if and how these three highly prevalent disorders may interact to exacerbate the risk for cardio – and cerebrovascular morbidity and mortality.

Clinical application: As a consequence of the complex relationship between depression and OSA, the assessment of a patient's individual sleep history should be included in the standard psychiatric clinical interview, and specifically in the assessment of a depressive syndrome. A clinician should suspect OSA particularly in those depressed patients who present with its cardinal symptoms, namely, 1) loud snoring or

intermittent pauses in respiration, as witnessed by a bed partner, associated with 2) excessive daytime sleepiness (EDS). Given that patients often deny the latter, standardized questionnaires such as the Epworth Sleepiness Scale (ESS)⁷⁰ or the Functional Outcome Sleep Questionnaire (FOSQ)⁷¹ are useful tools to assess EDS. The ESS asks the patients to rate their chances to fall asleep during periods of relaxation or inactivity (such as reading, watching television), but also in more active settings (driving a car, sitting and talking to someone). EDS is by far the most frequent daytime symptom of OSA, whereas nocturnal symptoms include restlessness, nocturia, excessive salivation and sweating, gastroesophageal reflux, as well as headache and dry mouth or throat in the morning on awakening. Furthermore, the clinical picture frequently includes obesity and hypertension, and, in those patients who are not obese, special facial abnormalities which narrow the upper airway, such as retrognathia or micrognathia.

However, it should be kept in mind that OSA may not be immediately apparent, but might present in an atypical fashion, with irritability, tiredness, disrupted sleep, difficulty concentrating, difficulties accomplishing tasks and generally decreased psychomotor performance.¹² Women are more likely to present with these symptoms,^{22,72,73} and have been suggested to be particularly underdiagnosed because of their atypical symptoms.⁷⁴ The importance of the sleep-wake complaints in a patient's depressive profile, and the onset of those complaints prior to the development of the depressive psychopathology should draw the clinician's attention to a potential underlying or coexisting OSA.⁷⁵

Third, particular attention should be paid to depressive patients who are resistant to treatment. In this case, OSA should be excluded as a major underlying contributing factor,⁷⁶ as treatment of OSA could improve not only the compliance to pharmacological antidepressant treatment, but also the treatment response rate for depression.⁷⁷ Fourth, comorbid disorders of OSA may also catch the attention of the treating psychiatrist. In addition to the outlined association with the metabolic syndrome, Farney et al. observed that the likelihood of OSA increased significantly when either antihypertensive or antidepressant medications had been prescribed.⁷⁸

Depressed patients with a suspected OSA should be referred to a sleep disorders center for evaluation by nocturnal polysomnography, to confirm the diagnosis of OSA or the presence of other forms of sleep disordered breathing, such as the upper airway resistance syndrome.⁷⁹ This is of particular importance, as some of the adjunct treatments to the current pharmacological treatment of depression may actually exacerbate the condition.

If the diagnosis of OSA has been established in a depressed patient, and treatment has been initiated, close follow-up of the improvement of the depressive symptoms might give some indications as to the extent to which the presence of OSA may have contributed to the depressive symptomatology. However, as Baran and Richert point out,⁴¹ the aforementioned diagnostic challenge of a depressive syndrome in the presence of OSA currently remains unresolved.

On the other hand, systematic assessment of depressive symptoms with standardized clinical questionnaires in OSA patients is generally part of the evaluation process in all major

sleep disorder centers. However, as these questionnaires have not been specifically designed to assess depression in OSA patients,⁸⁰ they might be inappropriate to assess depression in this population, given that it is still unclear if OSA and depression display a true comorbidity or only share similar symptoms.⁴¹ Typically, patients with severe depressive symptoms should be referred to a psychiatrist, particularly if such symptoms do not regress or if fatigue lingers after efficient treatment of OSA.⁸¹

Conclusion

Recent studies underscore the existence of a complex relationship between depression and OSA in terms of clinical presentation, underlying pathophysiology and treatment. It should incite the treating psychiatrist to be highly aware of a possibly underlying or coexisting OSA in depressed patients. Up to 20% of all patients presenting with a diagnosed depressive syndrome may also have OSA, and vice versa. This relationship might vary widely, depending on age, gender, AHI cut-off and general demographic and health characteristics of the population under investigation. Future clinical research in this area should specifically examine depressed patient populations, taking into account the different sub-type of mood disorders, and investigate a broader range of depressive symptomatology in OSA patients. Basic research should further investigate the causal relationship between depression and OSA, as well as the potential mechanisms by which both disorders may interact.

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Upper Airway Dynamics During Negative Expiratory Pressure in Apneic and Non-Apneic Awake Snorers

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Abstract

Background: The ability of negative expiratory pressure (NEP) technique to differentiate between awake snorers with and without obstructive sleep apnea-hypopnea (OSAH) was investigated.

Methods: Forty-eight subjects with sleep disordered breathing (SDB) and 7 healthy subjects, as non-snorers controls, underwent the NEP application of -5 and -7 cmH₂O in the seated and supine position during wakefulness, after performing a sleep study. The upper airway collapsibility was assessed by computing the volume exhaled during the first 0.5 sec. ($V_{NEP_{0.5}}$) and 1 sec. (V_{NEP_1}) following the NEP start.

Results: Patients with severe ($AHI \geq 30$) ($n = 19$) and mild-to-moderate ($AHI < 30$ and > 5) ($n = 15$) OSAH had lower $V_{NEP_{0.5}}$ (340 ± 88 ml) as compared to snorers ($AHI \leq 5$) ($n = 14$) (427 ± 101 ml; $p < 0.01$) and controls ($n = 7$) (492 ± 69 ml; $p < 0.001$) in the supine position with NEP -5 cmH₂O. Less significant differences among the different groups were observed for $V_{NEP_{0.5}}$ in the seated position with NEP -5 cmH₂O and in both positions with NEP -7 cmH₂O (only OSAH patients vs controls, $p < 0.001$). Similar results were obtained for V_{NEP_1} in either position by using both NEP -5 cmH₂O and -7 cmH₂O. In spite of this, a substantial overlapping of $V_{NEP_{0.5}}$ and V_{NEP_1} between snorers and OSAH patients did not allow to identify a reliable diagnostic cut-off level. An inverse correlation with AHI was found for $V_{NEP_{0.5}}$ in the supine position with NEP -5 cmH₂O ($r_s = -0.46$, $p < 0.05$) in severe OSAH patients.

Conclusion: The awake OSAH patients exhibit values of $V_{NEP_{0.5}}$ and V_{NEP_1} lesser than those of awake snorers. The NEP technique, however, appears to have a limited usefulness as clinical tool for routine screening of the OSAH patients during wakefulness.

Introduction

Among the mechanical factors that are believed to promote obstructive sleep apnea/hypopnea (OSAH), the increase in passive upper airway compliance, as assessed by the pharyngeal volume (area)-pressure relationship in the absence of upper airway dilator muscle activity, has been repeatedly emphasized.¹⁻⁶ This feature influences for a given transmural pressure the end-expiratory cross-sectional area at different levels of the upper airways and may be crucial for the development of upper airway narrowing and/or closure at the onset of inspiration during sleep, when the neural activation of upper airway dilator muscles decreases.^{7,8} Moreover, the patients suffering from OSAH exhibited less negative (sometimes positive) closing (or critical) pressure of the passive upper airways (i.e. the pressure inside the upper airways when they close), as compared to sex, age and body mass index matched snorers and normal subjects.^{3,9-11} The increased critical pressure that is considered to reflect a high extraluminal pressure has been ascribed in apneic patients to structural abnormalities such as para-pharyngeal fat deposits in obesity and/or reduced cross-section of bony structures of the lower face in cranio-facial anomalies.^{12,13} In fact, several observations suggest that either obesity or cranio-facial anomalies would act to increase the tissue pressure surrounding the pharyngeal airway, thus favoring OSAH by reducing the transmural pharyngeal pressure and making the upper airways easier to narrow for a given compliance. In addition, there is compelling evidence that the upper airways have a smaller lumen during wakefulness^{8,13,14} and sleep³ in OSAH patients, who show an increase in the upper airway resistance,¹⁵⁻¹⁸ often assuming an anterior-posterior configuration of their major axis with a prevalent lateral narrowing.^{8,19} These factors tend to increase both the pharyngeal compliance, which is volume and shape dependent, and the closing pressure. Recently, pharyngeal airway length has

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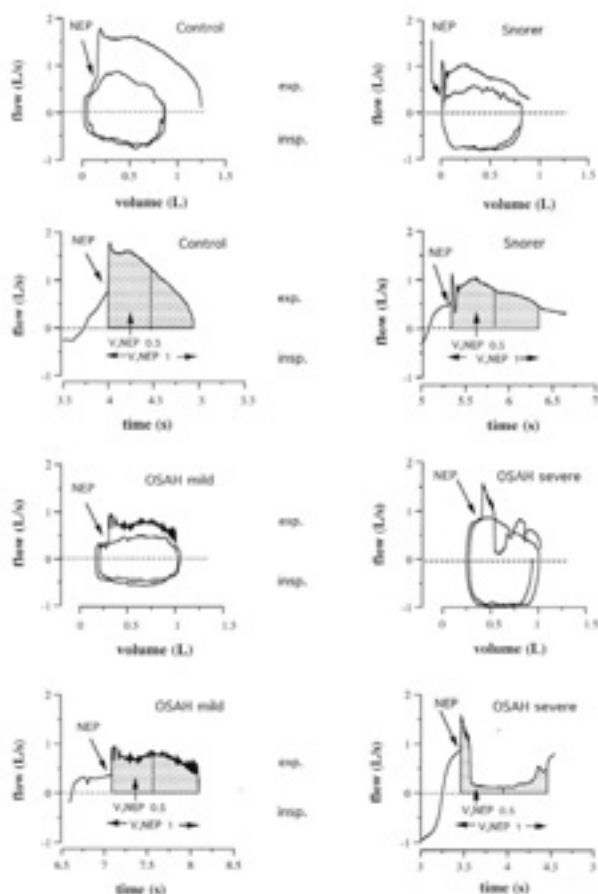


Figure 1
Supine tidal flow-volume curves (control and during NEP of -5 cmH₂O) and corresponding expiratory flow-time curves (only during NEP) in representative subjects of the different groups. The hatched areas under the flow measure the volume exhaled in the first 0.5 sec. ($V_{NEP 0.5}$) and 1 sec. ($V_{NEP 1}$) after NEP application.

been found to be greater in OSAH patients, possibly influencing its collapsibility.^{20,21}

Hence, several, concurrent, inter-related mechanisms (increased compliance, decreased transmural pressure, smaller size and greater length of the upper airways) might enhance the pharyngeal collapsibility in patients with OSAH.

Therefore, simple assessment of upper airway mechanics during wakefulness could identify OSAH subjects and select them for standard polysomnography. In normal awake subjects the application of small negative expiratory pressure (NEP) transients at the onset of resting expiration does not elicit reflex activity of the genioglossus nor changes in upper airway resistance per se.^{22,23} Under these conditions, the flow dynamics at the beginning of the expiratory phase during NEP application are expected to reflect the mechanical behavior of the pharyngeal airway in a “quasi-passive” condition even during wakefulness. Accordingly, the aim of our study was i) to investigate if volume exhaled during early application of NEP at the onset of quiet expiration at rest was different in OSAH patients, snorers and normal subjects, suggesting different degrees of pharyngeal collapsibility among these groups and ii) if these differences could be used to distinguish non-apneic from apneic snorers.

Methods

Subjects: In a prospective, randomized study we investigated at the Division of Pneumology of the S. Orsola-Malpighi Hospital of Bologna the early expiratory flow dynamics after the application of a small (-5 to -7 cmH₂O) negative pressure at the mouth in 48 awake male subjects coming from the Neurology Unit who had performed a polysomnographic study in the Sleep Center because of suspected sleep disordered breathing. We excluded those with obvious anatomical defects such as cranio-facial and/or severe otorino-laryngoiatric (ORL) abnormalities, or with neurological and endocrine diseases known to be causally associated with SDB. Subjects affected by cardiac and respiratory disorders capable of causing intra-thoracic tidal expiratory flow limitation (EFL) were also excluded, as well as obese subjects with tidal intra-thoracic EFL in either position. Subjects were not treated with drugs active on CNS or suffered from chronic alcoholism. Among the enrolled subjects 34 resulted affected by obstructive sleep apnea-hypopnea (OSA) and 14 were snorers without OSA (Sn). Seven male subjects, non-apneic, non-snorer, as assessed by nocturnal polysomnography, were recruited from the Hospital staff as controls. The study was approved by the local Ethics Committee and an informed consent was obtained from each subject.

Study design – Sleep study: All subjects were examined at the Sleep Center performing an overnight polysomnographic study by recording the following parameters: nasal pressure (by nasal cannula), oral flow (by thermistor), abdominal and rib cage movements (by piezo-sensors), oxygen saturation and heart rate (by finger oxymeter), snoring (by microphone), body movements and body posture. Respiratory events were defined as obstructive apnea in the presence of nose and mouth airflow cessation for at least 10 sec with concomitant inspiratory efforts and as obstructive hypopnea in the presence of discernable inspiratory airflow reduction with inspiratory efforts accompanied by a decrease of >3% in oxygen saturation. The results were expressed as the number of apnea and hypopnea per hour of sleep (apnea-hypopnea index, AHI).²⁴ The subjects were categorized according to AHI as non-apneic snorers (AHI ≤ 5) and snorers with mild-to-moderate (AHI <30 and >5) or severe (AHI ≥ 30) OSAH.

NEP testing: Subsequently, the subjects were sent to the Division of Pneumology to evaluate the upper airway mechanics looking at the flow-time relationship in the early tidal expiration during strict wakefulness. Expiratory flow dynamics was assessed during the application of a negative expiratory pressure at the mouth (NEP technique). NEP was applied randomly at two different levels, i.e. -5 cmH₂O and -7 cmH₂O, initially in the seated position and later, 10 minutes after assuming the supine posture. In both positions and at both levels of negative pressure, at least 5 NEP breath-tests were performed at intervals of 5–10 respiratory cycles, always when the patient had resumed regular breathing according to the spirogram that was continuously displayed on the computer monitor. In this respect, great care was placed to check the level of the end-expiratory lung volume. The expiratory flow recorded under each NEP application was measured in the first 0.5 and 1 sec from the onset of NEP administration to compute by time integration the volume exhaled in these time intervals, labeled hence for $V_{NEP 0.5}$ and $V_{NEP 1}$, respectively (Fig. 1). For all subjects in each experimental condition (different posture and negative pressure levels) the mean value of $V_{NEP 0.5}$ and

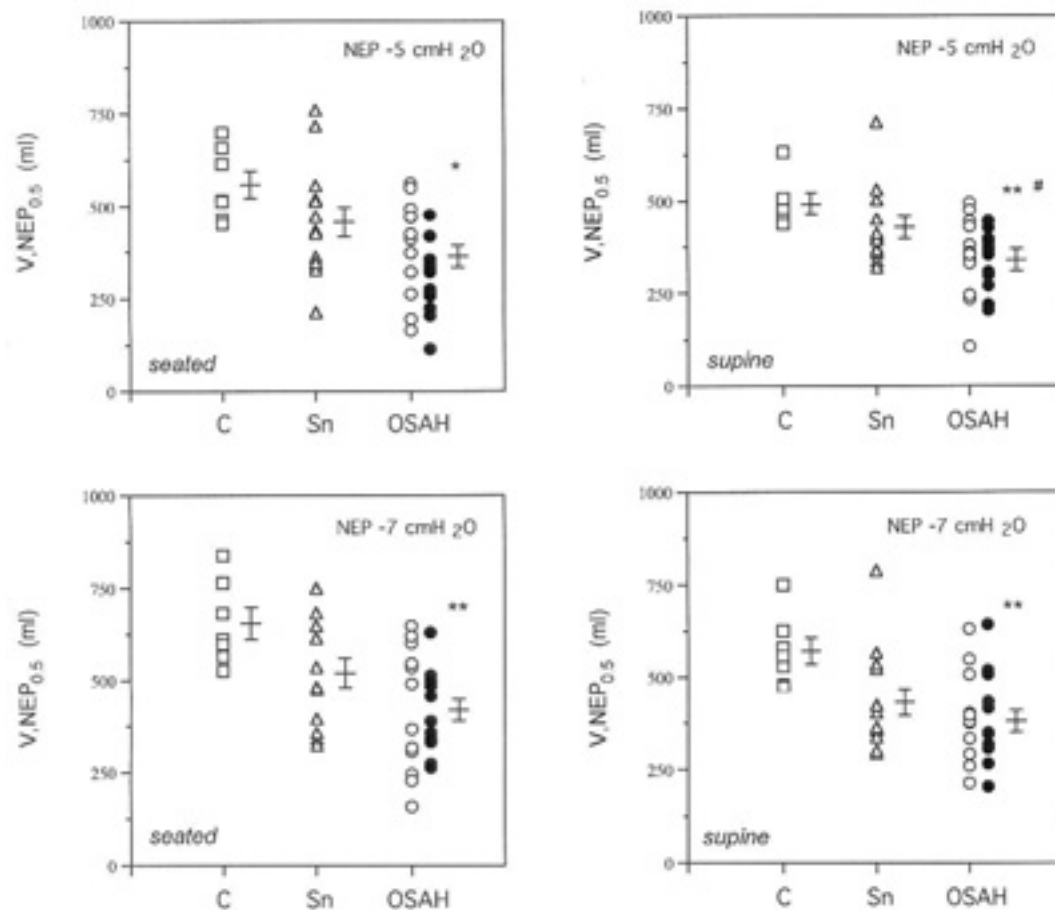


Figure 2
Individual values of $V_{,NEP_{0.5}}$ in seated and supine position at two NEP levels in patients with obstructive sleep apnea-hypopnea (OSA) (circles, white for mild-to-moderate OSAH and black for severe OSAH), snorers (Sn) (triangles) and controls (C) (squares).
* $p < 0.01$ vs C; ** $p < 0.001$ vs C; # $p < 0.05$ vs Sn.

$V_{,NEP_1}$ was calculated, after discarding the highest and the lowest value, by averaging those obtained during at least 3 acceptable NEP maneuvers. It should be noted that the NEP was applied unknown to the subject by a computer at the very onset of the tidal expiration. We also computed the differences between $V_{,NEP_{0.5}}$ and $V_{,NEP_1}$ and the corresponding volumes exhaled during preceding spontaneous expirations ($\Delta V_{,NEP_{0.5}}$ and $\Delta V_{,NEP_1}$) in the different groups of subjects. These measurements were performed in both positions and at the same different levels of NEP applied, aiming to normalize in each subject the $V_{,NEP_{0.5}}$ and $V_{,NEP_1}$ values for the baseline expiratory flows and volumes. The physician who performed

and assessed the NEP tests was blinded to the polysomnographic results.

Pulmonary function testing: All subjects underwent spirometric measurements using a computerized system ($V_{max} 22$; Sensor Medics, Yorba Linda, CA) in seated position. Slow vital capacity (VC) and three acceptable and reproducible maximal full flow/volume curves were obtained. Subjects inspired to TLC and then expired forcefully without an end-inspiratory pause to obtain forced vital capacity. The predicted values for volumes and flows were those proposed by the European Community for Coal and Steel.²⁵

Table 1: Anthropometric and functional characteristics of subjects.

	Controls	Snorers	OSA, mild	OSA, severe
Subjects (n)	7	14	15	19
Age (yrs)	40 ± 8	49 ± 13	49 ± 10	53 ± 8 *
BMI (kg/m ²)	24 ± 3	27 ± 4	26 ± 3	29 ± 3 *
FEV1 (% pred)	98 ± 10	96 ± 31	103 ± 25	95 ± 26
FVC (% pred)	97 ± 15	96 ± 24	100 ± 24	93 ± 20
FEV1/FVC (%)	88 ± 12	79 ± 11	81 ± 11	86 ± 1
AHI	2 ± 0.4	4 ± 2	18 ± 10	59 ± 16

BMI = body mass index; FEV1 = forced expired volume in the first second; FVC = forced vital capacity; OSAH = obstructive sleep apnea-hypopnea; AHI = apnea-hypopnea index; data are mean ± SD; * $p < 0.01$ vs Controls.

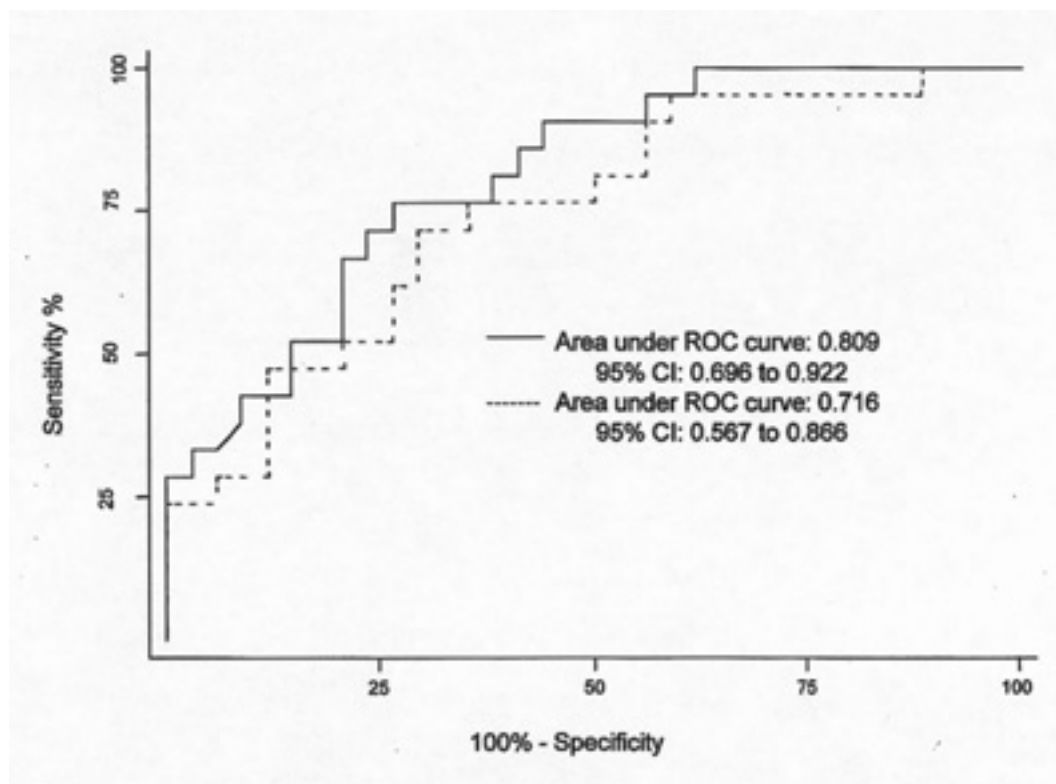


Figure 3

The receiver-operating characteristics (ROC) curves are shown for $V_{NEP_{0.5}}$ values during NEP ($-5 \text{ cmH}_2\text{O}$) both in supine (continuous line) and seated (dashed line) position in 34 patients with OSAH and 21 subjects without OSAH. The area under the ROC curves reflects the ability of $V_{NEP_{0.5}}$ to distinguish subjects without and with OSAH ($AHI > 5$).

Experimental NEP set-up: In both seated and supine position, all subjects wearing nose-clips breathed spontaneously room air through a flanged mouthpiece and a heated pneumotachograph (3700 series; Hans Rudolph, Kansas City, MO) connected to a differential pressure transducer (Raytech DP55 $\pm 3 \text{ cmH}_2\text{O}$; Raytech Instruments, Vancouver, BC, Canada) to measure the flow. The pneumotachograph was linear over the experimental flow range. Volume (V) was obtained by electrical time integration of the flow signal. Pressure was recorded at the mouth (P_m) via a rigid polyethylene catheter (internal diameter = 1.7 mm) connected to a differential pressure transducer

(Raytech DP55 $\pm 100 \text{ cmH}_2\text{O}$; Raytech Instruments). The pneumotachograph was assembled in series to a Venturi device that created a negative pressure in the circuit, whose magnitude could be precisely fixed. The application of the negative pressure did not affect the accuracy of the pneumotachograph which measured a flow less than 1 ml/s when the system was switched on. The Venturi device was connected to a solenoid valve (Asco electrical valve, model 8262G208; Ascoelectric, Ontario, Canada) controlled by a computer and automatically activated when the expiratory flow reached a pre-set threshold value (i.e.: 50 ml/s) and after a pre-set time delay (i.e.: 200 ms.).²⁶ In all instances the NEP application was timed to last until the lung volume corresponding to the end-expiratory lung volume of the previous control breath was reached or for at least 1.3 sec. The flow and pressure signals were amplified (AC bridge Amplifier-ABC module; Raytech Instruments), filtered through a low-pass filter at 50 Hz, sent to an A/D converter (Direc Physiologic Recording System; Raytech Instruments) connected to an IBM personal computer and sampled at 200 Hz. Both digitized signals were displayed in real time on the computer screen together with the volume signal. The tracings were continuously monitored both with respect to time and as flow/volume curves. All signals were calibrated independently and simultaneously recorded on the hard disk of the computer and were used for subsequent analysis. Data analysis was performed using data analysis software (Direc NEP, version 3.1; Raytech Instruments or Anadat, version 5.2; RHT-InfoDat; Montreal, Quebec, Canada).

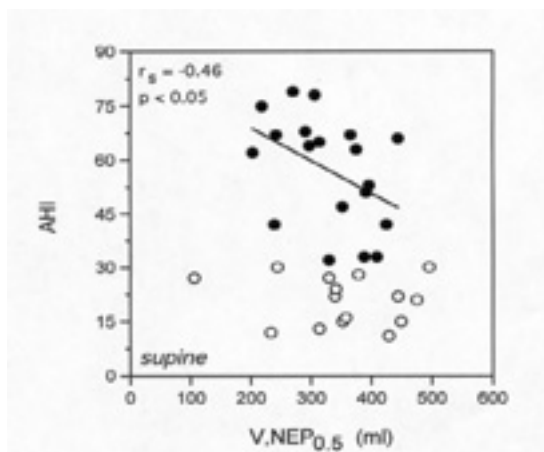


Figure 4

Relationship between AHI and $V_{NEP_{0.5}}$ in the supine position during NEP ($-5 \text{ cmH}_2\text{O}$) in OSAH patients (white circles = mild-to-moderate OSAH; black circles = severe OSAH). The regression line refers only to severe OSAH patients.

Statistical analysis: Data are presented as mean \pm standard deviation (SD). To assess and verify the normal distribution of the data in each group the Kolmogorov-Smirnov test was

Table 2: Values of V,NEP_{0.5} and V,NEP₁ at two different NEP levels in seated and supine position.

NEP	SEATED		SUPINE	
	-5 cmH ₂ O	-7 cmH ₂ O	-5 cmH ₂ O	-7 cmH ₂ O
V,NEP _{0.5}				
Controls	559 ± 98	655 ± 113	492 ± 69	571 ± 96
Snorers	457 ± 150	520 ± 147	427 ± 101	430 ± 134
OSAH	363 ± 123*	419 ± 132**	340 ± 88** #	379 ± 113**
OSAH, m	402 ± 129	428 ± 157	353 ± 103	387 ± 108
OSAH, s	332 ± 112	410 ± 112	329 ± 73	372 ± 119
V,NEP ₁				
Controls	1036 ± 134	1128 ± 158	832 ± 95	920 ± 136
Snorers	864 ± 246	930 ± 274	737 ± 194	755 ± 224
OSAH	708 ± 189*	781 ± 210*	628 ± 136*	669 ± 177*
OSAH, m	732 ± 202	766 ± 230	625 ± 159	666 ± 178
OSAH, s	688 ± 182	792 ± 199	629 ± 120	671 ± 180

OSAH = obstructive sleep apnea-hypopnea; m = mild; s = severe; data are mean ± SD; * p < 0.01 vs Controls; ** p < 0.001 vs Controls; # p < 0.01 vs Snorers

performed. Then, one-way ANOVA was used to compare data among groups both in seated and supine position and at different negative pressure and finally multiple comparisons, corrected by the Bonferroni method, were performed between groups, if allowed by the F-value. To assess differences in V,NEP_{0.5} and V,NEP₁ within groups between seated and supine posture and different levels of negative pressure a paired Student's test was applied. Correlations between quantitative variables were performed using the Spearman's rank-order test. A p value less than 0.05 was considered statistically significant. The receiver-operating characteristic curves (ROC) were performed to assess sensitivity and specificity of V,NEP_{0.5} and V,NEP₁ obtained with different levels of NEP in both positions to get optimal cut-offs.

Results: The anthropometric and functional characteristics of the subjects are shown in Table 1. Snorers and OSAH patients were well matched, but patients with severe OSAH were older and had greater BMI than controls (p < 0.01). No correlation, however, was present between V,NEP_{0.5} and V,NEP₁ and BMI in snorers or OSAH patients. None of the subjects had significant restrictive or obstructive ventilatory defect and exhibited tidal intrathoracic EFL in either position during NEP application.

The values (mean ± SD) of V,NEP_{0.5} and V,NEP₁ in both positions and NEP levels, are shown in Table 2. The individual V,NEP_{0.5} data in each group are shown in Fig. 2. Similar values of V,NEP_{0.5} and V,NEP₁ were obtained in subjects with mild-to-moderate and with severe OSAH in all experimental conditions and were treated as a single group for comparative analysis.

ΔV,NEP_{0.5} and ΔV,NEP₁ reflected exactly what was shown by V,NEP_{0.5} and V,NEP₁ with no additional advantage in order to distinguish the different groups. Therefore, we did not consider these time-consuming indices for subsequent analysis.

Within each group V,NEP_{0.5} and V,NEP₁ were significantly higher with NEP -7 cmH₂O than with NEP -5 cmH₂O in both positions, and with the same negative pressure higher in the seated

position than in the supine one (p < 0.05 for controls, p < 0.01 for snorers and patients with OSAH).

The patients with OSAH consistently exhibited values of V,NEP_{0.5} and V,NEP₁ much lower than control subjects (p < 0.001), but had values of V,NEP_{0.5} significantly reduced as compared to snorers only with NEP -5 cmH₂O in the supine position (p < 0.01) (Fig. 2).

The receiver operating characteristic (ROC) curves performed for V,NEP_{0.5} and V,NEP₁ in both positions at the two different levels of NEP showed similar areas with the highest value for V,NEP_{0.5} in the supine position using NEP of -5 cmH₂O (Fig. 3). Under these conditions, the optimal cut-off V,NEP_{0.5} value of 393 ml had a sensitivity of 76% and a specificity of 74% to detect the presence of OSAH with a likelihood ratio for positive results of 2.9. Accordingly, its positive and negative predictive value was 84% and 64%, respectively.

No significant correlation between V,NEP_{0.5} (in the supine position with NEP level of -5 cmH₂O) and AHI was observed in patients with OSAH (r_s = -0.31, r_s² = 0.10; 95%IC = -0.59 – 0.04). However, taking into account only the patients with severe OSAH (AHI ≥ 30), a significant inverse correlation was found between V,NEP_{0.5} and AHI (p < 0.05; r_s = -0.46, r_s² = 0.21; 95%IC = -0.76 – -0.01) (Fig. 4).

Discussion

The present study indicates that during wakefulness OSAH patients when compared to snorers and controls have greater collapsibility of the upper airways which can be easily assessed looking at the early expiratory flow dynamics after NEP application during tidal breathing and properly measured as V,NEP_{0.5} and V,NEP₁. Such measurements, however, are unable to distinguish on an individual basis apneic from non-apneic snorers because of the overlapping of the V,NEP_{0.5} and V,NEP₁ values between these groups of subjects. Nevertheless, our results provide support to the idea that a high degree of the upper airway collapsibility promotes OSAH, even if OSAH may

seldom occur in subjects with normal upper airway mechanics during wakefulness, suggesting the involvement of other pathogenetic factors.

Although our snorers had similar age, gender and BMI without obvious cranio-facial and ORL anomalies, lateral cephalometry or MRI studies of the pharynx were not performed, so we cannot exclude minor anatomic abnormalities in bony structure or soft tissue around the pharyngeal airway in OSAH patients. Conversely, careful inspection of the maximal and tidal expiratory flow-volume curves allowed us to rule out the presence of intrathoracic expiratory flow limitation during resting tidal breathing in all subjects. Therefore, we are confident that our subjects had no intrathoracic expiratory flow limitation which might have influenced the upper airway-related expiratory flow dynamics when NEP was applied.

The usefulness of the NEP method to assess the upper airway collapsibility was previously tested in 16 awake subjects known to suffer from sleep-disordered breathing.²⁷ In contrast to snorers, all patients with OSAH ($n = 8$) showed a substantial portion ($>30\%$) of the expiratory tidal volume throughout the NEP application ($-5 \text{ cmH}_2\text{O}$, in the supine position) with lesser expiratory flow than the one recorded during the previous control tidal expiration.

Subsequently, in a group of 19 patients with OSAH when NEP was applied (-5 and $-10 \text{ cmH}_2\text{O}$, in the supine position) the expiratory flow was reduced, when compared with the corresponding spontaneous expiratory flow, during a relevant part of the tidal expiration ($>20\%$) in those ($n = 13$) with a higher mean apnea-hypopnea index (AHI).²⁸

In these studies a significant correlation was found between the percentage of the tidal volume during the NEP application with lower expiratory flow than during the spontaneous breathing and oxygen desaturation index (ODI), in the former, and ODI and AHI, in the latter.^{27,28} Hence, the NEP method appeared suitable in order to detect an increased pharyngeal collapsibility in patients with OSAH during wakefulness and perhaps able to predict the severity of OSAH.

Recently, using the same criteria, a large cohort of snoring subjects was examined to assess the capacity of the NEP method to screen apneic from non-apneic subjects.²⁹ In this study a sensitivity of 81.9% and specificity of 69.1% in predicting OSAH was found when the expiratory flow during NEP ($-5 \text{ cmH}_2\text{O}$ in supine position) was below that of the previous control expiration for $\geq 27.5\%$ of the tidal volume. In addition, a significant correlation between NEP induced flow analysis and OSAH severity, as assessed by AHI, was found in the supine position using $-5 \text{ cmH}_2\text{O}$ of NEP with a coefficient value ($r_s = 0.51$) similar to the one we obtained in the severe OSAH patients ($r_s = 0.46$).

All of these studies, however, are based on the assumption that abnormal upper airway collapsibility is present or can be identified only when the expiratory flow during NEP becomes lower than the control one. Moreover, such finding has been erroneously taken as a marker of expiratory flow limitation. In contrast, an increased pharyngeal collapsibility can also be reflected by a smaller increase of expiratory flow during NEP. We believe that this flow has to be measured whether or not it is higher, lower or initially higher and then lower (or vice versa)

than the flow of the previous tidal expiration. Indeed, judging as abnormal (or quantifying the severity of) the upper airway collapsibility only by computing the percentage of the tidal volume where the expiratory flow during NEP application becomes lesser than the one exhibited in the previous expiration is a poorly reliable tool. This is because such measure is too dependent from the preceding control tidal breathing and because the expiratory flow profile is often erratic in the same subject during repeated NEP tests; in addition, several apneic patients do not show such phenomenon constantly.²⁷⁻²⁹ In order to overcome these problems, recently Tamisier and colleagues investigated a quantitative index corresponding to the ratio of the area under the expiratory flow/volume curves between NEP (-5 and $-10 \text{ cmH}_2\text{O}$) and atmospheric pressure for the same tidal volume in awake subjects with sleep disordered breathing (SDB) and control subjects, both in supine and sitting position.³⁰ They found that this index was significantly different between controls and SDB subjects in all measurements, decreasing with the severity of the SDB. Moreover, in the supine position when $-5 \text{ cmH}_2\text{O}$ NEP was applied, a given threshold of this index had a positive predictive value of 88.6% and a negative predictive value of 80% to screen subjects with SDB. The Authors concluded that the NEP-related quantitative index may be useful to detect abnormal upper airway collapsibility in awake subjects with SDB. However, some limits of this study are obvious such as the lack of subjects with mild OSAH ($\text{AHI} < 15$ and > 5) and the age of the controls who were much younger (34 ± 12 yrs) than the patients with OSAH. Furthermore, the application of NEP near end expiratory lung volume tends to elicit reflex activation of genioglossus.²² This can unpredictably influence the area under the final part of the expiratory flow/volume curve during NEP both in controls and SDB subjects, affecting the quantitative index used to assess the upper airway collapsibility.

In a very recent paper Insalaco and coworkers used the drop of expiratory flow under NEP ($\Delta V\text{-NEP}$), expressed as percentage change of peak expiratory flow under NEP, as index of upper airway collapsibility to detect OSAH in patients with sleep disordered breathing. Although this index was a better indicator of OSAH severity when compared to the previous ones, they reported, at best, a determination coefficient equal to 0.32 between the AHI and $\Delta V\text{-NEP}$,³¹ using NEP of $-10 \text{ cmH}_2\text{O}$ in the supine position. An inherent problem with this approach is that $\Delta V\text{-NEP}$ does not take into account the duration of the expiratory flow drop under the NEP application, while it is very clear from the flow-time tracings given by the same Authors that this transient may last very differently with the same percentage value of reduction.

By time-integration of the expiratory flow in the first 0.5 and 1 sec after the application of a given level of NEP one can easily calculate the expiratory volume exhaled in a preset time in a given body position during wakefulness and use this parameter as an index of the mechanical properties of the upper airways at the onset of expiration when the genioglossus does not appear reflexively activated.²² Therefore, the novelty of this study is the utilization of a method which, still adopting the NEP technique, is more reliable to assess and measure the upper airway collapsibility because it is quantitative, and it is not influenced by the flow of the preceding tidal expiration and by the effect of neuromuscular factors.

$V_{\text{NEP}0.5}$ and $V_{\text{NEP}1}$ values were reduced in the supine position

at each level of applied NEP in all groups, likely to reflect a posture-related increase in the upper airway resistance.^{18,23,32,33} Therefore, $V_{NEP_{0.5}}$ and V_{NEP_1} measurements appear to be influenced by the baseline expiratory upper airway resistance which has been shown to be higher in OSAH patients, probably because of minimal structural abnormalities (abnormal hyoid bone position and increase in soft pharyngeal tissues)²⁰ and related shape changes. It is conceivable that lower $V_{NEP_{0.5}}$ and V_{NEP_1} found in our OSAH patients may be partly due to reduced baseline upper airway caliber which, on the other hand, is expected to increase the pharyngeal compliance and finally the upper airway collapsibility in these subjects.²¹ However, the expired volume in the first 0.5 or 1 sec was lower during NEP than during the previous control expiration in either position in about 15–18% of our apneic snorers. This never occurred in snorers and controls. This fact strongly suggests that in OSAH patients a brisk narrowing of upper airways is elicited by the sudden NEP application, the magnitude of which is largely depending on the pharyngeal collapsibility under the prevailing circumstances and substantially reflected by the $V_{NEP_{0.5}}$ or V_{NEP_1} values. In line with this reasoning, the early expiratory flow during NEP was often below the isovolume spontaneous expiratory flow, particularly in OSAH patients (see Fig. 1), as also shown in previous studies.^{22,27,28}

Under these experimental conditions, $V_{NEP_{0.5}}$ was significantly lower in apneic than in non-apneic snorers when measured in the supine position utilizing the smallest level of NEP (i.e.: -5 cmH₂O in our study). Thus, the lower the value of $V_{NEP_{0.5}}$ (or V_{NEP_1}), the higher the possibility for snoring people to have OSAH. Indeed, according to this method an increased pharyngeal collapsibility even during wakefulness affects the vast majority of snorers who have OSAH. This information is obtained in a rapid, simple and non-invasive way without cooperation of the subjects who can be studied when awake, repeatedly and in different body position. In this respect it has to be stressed that it is not necessary to control with regards to baseline spontaneous tidal volumes and flows. Indeed, $\Delta V_{NEP_{0.5}}$ and ΔV_{NEP_1} did not perform differently or better to distinguish between snorers and OSAH patients than $V_{NEP_{0.5}}$ and V_{NEP_1} .

Unfortunately, the ability to differentiate snorers with or without OSAH was not sufficient, at least within our capabilities, to recommend this technique and related parameters as a reliable diagnostic tool to obviate sleep studies or even to select subjects for polysomnographic evaluation. Lower levels of NEP (i.e.: -2 or -3 cmH₂O), however, might be more useful for this purpose and deserve to be tested in the future.

Three further comments need to be made. Firstly, generally a high collapsibility of the upper airways does not seem sufficient to cause OSAH since several snorers without OSAH exhibited similarly reduced values of $V_{NEP_{0.5}}$ or V_{NEP_1} . Secondly, other factors must influence the severity of OSAH, as assessed by ODI and AHI, because no different values of $V_{NEP_{0.5}}$ (or V_{NEP_1}) were found in any position or with different levels of NEP between mild-to-moderate and severe OSAH patients. Thirdly, some OSAH patients have surprisingly high values of $V_{NEP_{0.5}}$ (or V_{NEP_1}) comparable to those of the controls, showing a normal upper airway collapsibility during wakefulness, and thus suggesting different state-related factors leading to OSAH or a site of upper airway obstruction during sleep only at naso-pharyngeal level which cannot be directly assessed with this technique.

Finally, contrary to the opinion of the other authors who used the NEP technique to detect OSAH patients during wakefulness,²⁷⁻³⁰ we have to stress that, although the results obtained with $V_{NEP_{0.5}}$ were similar or even better than the previous ones,²⁷⁻³⁰ whatever NEP-related parameter is adopted, presently this tool is not sufficiently capable of revealing OSAH on an individual basis for clinical purpose.

In conclusion, the NEP technique when properly used is potentially useful to study upper airway collapsibility in patients with OSAH during wakefulness in order to better understand its main mechanisms, to assess in the long term the effects of various interventions, and possibly for selecting non-apneic snorers to follow up. On the other hand, it cannot be recommended for routine OSAH screening in awake snorers who should subsequently be subjected to sleep studies.

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Who Should Have A Sleep Study For Sleep Related Breathing Disorders?

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By the time children are 5 years old more of their life will have been spent asleep than awake. Sleep medicine is therefore especially relevant in pediatrics. However, one recent survey showed that pediatricians' knowledge of sleep medicine is poor and that few pediatricians enquire about sleep as part of their general consultation.¹

Ventilatory function is physiologically reduced during sleep in adults and children. Therefore, respiratory disorders are exacerbated and may only be clinically apparent during sleep. Assessing respiratory status only when a child is awake will underestimate the severity of sleep related breathing disorders or miss them altogether. Such failure to recognize sleep related breathing disorders can have significant adverse consequences on children's physical health and on their behavior and learning.

How are sleep related problems identified? The first step towards identifying a sleep related breathing disorder is to take a careful history.

Symptoms during sleep and wakefulness should be enquired about as part of the general pediatric consultation (table 1). Symptoms of sleep disturbance are commonly reported by parents and include behavioural problems, parasomnias, and insomnia.² The commonest symptom associated with possible sleep disordered breathing is snoring, which may occur occasionally, only in association with upper respiratory infection or seasonal rhinitis, or on the majority of nights, termed habitual snoring. A history of snoring may be accompanied by reports of apnea or dyspnea associated with cessation of the respiratory noise. Such events are frightening to parents who may then maintain increased vigilance over their child during the night. Restless sleep with frequent changes of body position may indicate subcortical arousals.³ Children may sometimes adopt unusual sleeping postures, such as hyperextension of the neck to increase airway patency.

Autonomic disturbances, including heart rate variability,⁴ profuse sweating, and nocturnal enuresis,⁵ have been reported in children with sleep disordered breathing.

Children with breathing disturbances during sleep may be difficult to rouse or irritable on waking. Hypoventilation during sleep can be associated with the presence of morning headaches, vomiting, and lack of appetite for breakfast. Daytime symptoms include mouth breathing in children with adenoidal hypertrophy. Excessive daytime sleepiness is less common in children than in adults with sleep disordered breathing.⁶ However, behavioural disturbances such as hyperactivity or aggression may occur,⁷ and chronic sleep disturbance is associated with learning difficulties,⁹ developmental delay, failure to thrive, and cardiovascular dysfunction. Populations of children at increased risk of sleep related breathing disorders include those with adenotonsillar hypertrophy, craniofacial abnormalities, obesity, chronic respiratory or chest wall disease, and neuromuscular disorders affecting upper airway control and respiratory muscle function.

Physical examination should include assessment of factors predisposing to sleep related breathing disorders and of potential consequences of sleep disordered breathing. The former will include careful examination of the upper airway, looking particularly for signs of adenotonsillar hypertrophy, the commonest cause of increased upper airway resistance during sleep in children. Nasal patency should be assessed and the presence of craniofacial and palatal abnormalities noted. These include syndromes that affect the development of the mid-face and mandible, such as Pierre Robin, Apert, Treacher Collins, Charge, Goldenhar, and Pfeiffer,¹⁰ and conditions that may be associated with multifactorial sleep related breathing disturbances, for example achondroplasia,¹¹ in which central and obstructive apneas and chest wall restriction can all contribute to sleep related breathing disturbances. Children who have had palatoplasty for cleft palate may also have narrow posterior airways and be at risk of obstructive sleep apnea.¹² Respiratory examination, including measurement of respiratory function in appropriately aged children with suspected

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Table 1 Reported features that may suggest a sleep related breathing disorder

Features during sleep	Snoring Witnessed apnoeas Cyanosis Parental concern about their child's breathing Restless sleep Unusual sleeping posture
Symptoms on waking	Difficult to rouse in the morning Irritability/bursts of anger on waking Morning headaches or vomiting Lack of appetite for breakfast
Daytime features	Mouth breathing Excessive daytime sleepiness Hyperactivity/behavioural disturbance Learning/memory difficulties Developmental delay Poor growth

pulmonary or chest wall disease should be performed. The contribution of neuromuscular diseases to sleep disordered breathing should be considered in children with disorders affecting muscle strength and tone, including cerebral palsy, congenital and acquired myopathies and muscular dystrophies, particularly in association with kyphoscoliosis, and disorders affecting control of upper airway tone and reflexes, such as bulbar or pseudobulbar palsy.

Potential complications of sleep disordered breathing include failure of expected growth.¹³ Cardiac examination is usually normal, although signs of pulmonary hypertension may be present. Systemic hypertension is probably less common in children than in adults with obstructive sleep apnea but has been described.^{14,15} Cor pulmonale was described in earlier studies but is uncommonly seen, possibly due to earlier recognition and intervention of severe obstructive sleep apnea.

Although clearly important, clinical history and examination alone are unable to differentiate between children with and without significant sleep related breathing disorders. Symptoms are common; the prevalence of habitual snoring in a general population of children is 10%.¹⁶ However, most habitual snorers will have primary snoring, characterised by the absence of associated hypoxaemia, hypercapnia, sleep disruption, or daytime symptoms. This is a benign condition that does not require treatment. Only a small proportion of children who habitually snore have obstructive sleep apnea requiring treatment. Therefore, attempts have been made to devise screening methods to identify children at risk of significant sleep related breathing disorders.

Brouillette and others¹⁷ designed a clinical scoring system based on three questions about breathing during sleep. When applied to a general pediatric population, this was able to discriminate between healthy children and those with severe obstructive sleep apnea syndrome (OSAS) but did not identify those with mild to moderate OSAS. Carroll and coworkers¹⁸ extended this scoring system and applied it to a population of children referred to a sleep clinic for assessment of snoring or difficulty breathing during sleep. In this setting it was not possible to reliably distinguish primary snoring from OSAS using the clinical history alone. Preutthipan and others¹⁹ studied parents' ability to predict the severity of childhood OSAS based on observation of their child's sleep. They showed that parents of

children with severe OSAS were more likely to report cyanosis, obstructive apneas, and extremely loud snoring. They felt the need to shake or watch their child more frequently during sleep and were afraid of their child's breathing at night. However, no single parental observation or combination of these could be used to confidently predict severe OSAS. Other investigators have also shown that clinical evaluation alone is not sufficient to identify children with significant sleep related breathing difficulties.^{20,21} A group at high risk for severe obstructive sleep apnea can be identified but milder degrees may be missed. Therefore, some form of sleep study is advisable for further evaluation of symptomatic cases.

What investigations are available?

Overnight polysomnography (PSG) in a sleep laboratory is considered to be the gold standard investigation for suspected abnormal breathing during sleep in children. A dedicated pediatric sleep laboratory, which can accommodate the unique needs of children, is the ideal setting for such investigations. Studies in adult laboratories may be suboptimal and will be misinterpreted if adult diagnostic standards are applied. Despite the fact that young children take frequent naps, PSG is best performed at night during natural sleep. Marcus and others²² reported that nap studies had a positive predictive value of 100%, but a negative predictive value of only 20% for sleep disordered breathing. Nap studies can be useful for screening but are of limited diagnostic value, as they may not include episodes of rapid eye movement (REM) sleep; the behavioural state during which abnormalities are most likely to be seen. There is also some evidence that a sleep study is more likely to be abnormal in the later part of the night, which would be missed by a nap study. Sedatives should not be used to induce sleep for PSG as they depress upper airway dilator muscle function and may induce worse apnea in children predisposed to OSAS.²³

PSG simultaneously records a number of physiological variables, which can be selected depending on the clinical context in which the study is being carried out. They typically include respiratory movements, gas exchange, cardiac rate and rhythm, sleep state, and muscle activity. Respiratory effort can be assessed by simultaneously recording chest and abdominal wall movement using inductance plethysmography. Paradoxical inward rib cage movement (PIRCM) during inspiration is associated with upper airway obstruction during sleep.²⁴ However, the usefulness of this measurement is limited in infants and young children, in whom paradoxical rib cage movements occur physiologically during REM sleep. A more accurate way of measuring respiratory effort utilises oesophageal pressure monitoring, but this is more invasive and the presence of an oesophageal manometer can interfere with sleep, making it unacceptable to many children. Airflow at the nose and mouth are seldom measured directly but proxy measures indicating the presence of gas flow, such as temperature change measured with a thermistor, can detect apneas. Oxygenation is measured by pulse oximetry, and carbon dioxide tensions can be measured non-invasively using an end-tidal CO₂ catheter or transcutaneous CO₂ electrode.

Sleep staging ensures that the study includes periods of REM sleep. It also allows arousals from sleep, including subcortical arousals, to be identified, and hence provides information on sleep quality. Staging sleep involves the combined measurement of the electroencephalogram (EEG), electro-oculogram (EOG)

to record rapid eye movements, and the electromyogram (EMG) to record submental and tibial muscle activity, thus allowing movement arousals to be detected. There is some debate about the value of precise sleep staging in the diagnosis of straightforward conditions such as obstructive sleep apnea in an otherwise healthy child with adenoidal hypertrophy, in which case quiet sleep can be differentiated from active sleep using cardiorespiratory and behavioral variables. Additionally, advances in technology, such as neural network analysis,²⁵ have the potential to simplify this process.

An audio video recording during sleep is usually performed as part of the PSG as it is helpful in correlating physiological disturbances with clinical or behavioural findings. A trained technician is required to supervise the study to assure quality. Therefore, PSG is expensive and time consuming to perform. Additionally, there are limited resources for full polysomnography in children in the United Kingdom and other countries. Therefore, researchers have been prompted to evaluate other options for the assessment of sleep disordered breathing either as diagnostic or screening investigations.

Pulse oximetry is the most widely used of the available screening methods. In some circumstances it can be useful, but it does have significant limitations. The finding of intermittent episodes of hypoxemia in a snoring child is highly suggestive of OSAS. Stradling and others showed that pulse oximetry had 93% sensitivity and 86% specificity for detecting OSAS.²⁶ Brouillette and others²⁷ showed a high positive predictive value for pulse oximetry but also a high false negative rate. Sleep related breathing problems are more likely to occur during rapid eye movement (REM) than during non-REM sleep. It is not possible to determine if adequate periods of REM sleep have been included in a sleep study using pulse oximetry alone. Some children who snore have significant disturbance in their breathing and sleep without recurrent episodes of hypoxemia. There is evidence that continuous partial airway obstruction may be the most common presentation of disordered breathing during sleep in children of all ages,^{28, 29} and this will not be detected by pulse oximetry. Additionally, pulse oximetry is not a reliable indicator of severity of OSAS.³⁰ This is potentially important in preoperative assessment, particularly of high risk children with adenotonsillar hypertrophy who have an increased risk of perioperative complications with severe disease. Pulse oximetry does however have an important role in assessing oxygenation during sleep in children with chronic lung disease and neuromuscular disorders.

Audio and video taping have also been used to screen for sleep disordered breathing. Recording the snoring sound can be used to detect apneas, but it cannot differentiate between central and obstructive apnea.³¹ Goldstein and colleagues³² found that a sound recording was positive when compared to PSG only 50% of the time. Lamm and others³³ found that home audiotapes were not sufficiently specific to reliably distinguish primary snoring from OSAS. A videotape of a child during sleep can provide useful information. It allows the physician an opportunity to observe disturbed sleep. However it is not practical in a clinical context to record and view more than a limited portion of the sleep period. The severity of sleep disordered breathing may vary throughout the night. The design of sophisticated computer systems for analysing video material may circumvent this problem. Combining audiotaping with pulse oximetry adds to the diagnostic value;³¹ however, lack of

arousal data and information to stage sleep remains a problem.

Due to the limitations of single channel recording systems, attempts have been made to develop simple multichannel devices that are suitable for unattended home use or with minimal supervision. There is limited evidence of the performance of these devices in children to date, but recent studies of such monitors compared in both laboratory and home conditions with PSG, have shown that obstructive apnea/hypopnea syndrome in adults can be diagnosed satisfactorily in a substantial proportion of cases.³⁴ Although such comparisons do not exist for children, unattended home PSG has been evaluated in a research context and found to provide acceptably high quality data.³⁵ Therefore, this represents a potentially useful and cost effective approach to the diagnosis of obstructive apnea in children that deserves further evaluation.

What abnormalities can be detected?

Obstructive sleep apnea and upper airway resistance syndromes: The most common indication for performing sleep studies in children is for the detection of obstructive sleep apnea syndrome (OSAS). OSAS in children is characterised by recurrent events of partial or complete airway obstruction during sleep, resulting in disruption in normal ventilation and sleep patterns,³⁶ but rarely with prolonged apnea. Episodes of obstruction occur primarily during REM sleep, in contrast with obstructive apneas in adults, which are mostly non-REM phenomena. The prevalence of OSAS in preschool children is estimated to be 1–3%.^{37, 38}

The majority of cases of OSAS in children are associated with adenotonsillar hypertrophy. It is most commonly diagnosed between the ages of 2 and 8 years when the tonsils and adenoids are largest in relation to the upper airway size. However, the symptoms of OSAS are not simply related to structural narrowing of the airway by physical obstruction. This is supported by studies which have shown no correlation between upper airway or adenotonsillar size and OSAS,^{39, 40} and by studies in which children have failed to show improvement after adenotonsillectomy despite the lack of other risk factors for OSAS.²¹ A combination of structural and neuromotor abnormalities is likely to be important for OSAS to develop. The role that these two factors have will vary in different individuals. In children with adenotonsillar hypertrophy, structural factors will tend to predominate, although subtle neuromotor abnormalities are likely also to be present.⁴¹ In children with cerebral palsy and neurodisability, it is more likely that neuromotor factors will be to the fore.

The classical picture of OSAS in which snoring is associated with obstructive apnea and hypoxemia represents only a small proportion of children with sleep disordered breathing. It is now widely recognised that a spectrum of abnormalities exists⁴² between primary snoring and classical OSAS, with two further conditions, upper airway resistance syndrome and obstructive hypoventilation being intermediate between the extremes. It is also recognised that children may move up or down this spectrum in response to seasonal variations and with age or growth. Therefore, these should not be regarded as static conditions. Upper airway resistance syndrome (UARS) is characterised by increased upper airway resistance and increased work of breathing during sleep sufficient to cause frequent microarousals (brief arousals, <15 seconds) from sleep,

which lead to excessive daytime sleepiness and diminished neurocognitive function. In obstructive hypoventilation, increased airway resistance sufficient to cause partial airways obstruction and hypoventilation occurs, leading to peak end tidal $\text{CO}_2 > 55$ mm Hg or end tidal $\text{CO}_2 > 45$ mm Hg for more than 60% of the total sleep time. Snoring is common to all of these conditions. UARS and obstructive hypoventilation are not detectable using single channel screening, such as oximetry, but multichannel systems have the potential to identify obstructive hypoventilation and may also be useful in screening of UARS, the clinical significance of which has yet to be fully determined in children.

Other conditions: In children with chronic lung disease and limited pulmonary reserve, such as infants with chronic lung disease of prematurity and children with cystic fibrosis, the normal effects of sleep on respiratory function can result in significant ventilatory and gas exchange abnormalities.⁴³ Children may require higher inspired oxygen concentrations during sleep, whether or not supplemental oxygen is needed during wakefulness. These children can be identified by continuous assessment of oxygen saturation during sleep.

Children with neuromuscular disease, especially those with progressive conditions such as Duchenne muscular dystrophy, will eventually develop respiratory disturbances during sleep.⁴⁴ These are most pronounced during REM sleep due to diminished respiratory drive, atonia of the upper airway and intercostal muscles, and dependence of respiration on diaphragmatic function. Both obstructive apnea and alveolar hypoventilation can occur. Progressive scoliosis is often a contributing factor in these children. Mild hypercapnia and REM sleep desaturation are the first abnormalities to be observed and can be detected by combined recordings of gas exchange using oximetry and end tidal CO_2 . Treatment is limited to supportive measures but these can prolong the duration and, most importantly, improve the quality of life for these patients.

Sleep studies will also identify conditions in which there is an underlying abnormality in the central control of respiration. These conditions may be primary, such as congenital central hypoventilation syndrome (CCHS), or secondary to diseases of the spinal cord or brain stem. CCHS may range in severity from mild alveolar hypoventilation during sleep with adequate ventilation during wakefulness to complete apnea during sleep and severe hypoventilation even when awake. Infants usually present with cyanosis and respiratory failure, or occasionally apnea at birth. Rarely, infants present later with apparent life threatening events or cor pulmonale. Definitive diagnosis requires careful evaluation using PSG, including measurement of ventilation during wakefulness, REM, and non-REM sleep states. Treatment of CCHS is with long term support of respiration. As ventilation requirements will change over time in such patients it is necessary that PSG should be repeated at regular intervals. It is our practice to do so on a six monthly basis.

Consequences of sleep disordered breathing in children

Failure to recognise sleep disordered breathing in children can have significant consequences on growth, cardiac, and neurological function. Early surveys of children with severe OSAS reported failure to thrive in 27–56% of cases.^{13,45} Increased recognition of OSAS and earlier intervention has made failure to

thrive the exception in recent times. However, children with OSAS still tend to have a growth spurt following adenotonsillectomy.⁴⁶ This would appear to be due to decreased work of breathing postoperatively rather than to increased caloric intake.⁴⁷ Two studies have suggested that endocrine factors may also have a role. Increases in insulin-like growth factor (IGF-1) and its binding protein have been shown after adenotonsillectomy in children with OSAS.^{48,49}

Recurrent nocturnal hypoxemia, hypercapnia, and respiratory acidosis can lead to pulmonary hypertension and on to cor pulmonale and congestive heart failure. This used to be a common presentation of OSAS in childhood but is now rarely reported. However, asymptomatic degrees of pulmonary hypertension may be more common than previously appreciated. Tal and others have shown reduced right ventricular ejection fractions in 37% of children with OSAS, although only 7% had clinical evidence of pulmonary hypertension.⁵⁰ All these children showed normalisation of heart function after surgery. Routine screening of children with suspected OSAS with ECG or echocardiogram is unlikely to be worthwhile.

Systemic hypertension is a common complication of OSAS in adults but less frequently reported in children. Marcus and colleagues found that children with OSAS had a significantly higher systemic diastolic blood pressure (but no difference in systolic pressure) than children with primary snoring.¹⁴ This observation raised concerns about the long term consequences to adult health of albeit mild increase of blood pressure during childhood associated with OSAS.

Children with sleep disordered breathing have been shown to have a high incidence of neurocognitive and behavioural disturbances.^{51–54} These include attention disorders, memory and learning disabilities, school failure, developmental delay, hyperactivity, aggressiveness, and withdrawn behaviour.⁸ Behavioral symptoms may be the primary clinical manifestation of sleep disordered breathing. Guilleminault and others showed that children aged 6 years and over who were referred to a sleep disorders clinic were frequently seen by the school counsellor before coming to the clinic, and concerns about attention deficit disorder and special educational needs had been raised.⁵² Rebellious behaviour was encountered more often than frank sleepiness. O'Brien and colleagues identified a high prevalence of sleep disordered breathing in children aged 5–7 years with mild attention deficit hyperactivity disorders (ADHD) compared with children with severe ADHD or none.⁵³

Further evidence for a link between behaviour and neurological symptoms and sleep disordered breathing comes from studies that have shown improvement in these symptoms after treatment with adenotonsillectomy.^{8,54} Gozal performed screening for sleep disordered breathing in first grade students who were performing in the lowest (10th) centile of their class. He found that a surprisingly high proportion (18%) were snorers with associated nocturnal gas exchange abnormalities. Children treated with adenotonsillectomy showed improvement in their grades the following year, whereas those left untreated did not.

Guidelines for referral and investigation of suspected sleep disordered breathing in children

The American Academy of Pediatrics has recently published clinical practice guidelines on diagnosis and management of

OSAS in children.⁵⁵ Although there are currently gaps in the evidence, the following is suggested as an approach to the recognition of OSAS in children:

(1) The possibility of obstructive sleep apnea should be considered in children with habitual snoring, although the majority of these children will have primary snoring. Although clinical assessment is poor at discriminating primary snoring from OSAS, symptoms or signs suggestive of the latter should prompt further investigation. In the presence of significant complications, such as cardiorespiratory failure, investigation should be urgent in a specialist center.

(2) Single channel systems, such as overnight oximetry, may be helpful if they show positive results in the context of a suggestive history of uncomplicated OSAS. However, a normal study does not exclude OSAS and polysomnography remains the gold standard investigation. Unattended home studies using multichannel systems appear promising and deserve further evaluation in this context.

(3) Complex and high risk patients, such as those with craniofacial abnormalities, neuromuscular disorders, and suspected central hypoventilation, should be referred to a specialist centre for further investigation.

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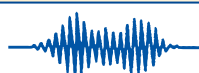
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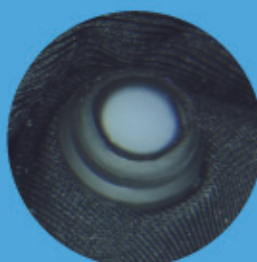
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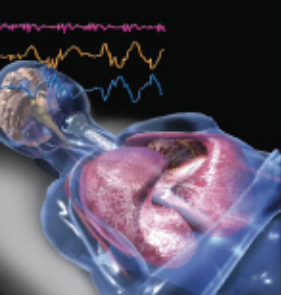
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