

SLEEP INTERNATIONAL

THE GLOBAL JOURNAL OF SLEEP MEDICINE



Normative Sleep Data
CPAP
Sleep Apnea
Oxygen Therapy

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the adults interviewed, 17.4% reported that they regularly had insomnia or trouble sleeping. Difficulty sleeping was more common in women than men, most prevalent between ages 45 and 64, and was associated with obesity, hypertension, congestive heart failure and anxiety or depression. Of those with insomnia or trouble sleeping, 4.5% reported that they had used alternative therapies to treat the condition, which is equal to about 1.62 million adults in the general population. Survey respondents who were younger and who had a higher level of education were more likely to use complementary and alternative medicine (CAM) to help them sleep. Among those who use CAM therapies for their insomnia, 60.7% told their conventional physician. Sixty-five percent used biological methods, which include herbal medicines, diet interventions and vitamin therapy, and mind-body therapies such as meditation were used by 39%. Fifty-six percent reported that the therapy was very important to their health and wellbeing. Forty-nine percent of those who used herbal medicine and 48% of those who used relaxation therapy reported that CAM helped alleviate their condition.

IN A NUTSHELL

Here's a thumbnail description of the history of sleep research, from Schweiz Rundsch Med Prax, "The history of sleep research in the 20th century," by J. Mathis, Neurologische Universitätsklinik, Inselspital, Bern. Not until the 19th century theories on sleep were based upon experimental findings in animal and humans. The so-called hypnotoxin theory culminated, when Legendre and Pieron successfully induced sleep in a dog by transmission of cerebrospinal fluid from a dog deprived of sleep. The main discussion concerning the origin of sleep has been the question if sleep is a passive or an active state. Similarities with coma, the positive Babinski sign and pathoanatomical findings in patients who died after encephalitis lethargica were the arguments for the "deafferentiation hypothesis." Bremer's classical brainstem-transsections in cats confirmed this idea. Pavlov was the major representative of the idea that sleep was due to a general inhibition of the brain. Hess induced physiological sleep in cats by electrical stimulation of the diencephalon, proving the active nature of sleep. The introduction of the EEG in animals by Caton and in humans by Berger allowed for the first time the measurement of sleep depth without waking the sleeper. After discovery of the REM sleep periods by Aserinsky and Kleitman in 1953 and the demonstration of periodical sleep cycles by Dement and Kleitman, polysomnography with simultaneous whole night recording of EEG, EMG, electrooculogram and other physiological parameters was established as the major diagnostic tool in sleep disorders. One of the most important questions about the function of sleep is still unresolved. NREM sleep is believed to have a restorative function, whereas REM sleep might be involved in learning processes. According to the sleep interpretation of Sigmund Freud, the dream content represents endogenous wishes which cannot be expressed during wakefulness because of an internal "sensor." A more recent theory by Hobson explains the dreams by a very unspecific brainstem activity occurring during REM sleep which projects to the frontal brain and activates stored memory. The most important sleep disease of the 20th century is certainly the sleep-apnea syndrome. The pathogenetic significance of the apneas during sleep, however, were recognized in 1965 only by Gastaut and at the same time by Jung and Kuhlo. Treatment for insomniacs was restricted for many years to alcohol, opium and barbiturates. Following the horrible sequelae of thalidomide

News

□ December-January 2006/2007

STROKE

Older adults with sleep apnea may face a more than doubled risk of stroke. Researchers found undiagnosed sleep apnea increased the risk of stroke by 2.5 times among the elderly. Previous studies have linked severe sleep apnea to strokes in middle-aged adults, but researchers say this is the first study to show an increased risk associated with the sleep disorder among older adults. In the study, published in *Stroke: Journal of the American Heart Association*, researchers followed nearly 400 adults between the ages of 70 and 100 for six years. Each was evaluated for sleep apnea at the start of the study. During the study period, 20 strokes were reported. Participants with previously undiagnosed severe sleep apnea were 2.5 times more likely to have a stroke, regardless of their other traditional stroke risk factors such as high blood pressure, smoking, and cholesterol levels. Researchers at the Hospital de Navarra in Pamplona, Spain say the findings add to recent studies that suggest sleep apnea may be a risk factor for stroke. For example, a 2005 study in middle-aged adults, published in the *New England Journal of Medicine*, showed those with sleep apnea were three times more likely to suffer a stroke. Until now it was believed that undiagnosed severe sleep apnea among the elderly was less of a health risk compared with middle-aged people. But they say this study highlights the need for screening for the sleep disorder in older as well as younger people.

SKIP THE DOCTOR

More than 1.6 million US adults are estimated to use complementary and alternative therapies to treat insomnia or trouble sleeping, according to the results of a national survey published in a recent issue of *Archives of Internal Medicine*. Nontraditional approaches include herbal medicines and relaxation techniques. Researchers at the National Center for Complementary and Alternative Medicine, National Institutes of Health, analyzed data from a national survey of 31,044 adults. Of

therapy in 1956, a more efficient treatment was available through the introduction of benzodiazepines after 1960.

In the 19th century, sleep was thought to be related to blood pressure lack of it in the brain. Or, it was thought, toxic substances like cholesterol, carbon dioxide or so-called urotoxins had accumulated in the brain that caused sleep. These toxins were believed to have leached away as the person slept. By the mid 19th century, neuronal theories posited that neurons were paralyzed as the sleeper slept, and couldn't communicate with other cells.

PRODUCTS

SMART SLEEP

Respironics announced the release of the BiPAP M Series with Bi-Flex product line which includes the state-of-the-art BiPAP Auto M Series and the BiPAP Plus M Series sleep therapy devices. Developed as an alternative for patients who have difficulty complying with Continuous Positive Airway Pressure (CPAP) devices, BiPAP devices continue to be reliable, comfortable choices for adults who have obstructive sleep apnea (OSA). The BiPAP Auto M Series combines auto adjusting bi-level pressure delivery with the breath-by-breath pressure relief of Bi-Flex, all in the small, sleek, easy-to-use M Series design. A proactive, multi-level algorithm analyzes several parameters to monitor and respond to a patient's breathing. It determines how much of a response is necessary to eliminate events and position the patient with a more appropriate pressure, as well as compensate for elevated leak levels and variable breathing. Bi-Flex technology "softens" the airflow in inhalation and exhalation to provide increased pressure relief, making breathing more comfortable for the patient. Digital Auto-Trak Sensitivity works with Bi-Flex and the auto algorithm to track each breath so that the device can cycle between inspiratory and expiratory pressure based on the patient's breathing. The result is more natural and comfortable therapy. The BiPAP Auto M Series also features Respironics' new "smart ramp" technology that enables patients to benefit from the added comfort of ramp without risk of impacting therapy. The smart ramp technology will detect and treat events while ramp is activated. When combined with Encore Pro SmartCard, BiPAP Auto M Series can record events like snores, apneas, hypopneas and leak to provide insight into patients' therapy. An optional integrated heated humidifier features an easy-turn dial to get the right setting and does not need to be reset if therapy is temporarily suspended. Plus, the hidden water chamber is easy to use and fill, and delivers continuous humidification throughout the night. The BiPAP Plus M Series provides bi-level therapy with the comfort of Bi-Flex plus basic compliance data for easy phone-in reporting by patients. Users will find the products easy to operate, with three primary control buttons and additional options for the proactive patient. Contact respironics.com.

COMPREHENSIVE

CASMED offers a comprehensive family of products for all your apnea monitoring needs. For home use, the Ami Plus monitor provides a built-in modem, is lightweight, portable and easy to use. In the hospital environment, the CASMED 511 monitor offers heart and respiration monitoring, can be configured with an optional pulse oximeter, and can easily

interface with a nurse call system. The CASMED Express software allows users to quickly access, review and analyze data from either the Ami Plus or the CASMED 511. For more information, call 800-227-4414 or visit our web site at www.casmed.com.

EXECUTIVE PROFILE

ActiGraph, LLC

John Schneider

John Schneider is Director of Research and Development, ActiGraph, LLC, theactigraph.com.

Please describe your product(s) or product line and what sets it apart from other products in the field.

The ActiGraph is the first company to use digital accelerometers in its activity monitors, making them the most accurate activity monitors on the market today. The USB connection along with the web-based software makes it very easy to use. It is fast becoming the most widely used activity monitor in the world.

How does your product or improvements in your product directly affect patient care?

The ActiGraph is a small device that can be worn like a wrist watch by a patient during sleep analysis to determine sleep/wake patterns. Because of its small, unobtrusive design, it can be worn inside of the sleep lab during other tests, or outside of the lab at the patient's own home, this will help the physicians determine if the patients have a sleep problem.

Tell us about advances in the area your product serves or in treatment modalities for the clinical condition your product addresses.

The ActiGraph and its accompanying web-based software allow the doctors or technicians to monitor sleep hygiene, sleep latency, and sleep efficiency.

Discuss your R&D process, including how you decide on new features for your product.

We have a big advantage over large business which is being able to implement changes in our products/processes to improve on them as we receive feedback from both end-users and staff.

Discuss the services you offer to educate clinicians and healthcare professionals about the uses of your product.

We have the normal brochure folders, user manuals, and several informational sheets that help these professionals. We take pride in our customer service but of course, our goal is to make it as simple as possible.

Please discuss the role of clinicians in developing and upgrading your products.

ActiGraph is always looking for new ways to improve the products and software that we offer, and researchers, clinicians, and doctors are the most important part of that. We are constantly asking our users how we can make the ActiGraph better.

What new technology do you see as having an impact on your area of specialization?

We are excited about becoming wireless, which will allow us to pursue many other areas and fill in some technology gaps in health care.

How does the international marketplace and international clinical community impact your research, development and product placement?

Serving close to 50 overseas countries, we are deeply impacted by the international community. In many ways, we learn a lot about how do things from them.

Tell us how you use conferences, forums, seminars and such to promote your product and its efficacy.

We know that attending conferences and seminars are a wonderful way to not only promote and educate people about the ActiGraph, but also so we can learn more about what other companies, researchers and clinicians are doing to impact the study, diagnosis and treatment of sleep.

Braebon Diagnostics

Michael Clark

Michael Clark is Director of Marketing and Sales – North America, for Braebon Diagnostics, braebon.com.

PRODUCT DEVELOPMENT

Braebon is aware there was a need for a complete family of sleep diagnostic products supplied from a single company. These include sensors, sleep disorder screeners, complete PSG diagnostic systems and outcomes data management software. This array of products from a single provider allows an individual setting up a sleep testing facility to only deal with one company for all their equipment needs, accessories, training and support.

USER INPUT

Most of what we do is driven directly from users and potential customers. The management at Braebon is also very experienced in the development of sleep diagnostic equipment and management software. The management group at Braebon has many contacts in the field of sleep medicine that go back over 30 years so we constantly tap into that resource to make sure new product development is on the right track.

WISH LIST

All our products are driven from the same philosophy meaning they should be easy to use, very reliable, well supported and reasonably priced. This is our wish list that we apply to all product development and continue after the sale. We listen carefully to our installed base and future customers to provide us with an ongoing wish list of product features that get added on a regular basis.

PRICING

All Braebon products are the most reasonably priced in the sleep industry. Since reimbursement levels have dropped over the years and operating costs have increased we have made a determined effort to keep pricing at a more reasonable level. By designing products that are easier to learn and use we have

been able to reduce the amount of training and after sale support normally required. Replacing traditional on-site demonstrations with live web demos has also reduced selling costs.

QUALITY CONTROL

All Braebon products are developed and manufactured in house under strict ISO 13485 guidelines. We have resisted the opportunity to shift manufacturing “offshore” but instead concentrated on more efficient “at home” manufacturing techniques. This allows us to provide very high quality products that were designed, developed, manufactured and tested all in the same facility. The benefit to the end user is a product that is more reliable with extended warranties.

USER SUPPORT

All Braebon products are supported 24/365 with experienced staff. This means you can call anytime day or night any day of the year and get the person you need to solve the problem. We also offer a Rapid Replacement Program which means a defective component can be shipped out for same day delivery. Most of our products also have extended or industry leading warranties with no questions asked when it comes to replacing a defective component.

INTERFACE

Braebon also has OEM relationships with a number of other sleep equipment vendors. Since we specialize in high quality sensors, miniature screening devices, compact PSG diagnostics and outcomes data management software, there has been a growing demand to incorporate Braebon parts into their systems. In the future you will see a number of sleep diagnostic products that will be powered by Braebon.

Embla

Kassandra Keller

Kassandra Keller is Director of Marketing for Embla.

What led you to develop the products you wish to discuss?

Embla is a Global company so we have developed a product portfolio that ranges from simple 2 channel screening devices to 64 channel research level polysomnography amplifiers together with the software to drive them. It is estimated that about 60 million Americans alone suffer from some form of sleep disorder that can lead to a series of other health issues from hypertension to heart attack and stroke. The solution to many of these sleep disorders is available through diagnostics and treatment. Unfortunately the medical community is not clear on how these patients should be diagnosed and varies from favoring home based technology in Europe and much of the rest of the world to full PSG in the United States. In addition, we have seen sleep diagnostics moving away from the purely research labs into clinical facilities that are demanding more information than just the clinical sleep diagnosis and require business software that will help them manage their sleep labs from patient scheduling to resource loading, marketing information and outcomes analysis. To address this need Embla has also developed the Enterprise system that does exactly that. A full range of Global products that allows sleep physicians and practitioners to treat a very under served population throughout the world.

Closer to our Customers...

(but don't just take our word for it.)

"Our relationship with Embla, formerly Medcare, has been mutually beneficial both educationally and professionally. Every piece of our future 30 bed facility will be networked together and they have helped us towards our pending 1st CoA PSG Accredited sleep program". – Andy Desrosiers, Holy Family Hospital, Massachusetts, USA



"The Embletta is a powerful diagnostic tool. It provides a wealth of information and a great deal of detail. At the same time it is easy to learn and simple to use with excellent reliability. Once we received our first Embletta, we stored our other devices on the shelf". – Paul R. Murphy, RPSGT, Sahlgrenska University Hospital, Gotaborg, Sweden

"At Scansleep, we use Embla, Embletta, Somnologica and Enterprise in all our clinics. All of the hardware has been extremely stable and user-friendly. We are also enthusiastic users of the software applications". – Soren Berg, M.D. PhD, Copenhagen, Denmark

Somnologica™

"The Xactrace Belts are the best way to measure breathing effort and are smoothly interfaced with the Rembrandt Sleep system".



REMBRANDT

– Jim Wilcox, RPSGT/CRT,
All Children's Hospital,
St. Petersburg, Florida, USA

"I have been using Embla, formerly Medcare, equipment since 2001. Starting out with 2 beds, we are currently running 10 beds. I have used Artisan, Monet and the Embla N7000, and have been amazed by their reliability and ease of operation. Scoring and analysis modules are friendly and flexible and I would highly recommend all of the products we have used from Embla". –

*Michael D. McDannold, RPSGT,CRT
Vermont Medical SDC, Vermont, USA*

To learn how we can get closer to you too, please call us at 1.888.662.7632 or visit us at www.embla.com




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What level of user input has gone into the design and development of your product? How do you coordinate comments from clinicians and users into your design and production?

Our goal is to be closer to our customers in everything that we do. A big part of that is working directly with existing customers and prospects to understand what they need to provide better diagnosis to patients and run more effective businesses. We do this through our ongoing program of user group meetings and focus groups that allow us to explore where we need to develop our products, the issues and our future.

We also work directly with key opinion leaders and customers throughout the world to help define the vision for our products. As a company we firmly believe in having strong processes and controls around our R&D teams while at the same time creating a fast and responsive development organization to constantly improve our products. Our R&D teams are directed by feedback from the Marketing teams that create customer requirement specifications. Beyond the initial design stages, we also involve customers in the latter stages as well to assure that the features they asked for are functioning as they requested during our Beta trials. This process assures that we involve our customers in every step of the design and implementation process from conception to execution.

What is your wish list for future improvements and advances for this product?

By continuing to offer improved solutions to our customers we provide them with the tools necessary to directly improve patient care. We have done this through analysis techniques such as PTT and more recently CAP analysis but also through our Enterprise Business Solutions offerings. The Embla product portfolio makes it easier for sleep facilities to track their patients before and after the diagnosis to improve outcomes regardless of their reimbursement model or location in the world. We will always be on the cutting edge of technology and are very excited about our upcoming releases.

What features do you plan on adding to your product in the future?

As I have said before we are driven by our global customer base throughout the world. This feedback is moving us to develop enhancements that assist with the accreditation process, increase efficiency, more portable home study devices, screeners and are also embracing technologies such as wireless connectivity to help our customers stay current in this dynamic field.

How did you determine the price for this product and how do you apportion costs for R&D into the design/production/sales process?

Prices for diagnostic equipment continue to drop as technology advances but the product Embla offers goes beyond the equipment itself to the customer support that is a large focus for us. As a result, we are not the least expensive equipment available, but we believe we are the best value for money. Prices are set so that we are profitable and can continue to support the level of R&D and support that our customers demand.

Please discuss your company's quality control process and the benefits of this process for the clinicians and healthcare professionals who use your product.

Quality is of paramount importance to Embla and we are

certified in accordance with ISO 13485:2003, ISO 9001:2000 and the Canadian CMDCAS. Our products fulfill the requirements of the MDD 93/42/EEC European Directive and the U.S. FDA Quality System Regulations. By maintaining a full quality assurance system, customers can be assured that products are safe and reliable and meet customer requirements.

Discuss support you provide for product users.

Embla technical support is available 24 hours a day, seven days a week at 888-662-7632. We also have an interactive Web-Ex program that allows us to see exactly what the user is seeing, giving us the ability to find and solve a user's issue, quickly and correctly.

Embla also recently implemented a new global support team consisting of 20 clinical and product specialists based in the US and Europe supporting a worldwide network of distributors and direct sales. The centralized and expanded support teams, working closely with distributors, customers and partners throughout the world, are continually improving the company's technical support through a global knowledge base and ability to share that knowledge quickly and efficiently. We have also recently invested in an automatic call distribution system allowing our support team to track call volumes, call answer times, staff performance, and average call times assuring that the company is staffed appropriately. Building strong relationships and confidence with our customers will be the key to our success and is our goal with each and every call answered.

Cadwell Laboratories

Bill Antilla RPSGT

Bill Antilla is Senior Product Manager, PSG/EEG/LTM Diagnostics, Cadwell Laboratories.

What led you to develop the products you wish to discuss? That is, requests from clinicians, evidence of need, in-house advances in related development.

Cadwell Labs is in the process of completing development on our new Easy III data acquisition system for epilepsy monitoring, critical care neurological monitoring, clinical EEG, and PSG (polysomnography) monitoring. We introduced our first neurodiagnostic product in 1979 and this began the trend of microprocessor based neurodiagnostic instruments. Since then we have become known for our technical innovation, product reliability and after sale customer support. Our own family of customers has made it clear that they want Cadwell to deliver a new generation of products that will deliver the same innovation and reliability they have come to expect for the last 27 years.

What level of user input has gone into the design and development of your product? How do you coordinate comments from clinicians and users into your design and production?

Cadwell aggressively seeks input from the market place. If you have ever attended any of the larger conventions that we exhibit at, you will notice a sea of Cadwell people and customers in our booth. The owners of our company (John and Carl Cadwell) are adamant that we listen carefully to our customers. John and

Carl Cadwell attend many of our major meetings, discussing new and future products, concepts and features. It is not uncommon for our company to hold impromptu brainstorming sessions where our own employees discuss and recommend ideas and solutions based on input from our customers.

We are also not shy about adding key people to our Cadwell team that assist us in keeping our products competitive. We have some of the best sales, marketing, and engineering professionals you will find in our industry. We have hired managers from outside our industry and from our competitors in this regard. We utilize in-house product managers to prioritize and implement new product features for each of the markets we compete in.

What is your wish list for future improvements and advances for this product?

Our wish is to continue providing highly reliable and technologically advanced diagnostic products that assist our customers in diagnosing and treating patients. We are using some of the newest software programming tools available in the market place to create a new, more efficient software interface. Not only has the look of our software changed, we have added features that allow our customers to track and exchange data over networks and the internet.

What features do you plan on adding to your product in the future?

We are continually in step with some of the latest changes occurring in the marketplace. We are programming new methods and tools that assist our customers in sleep staging and sleep event scoring. We also are implementing workflow tools that help (rather than distract) the user. Finally, new HIPPA features will assist our customers in meeting new guidelines and patient confidentiality requirements.

How did you determine the price for this product and how do you apportion costs for R&D into the design/production/sales process?

We use several methods to assure our pricing is competitive in the market place. Several years ago we made a decision to deliver high value products at a competitive price. For example, MD Buyline recently listed our Easy II EEG system as having the highest satisfaction rating and the lowest price. That's the right combination that our customers appreciate!

Discuss support you provide for product users.

Cadwell offers a variety of support plans to meet the needs of our customers. We offer 24/7 telephone support to all our customers at no charge. Customers under warranty or service contract can also get remote web based support from our home office in Kennewick, WA. Customers simply log onto our www.cadwell.com web page and enter a code supplied by Cadwell. Within seconds we can access our customer's computer and efficiently identify and resolve problems.

Resmed

Ann Tisthammer

Ann Tisthammer is VP Clinical Education, Americas, ResMed.

Who is responsible within your company for training and education of your staff and your customers?

As a market leader in the field of sleep-disordered breathing, ResMed has a Clinical Education team responsible for the development of training and education initiatives for its customers and their patients. ResMed's Clinical Education team is made up of a dedicated group of clinicians with extensive backgrounds in both cardiopulmonary medicine and sleep. Internally, ResMed's award-winning Learning Center is responsible for the training and education of our field representatives and in-house staff. The Learning Center team combines product and industry knowledge with corporate training expertise to develop and support ResMed employees.

What types of education do you provide?

We offer clinical and sales training at regional and branch levels; clinical in-services, from product application to detailed disease processes; the opportunity for continuing education unit (CEU) credits; and access to our clinical literature library with over 1,600 articles on the topic of sleep-disordered breathing.

How do you manage "off-hours" assistance for clinical questions?

Our team of clinical specialists support and assist our customers around the clock. They are trained in ventilation, titration techniques and diagnostic procedures to answer any clinical questions HME providers, physicians or sleep clinicians may have. In addition, our customer service representatives assist with day-to-day queries, from product support to clinical questions. We also offer multiple online resources, including therapy tips and product information for patients at MyResMed.com, as well as information for undiagnosed sleep apnea patients at HealthySleep.com. In addition, we offer a Reimbursement Hotline for customers with questions regarding reimbursement guidelines at (800) 424-0737.

Do you provide technical service support, and of what nature?

As a branch of our Customer Service department, we have a team of technical experts available to support our customers with technological questions and concerns.

What do you feel is important to support the customer/end-user of your product?

ResMed is in business to help save lives and improve patients' health. Patients undergoing treatment for sleep-disordered breathing need support in order to adhere to therapy, and promoting adherence is among our main objectives. Aside from innovative technologies that make therapy effective and comfortable, we provide our end-users with various sources of support. MyResMed.com, a new website that offers comprehensive online support, provides information specifically for CPAP users such as therapy tips, cleaning guides, answers on insurance questions, product information and customizable replacement reminders. Our customer service representatives and regional clinical specialists understand patient needs. We also guarantee quality products to our customers, and we are so

confident of our product reliability that we back them up with quality guarantee programs.

What activities does your company undertake to promote the product?

ResMed reaches its customers primarily through our team of experienced field sales representatives. We also participate in various medical and scientific conferences throughout the year to promote awareness of sleep-disordered breathing and treatment. We have relationships with multiple major trade publications and advertise extensively with a variety of audiences.

How does your company reach out to its customers regarding product performance and R&D?

Our field sales team interacts directly with customers to understand their business needs and deliver practical, accessible solutions for their businesses. Our product development team is in regular contact with field reps and customers alike in order to ensure that our offerings reflect the voice of our customer. In addition, we regularly conduct market research across all regions to guide and inform our product development and marketing strategy.

What mechanisms are in place to assist hospitals in their educational requirements and ongoing education?

ResMed's Clinical Education team works with our field representatives to assist hospitals and sleep labs with their educational needs. We offer specific training in ventilation, titration techniques and diagnostic procedures, with the opportunity for continuing education units (CEUs) to respiratory therapists, nurses, registered sleep technicians and case managers.

Where do you see the future of your product in relation to end-user requirements?

ResMed is the global market leader in the sleep-disordered breathing industry, offering diverse high-quality products which maximize patient compliance. We focus on developing technologies that are more effective and more comfortable, to open new markets and treat a larger number of patients. We are the leader in mask technology, and were the first to gain FDA clearance for treatments for central and complex sleep apnea, as well as pediatric sleep apnea. We are always seeking ways to treat a broader range of patients more comfortably and effectively than ever before.

NEWS FEATURE

A BRIEF HISTORY OF SLEEP

Information for this article was redacted from "Talk About Sleep," © 2000-2006 Talk About Sleep, Inc, Burnsville, MN.

In the 19th century, sleep was thought to be related to blood pressure or lack of it in the brain. Or, it was thought, toxic substances like cholesterol, carbon dioxide or so-called urotoxins had accumulated in the brain that caused sleep. These toxins were believed to have leached away as the person slept. By the mid 19th century, neuronal theories posited that neurons were paralyzed as the sleeper slept, and couldn't communicate with other cells.

By the end of the 1800s, it was thought that sleep was caused by some sort of off-switch. Some basic experiments related to

sleep were performed by Luigi Rolando, who induced permanent sleepiness by cutting out cerebral hemispheres in bird brains. While this pioneering research certainly made its mark (especially on the birds), a new paradigm, chronobiology, was introduced by Linnaeus, who studied biological rhythms.

Many of these studies were carried out by botanists, who studied biological cycles and their relation to the environment. Two scientists, Davy and Ogle, used themselves as models to study body temperature. This led to investigations of physiological states evident in sleep as these states manifested themselves in dreaming versus non-dreaming periods. Variations in sleep states had not gone unnoticed, even the ancient Greeks knew about them, and Sigmund Freud noted that paralysis of the muscles hindered dreamers from physically mimicking their dreams.

But sleep researchers still couldn't accurately describe many sleep problems such as apnea, narcolepsy and insomnia. Interestingly, the writer Charles Dickens was among the first to record sleep apnea, in *The Pickwick Papers*. In fact, obstructive sleep apnea used to be referred to as Pickwickian Syndrome.

MARCH OF (SLEEPY) TIME

Biological timing systems as etiologies of sleep were popular in the early 1900s, based on studies of bees, which led to studies of circadian rhythms, involving research of light and dark cycles to demonstrate the effects of illumination on sleep cycles. Research on rodents and on lesions in the hypothalamus eventually led to currently well-known theories about the biological clock, so named by Erwin Bunning in 1935. Later studies using EEG techniques confirmed the presence of REM sleep. Chemical explanations of sleep states were also posited, with experiments involving the injection of sleep toxins into dogs, but these didn't pan out. The famous dog researcher Pavlov posited that sleep was caused by brain inhibition and its action on the central nervous system.

Meanwhile, two opposite theories about sleep fought it out, one saying sleep was controlled by a sleep center, the other that it was influenced by a waking center. Both these theories were based on the idea that there was a localized site of sleep, as it were, a theory bolstered by evidence of the effects of viral encephalitis and damage to the proptic area in the hypothalamus. Experiments in the 1930s confirmed that, indeed, brain stimulation in the region could induce sleep.

The "father of sleep research," Nathaniel Kleitman, also focused on circadian rhythms and the influence of the cerebral cortex, and argued that inaction and "fatigue" of the central nervous system is what caused sleep. Later research discovered that skeletal muscle inhibition resulting in sleep came from the lower brainstem, leading to a physiological model of sleep mechanisms.

UP TO THE MINUTE

A convergence of all these theories takes us up to the previous century, when sleep research really took off. Studies with starlings in flight presented evidence of how internal clocks adjusted to light as a regulatory compass. Studies on fruit fly larvae noted the influence of temperature variations, and to some extent undermined the circadian theory. The notion of a biological clock was firmly rooted by the early 1960s, reinforced by studies of people in unlit or artificially lit bunkers during World War II, leading to a mapping of sleep cycles in the absence of external stimuli. Results showed that light-dark cycles played their part, but that hormones secreted around the clock, which regulated body temperature, also had their role in sleeping and

waking cycles. In the early 70s, geneticists discovered the complementary roles of heredity and genes and the workings of internal biological clocks. Further work on shallow and deep sleep states continued apace, with concrete tracking of REM, which further enhanced the growth of sleep studies. The upshot of all this is that sleep was confirmed as a multi-faceted, dynamic state, influenced by a variety of factors, a combination of biology, chemistry, genetics, and environment. Standardized criteria for testing was introduced in the late 60s and 70s, with a scoring system for sleep stages, and the Multiple Sleep Latency Test developed by William Dement. Other parameters for charting sleep were also developed, such as the Epworth Sleepiness Test and the Stanford Sleepiness Scale. In the meantime, biological/chemical research continued apace, and peptides were used to induce sleep in laboratory rats. However, that chimera, the sleep center, still hasn't been discovered.

TREATMENTS

As research about how sleep works developed, so did treatments for sleep disorders. Insomnia was treated by hypnotic medications, hypnosis, and forms of meditation. Stimulants were prescribed for narcolepsy. The connections between sleep and respiration, first hypothesized by Dickens in those Pickwick Papers, became firmly established throughout the 50s and 60s. Nasal CPAP made its entrance in the early 1980s, and gained the popularity it still enjoys. As far as pharmacological approaches, psychoactive drugs and barbiturates were prescribed for many sleep disorders, of which there are now seven dozen.

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Normative Sleep Study Data in Infants 2 Weeks to 6 Months of Age

Richard A. Hardoin, MD, FAAP, Judith A. Henslee, LMSW

Although numerous studies have been done to establish normative values for individual physiologic parameters in sleeping infants, no large scale study has been done to assess the interrelationship of multiple physiologic parameters and the influence of time of night and position on these parameters. Through the evaluation of 200 healthy infants, two weeks to six months of age, a clearer picture of normal infant sleep physiology has emerged. This understanding of what is "normal" should aid in the identification of abnormal patterns which may predispose infants to neurological deficits, growth retardation, and possibly even life threatening events.

Five hundred twenty-three newborn infants qualified to participate in the study over a twenty month period. Two hundred randomly selected, healthy control infants were evaluated polygraphically for one eight-hour period at 2, 4, 6, 8, 12, 16, 20, or 24 weeks of age. Oxygen saturation, digital pulse, ETpCO₂, air flow via nasal cannula, respiratory rate and pattern, heart rate and pattern, abdominal movement and EKG were all recorded digitally. Affect of position (prone, supine, side) and time of night on physiological parameters was also evaluated. All studies were computer analyzed and technician reviewed prior to generation of a final report. Studies were then re-analyzed by position. Summary data was automatically imported into a relational database.

For the normal population of infants 2 to 24 months of age, brief central apneas (>15 seconds) and periodic breathing were common. Despite these findings, oxygen hemoglobin saturations were stable. Prolonged central apneas of ≥ 15 seconds were rare in the population studied. Only 11 infants (5.5%) had any central apneas of ≥ 15 seconds during the eight hour study. The study population demonstrated good airway patency. No obstructive apneas (>6 seconds) were observed in 91% of the 188 infants who were able to tolerate the nasal cannula. 91.5% of all infants studied had maximum end-tidal pCO₂ values of ≤ 50 , and heart rates tended to stay within the range of 113 to 169 BPM. Sleep position and time of night had a small, but significant affect on ETpCO₂. Oxygen saturations tended to be stable for all age groups

studied. The mean oxygen hemoglobin saturation for all ages was 98.48%. Neither time of night nor sleep position exerted any significant influence on the O₂ desaturation density -90. Only 4 out of 200 studies identified bradycardias which were sustained for 3 seconds or longer. No bradycardias were identified in any normal infants >6 weeks of age. Marked changes in respiratory parameters were observed at 8 weeks of age, when troughs were documented for apnea density, percent periodic breathing, lack of air flow, maximum ETpCO₂ values, and O₂ desaturation density-90% values during quiet sleep.

Being able to monitor infant physiological data more effectively during sleep and awake periods is the key to protecting babies with cardiorespiratory irregularities. Companies like CASMED, makers of the Ami Plus home monitor and the CAS Express software, should be commended for their role in improving the technology of home infant monitoring. They make the healthcare provider so much more effective when reading infant monitor downloads by producing a machine that is truly a pleasure to work with. Not only is the data from their monitors so much easier to read, but they also allow the attending physician to look at more parameters, adjust for age of the patient, and do it all in less time.

Recently a private company, iSO-3, LLC, was developed to provide download analysis and interpretation services to DME companies nation-wide. iSO-3 is owned by Richard A. Hardoin, MD, FAAP and Judith A. Henslee, LMSW. Both have been active in the field of Sudden Infant Death Syndrome (SIDS) and care of high risk infants since they founded the Southwest SIDS Research Institute in 1984. Their experience, coupled with that of their highly trained staff, makes them uniquely qualified to meet download needs. Durable Medical Equipment (DME) companies and physicians receive prompt reading and interpretation of infant apnea/ bradycardia download data. If a download is considered to be significantly abnormal, the DME company and physician will be notified immediately, allowing for timely evaluation and treatment of unstable patients iSO-3 bills Medicaid, private insurance, or the family directly. Upon request, free "Safe Sleep" information is available. Further information about the services iSO-3 provides is available by calling the office at (979) 299-3476.

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Continuous Positive Airway Pressure Ameliorated Severe Pulmonary Hypertension Associated with Obstructive Sleep Apnea

Aiko Ogawa, Testsuro Emori, Wakako Sumita, Atsuyuki Watanabe, Hideki Fujio, Katsumasa Miyaji, Tohru Ohe

A 52-year-old obese woman was admitted to our institution for evaluation of dyspnea and pulmonary hypertension (PH). Polysomnography revealed severe obstructive sleep apnea (OSA) with an apnea hypopnea index of 99.8. Treatment with nocturnal continuous positive airway pressure (CPAP) resulted in correction of daytime hypoxemia, hypercapnia, and near-normalization of pulmonary artery pressure. To our knowledge, this is the most severe case of OSA-associated PH (~70 mmHg) reported to date, and it was successfully treated with nocturnal CPAP. This case demonstrates that OSA should be considered and polysomnography performed in all patients with PH, irrespective of severity, and that nocturnal CPAP has therapeutic effects on both OSA and daytime PH.

There is a close link between obstructive sleep apnea (OSA) and cardiovascular diseases.¹ In most patients, OSA is suspected based on clinical features such as witnessed apneas or excessive daytime somnolence, but in others, the sleep-related breathing disorder is not associated with any symptoms or signs. In such cases, presentation with systemic hypertension or pulmonary

hypertension (PH) may be an important clue to underlying OSA. Patients with dyspnea and PH sometimes suffer from severe OSA, and all-night polysomnography should be performed in such cases. Approximately 20% of patients with OSA manifest mild PH.^{2,3} Patients confirmed to have OSA are treated with nocturnal continuous positive airway pressure (CPAP), and CPAP has been shown to ameliorate OSA associated with mild PH.³⁻⁵

We experienced a patient with OSA and severe PH, both of which were dramatically ameliorated by nocturnal CPAP. Treatment resulted in a significant reduction of daytime hypoxemia and hypercapnia, and normalization of pulmonary artery pressure. We report this case to highlight the fact that even severe PH can be caused solely by OSA and can be treated with CPAP alone.

CASE REPORT

A 52-year-old obese woman visited our hospital in August 2003 with a chief complaint of dyspnea on exertion. She had been followed up for hypertension, hyperlipidemia and hypothyroidism for about 9 years. She was treated with meoprolol (60 mg/day), imidapril hydrochloride (5 mg/day), pravastatin (10 mg/day), and levothyroxine sodium (60µg/day) and was under good control. The past history included right total mastectomy for breast cancer with no relapse over the 15 postoperative years. One month before the current presentation, she developed shortness of breath on exertion with pretibial edema, which progressively worsened. Twelve-lead electrocardiography revealed normal sinus rhythm with negative T wave in V1 through V3. Echocardiography displayed right atrial and ventricular dilatation and pericardial effusion, which had not been documented previously (Fig 1). Pulmonary artery pressure was estimated at about 70 mmHg. Physical findings including obesity were suggestive of pulmonary thromboembolism.

She was admitted to the hospital for further evaluation of dyspnea and PH. At the time of admission, her height was 153 cm, her body weight was 100 kg and her body mass index was 42.7 kg/m². Physical examination revealed an arterial blood pressure of 138/96 mmHg and heart rate of 92 beats/min. Arterial blood gas analysis revealed a carbon dioxide partial pressure (PaCO₂) of 55.6 torr, oxygen partial pressure (PaO₂) of 45.9 torr, and oxygen saturation (SaO₂) of 82.8%. There was no cyanosis or finger

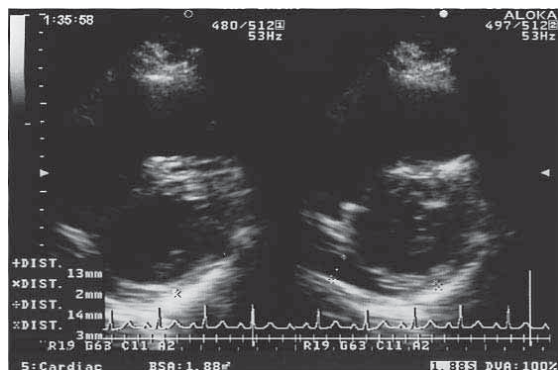


Fig. 1 Echocardiography on admission.

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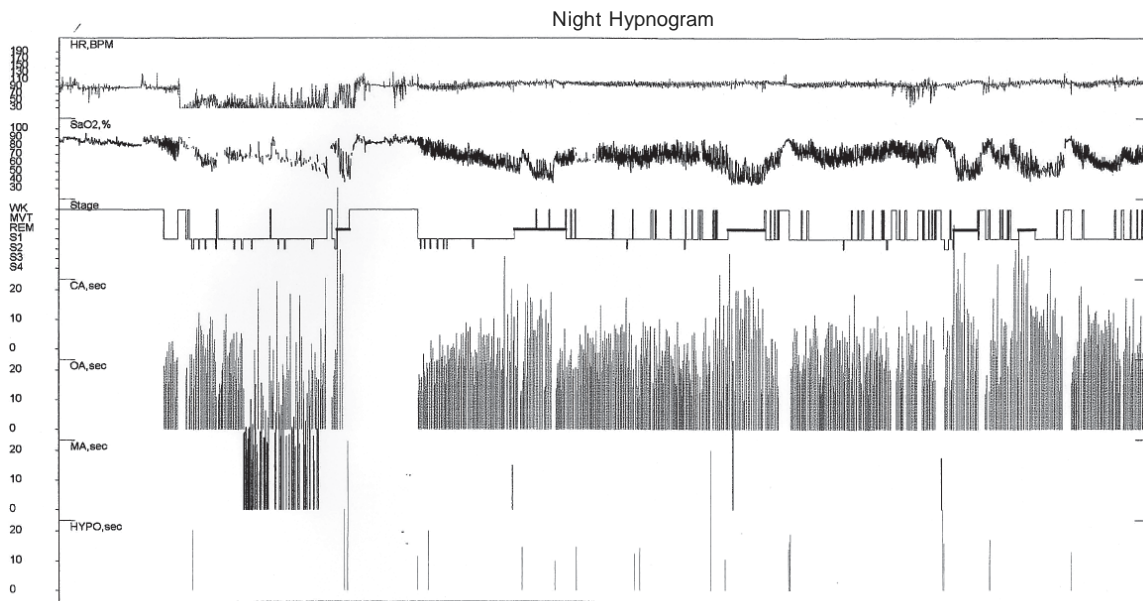


Fig. 2 Polysomnography: An overnight summary demonstrating the presence of OSA. HR, heart rate; SaO₂, atrial oxygen saturation by pulse oximetry; Stage, sleep stage; WKMT, movement when awake; REM, rapid eye movement; S1-4, non-rapid eye movement sleep; CA, central apnea; OA, obstructive apnea; MA, mixed apnea; HYPO, hypopnea.

clubbing. Jugular venous pressure could not be assessed because of obesity. No abnormal sounds were heard on cardiac or lung auscultation. Abdominal examination revealed no hepatomegaly or ascites.

A chest radiograph showed cardiomegaly with a cardiothoracic ratio of 62% and no abnormality of either lung field. Multislice CT scan with contrast enhancement revealed no evidence of

pulmonary embolism, deep vein thrombosis or other abnormalities. Lung ventilation-perfusion scintigraphy did not yield any findings supporting a diagnosis of pulmonary embolism. As she was a non-smoker and her lung function tests were normal, chronic obstructive pulmonary disease was ruled out.

During the examination of echocardiography, the patient fell asleep, and snoring and repetitive apneas were observed.

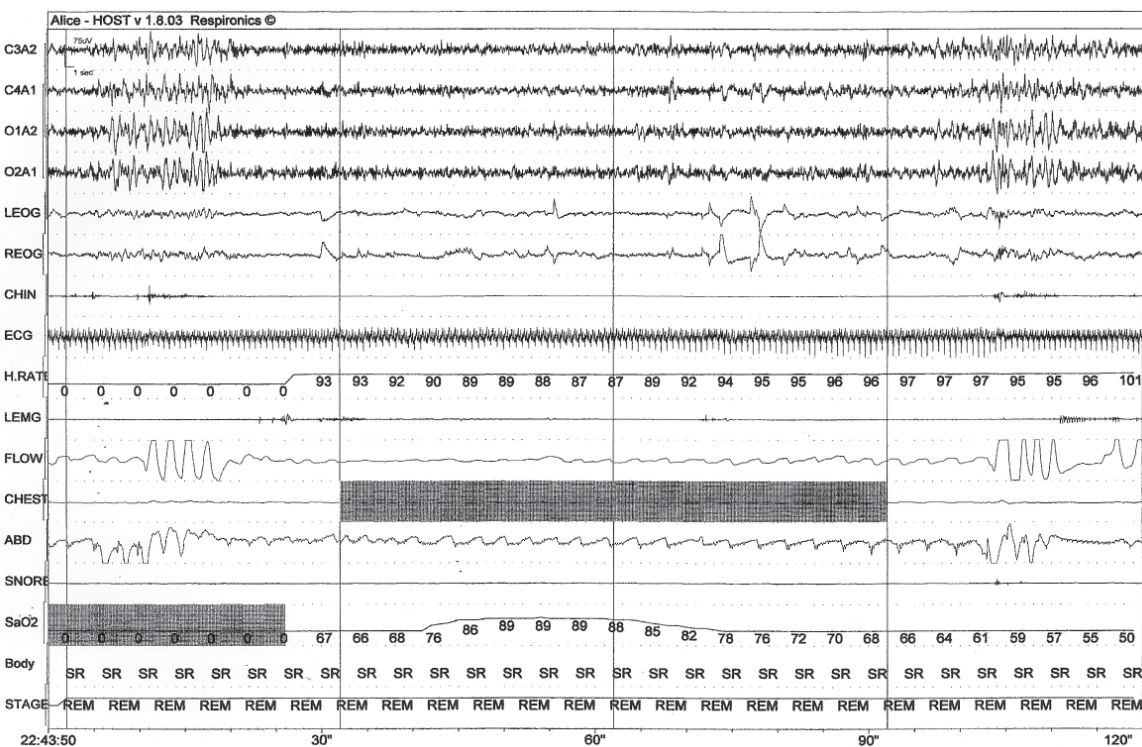


Fig. 3 Polysomnographic record demonstrating the longest OSA lasting 82 sec. C3, C4, O1 and O2: the 4 channels of the electroencephalogram; LEOG and REOG, the 2 channels of the electrooculogram; CHIN, chin muscle electromyogram; ECG, electrocardiogram; H.RATE, heart rate; LEMG, leg muscle electromyogram; FLOW, oronasal airflow; CHEST and ABD, motion of the chest and abdominal wall; SNORE, snoring sound; SaO₂, atrial oxygen saturation by pulse oximetry; Body, body position; STAGE, sleep stage.

Obstructive sleep apnea (OSA) was then suspected. A diagnostic full-night polysomnography was performed (Alice 4 Sleep Diagnostic System; Respironics, Inc., PA, USA) (Fig 2). The apnea hypopnea index was 99.8 per hour. The longest apnea lasted for 82 sec (Fig 3). The mean SaO₂ was 69% and the minimum SaO₂ was as low as 34%. Most of the apneic episodes were obstructive (91.0%), while 0.3% were central and 2.5% were scored as hypopneas. She had predominantly OSA. She was subsequently treated with nocturnal continuous positive airway pressure (CPAP; REMstar Auto; Respironics Inc., Murrysville, PA, USA). Following the application of CPAP, she immediately felt more alert during the daytime. She was able to read books again, something she had previously been unable to do for more than a few minutes without falling asleep.

Treatment with nocturnal CPAP resulted in improvement of daytime dyspnea and PH. Six days after starting CPAP, daytime arterial blood gas analysis revealed PaCO₂ of 46.9 torr, PaO₂ of 73.5 torr, and SaO₂ of 95.3% on room air breathing. Echocardiography showed a normal size right atrium and slightly dilated ventricle, and the pericardial effusion had disappeared. Pulmonary artery pressure was estimated at 37 mmHg. With a mean airway pressure of 7.4 cm H₂O, the apnea hypopnea index diminished to 5.2 per hour. After discharge from the hospital, she continued to use nocturnal CPAP. She has been followed for over 2 years, and dyspnea and PH have not recurred.

DISCUSSION

Several studies have examined the relation between sleep-disordered breathing and cardiovascular risk.¹ OSA is the most common form of sleep-disordered breathing and plays a role in the pathogenesis in systemic hypertension, congestive heart failure, arrhythmias, and atherosclerosis. It also correlates with PH. It is reported that approximately 20% of OSA patients without any other lung or heart disease develop mild PH.^{2,3} Alchanatis et al. reported that the emergence of PH is related to old age, greater body mass index and low PaO₂ during wakefulness.³ In the present case, the patient was 52 years old, had a body mass index of 43 kg/m², and manifested severe daytime hypoxemia on admission. According to the criteria of Alchanatis et al., she was thus highly susceptible to severe OSA with PH. Moreover, the case presentation corresponded with Pickwickian syndrome, which is characterized by severe obesity, daytime sleepiness, hypercapnia, and severe OSA.²

The patient's pulmonary artery pressure was estimated as 70 mmHg, and we were initially skeptical that OSA alone could have induced such severe PH. Patients with OSA generally have mild PH. In the 42 pulmonary hypertensive patients investigated by Laks et al., pulmonary artery pressure ranged from 20 to 52 mmHg and the average value was only 29 mmHg.⁶ Similarly in the 37 pulmonary hypertensive patients reported by Chaouat et al, pulmonary artery pressure ranged from 20 to 44 mmHg with an average of 26 mmHg.⁷ Because OSA is the only disease known to cause daytime hypoxemia and PH, we finally concluded that the severe PH in this patient was a complication of OSA. This is the first reported case of OSA associated with PH of this severity.

In patients with OSA, the combination of marked nocturnal hypoxemia with mild to moderate daytime hypoxemia could explain the development of PH. The mechanisms by which alveolar hypoxia leads to PH are thought to be both pulmonary vasoconstriction and remodeling of the pulmonary vascular bed.⁷ Obesity-related hypoventilation may also play a role in the

emergence of mild daytime hypoxemia and subsequently of mild PH.³

When patients are diagnosed with OSA, the standard treatment is nocturnal nasal CPAP.^{3,5} The effect of CPAP treatment on pulmonary hemodynamics and gas exchange in OSA has been thoroughly investigated. Sajkov et al. reported a decrease in pulmonary artery pressure and pulmonary vascular resistance in patients treated with CPAP.⁴ They also assessed the hypothesis that CPAP could reduce hypoxic pulmonary vascular reactivity, which is the propensity of the pulmonary circulation to constrict in response to hypoxic stimulus. In our case, day-time hypoxemia, hypercapnia, and PH improved markedly following treatment with CPAP, indicating that intermittent nocturnal hypoxemia associated with OSA causes pulmonary constriction, which is reversible with abolition of OSA by CPAP.

CONCLUSION

In this case, administration of nocturnal CPAP significantly improved not only OSA but also daytime hypoxemia, hypercapnia, and severe PH. This suggests that OSA was the only cause of severe PH. Obese patients who present with dyspnea, hypoxemia or PH, even if it is severe PH, should be suspected of having OSA and full-night polysomnography should be performed. Moreover, treatment of such patients with CPAP will result in the disappearance of symptoms and normalization of pulmonary artery pressure.

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Sleep Apnea

Nanaware Sameer, Kumar V, Gothi D, Joshi JM

ABSTRACT

Objective: To study clinical presentation of sleep disordered breathing (SDB) in children, their causative factors and response to treatment.

Methods: A retrospective study of clinical data and results of overnight polysomnography done at baseline and after therapy were reviewed in 56 patients under 18 years of age.

Results: Of the 56 patients included in the study 23 (41%) cases were positive for SDB. 12 (52.1%) patients had craniofacial abnormalities, 4 (17.3%) had neuromuscular and skeletal disorders, 2 (8.6%) had adenotonsillar hypertrophy, 1 (4.3%) had bilateral vocal cord palsy and 3 (13%) had sleep apnoea associated with multisystemic disorders. Post-operative data showed improvement in all 6 cases of craniofacial abnormalities and both cases of adenotonsillar hypertrophy. Positive airway pressure treatment was useful in cases with obstructive sleep apnea (OSA) due to vocal cord palsy, thoracic scoliosis, systemic disorders and central hypoventilation.

Conclusion: 41% of suspected cases were detected to have SDB. Craniofacial abnormality was the leading cause of OSA in the present study. Surgical correction improved symptoms apnea-hypopnea index (AHI) and desaturation in cases of craniofacial disorders and adenotonsillar hypertrophy. Vocal cord palsy, thoracic scoliosis, hypoventilation and systemic disorders associated OSA responded to positive airway pressure ventilation.

Sleep is a major physiological drive. The average child spends almost one half of his or her life asleep, thus respiratory disorders during sleep are of particular importance during childhood. Although some respiratory disorders such as sleep apnea occur only during sleep, virtually all respiratory disorders including upper airway obstruction, central hypoventilation, and chronic lung disease are worse during sleep than wakefulness. Obstructive sleep apnea (OSA) occurs approximately one-third as

often as asthma in children. The peak prevalence of childhood OSA is 2-8 years of age, the age when the tonsils and adenoid are the largest in relation to the underlying airway size.¹ Though the vast majority of cases of OSA in children are associated with adenotonsillar hypertrophy, OSA also occurs in children with upper airway narrowing due to craniofacial abnormalities or those with neuromuscular abnormalities such as hypotonia or muscular incoordination. Obese children are at a higher risk for OSA and its severity is proportional to the degree of obesity, though most children may not be obese but fail to thrive.² Surgery is the main modality of treatment in children with OSA especially for adenotonsillar hypertrophy and craniofacial abnormalities as the cause. Other treatment options include positive airway pressure therapy with continuous positive airway pressure (PAP) ventilation or Bilevel PAP ventilation. Role of oral appliances, uvulopalatopharyngoplasty and supplemental oxygen therapy has not been studied in pediatric patients having OSA.

Thus, the aim of this study was to analyze the clinical presentation of sleep disordered breathing (SDB) in children, their causative factors and response to treatment.

MATERIALS AND METHODS

A retrospective study of 56 patients less than 18 years of age referred for sleep disordered breathing (SDB) from various specialty units mainly neurology, maxillofacial surgery and pediatrics from January 1998 to July 2004 was carried out in a tertiary care referral center in Mumbai, India. Baseline limited polysomnography (PSG) using DENSA DMS-200 (UK) was done with nighttime recording of respiratory variables. The parameters considered in the study were:

- Nasal airflow detected using nasal flow sensor
- Heart rate and arterial oxygen saturation measured by finger oximetry
- Snoring by a snoring probe
- Thoracic, abdominal, and paradoxical movements using thoracoabdominal respiratory bands
- Limb movements using limb sensors.

Reports were analyzed with respect to the apnea-hypopnea index (AHI) and nocturnal desaturations. AHI of >5 and desaturations of <92% were considered as positive for diagnosis for obstructive

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sleep apnoea (OSA). Medical records of the patients with positive AHI were evaluated in detail. Symptoms noted in the records were history of snoring, nocturnal choking, arousals during sleep, excessive daytime sleepiness and nocturia. Other symptoms included abnormal movements during sleep, psychological or mood changes, delayed milestones, scholastic backwardness or poor concentration. History of atypical manifestations such as mouth breathing, irregular pattern of breathing, apneic episodes, anger spells, nocturnal enuresis, sleepwalking, speech disturbances and excessive weight gain were also available. Height, weight, body mass index, blood pressure, spirometry (available in 12 cases) with a flow volume loop (FVL) and 2-Dimensional echocardiography was obtained from the medical records. Post treatment PSG was available to 12 cases. Surgical treatment consisted of surgical release of the temporomandibular joint (TMJ) ankylosis, coronoidectomy either unilateral or bilateral, osteoentrotomy with interpositional arthroplasty with temporal fascia grafting, mandibular distraction, mandibular advancement and genioplasty either single surgery or a combination in cases of craniofacial abnormality, while those with adenotonsillar hypertrophy were subjected to tonsilloadenoid resection (TAR). Medical treatment was given in the form of positive airway pressure ventilation in cases where surgical treatment could not be offered as sleep study with these devices showed improvement in AHI.

RESULTS

Of the 56 patients included in the study below 18 years of age, 23 (41%) patients were detected to have SDB with age range of 4 to 17 years (mean age of 12.1 years). 15 (65.2%) were males and 8 (34.7%) were females. 12 patients (52.1%) were underweight, 2 (8.6%) patients were overweight and only 1 (4.3%) was obese. Snoring during sleep was seen in 21 (91.3%) cases, associated nocturnal choking and awakening in 4 (17.3%), excessive daytime somnolence (EDS) with early morning headache and nonrefreshing sleep in 4 (17.3%) and nocturia in 1 (4.3%) case. 8 (34.7%) patients had neurocognitive symptoms in the form of scholastic backwardness in 3 (13%) cases, psychological disturbance with mood changes, abnormal sleep movements and delayed milestones in 1 case each (4.3%) and mouth breathing, apneic spells, nocturnal enuresis, sleep walking, speech stuttering in 2 (8.6%) cases. Normal blood pressure was recorded in all cases.

Out of the 12 cases where spirometry could be performed, 5 (41.6%) showed variable extra thoracic upper airway obstruction on FVL. 2-Dimensional Echocardiography demonstrated pulmonary hypertension in 1 (4.3%) case having severe micrognathia with OSA.

Craniofacial abnormalities like TMJ ankylosis, retrognathia, micrognathia or an overlap of each other was seen in 12 (52.1%) cases. Of these, 1 patient had TMJ ankylosis associated with arthrogryposis multiplex congenita. Neuromuscular and skeletal disorders causing OSA was seen in 4 of the 23 cases (17.3%). Of these 4 patients, 3 had idiopathic thoracic kyphoscoliosis and 1 patient had scoliosis associated with Marfans syndrome. Adenoid-tonsillar hypertrophy was seen in 2 (8.6%) cases. Bilateral vocal cord palsy caused OSA in 1 (4.3%) case. OSA in 3 (13%) cases of systemic disease was due to achondroplasia, Laurence-Moon-Bardet-Biedl syndrome, and Albright's osteodystrophy with insulin resistance diabetes mellitus. One patient with nocturnal hypercapnoea, hypoxemia, hypoventilation and hypothalamic disorder was diagnosed to have late onset congenital hypoventilation syndrome (LOCHS).

All 6 cases of craniofacial abnormality where post-operative data was available showed improvement in symptoms and AHI. Both the cases of adenotonsillar hypertrophy improved post-operatively following tonsilloadenoid resection (TAR). Continuous positive airway pressure (CPAP) applied through a nasal mask was advised in patients with OSA due to vocal cord palsy, thoracic scoliosis and systemic disorders. Bilevel PAP ventilation with a backup spontaneous time (S-T) mode was advised in the case with LOCHS.

DISCUSSION

Symptoms, pathophysiology, polysomnographic findings, and treatment of pediatric OSA differ significantly from adult OSA. Adult OSA is usually associated with obesity whereas children with OSAS are usually underweight. This is because of failure to thrive and increased work of breathing during sleep. In our study 12 (52.1%) cases were underweight and only 3 (12.9%) were overweight or obese. Children with OSA appear to have a deficit in arousal mechanisms. Studies have shown that these patients have elevated arousal thresholds in response to hypercapnia and increased upper airway resistance.^{3,4} As a result, sleep architecture is preserved in children with OSA and therefore excessive daytime sleepiness, the cardinal symptom of OSA in adults, is uncommon.⁵ In the present study also, excessive daytime sleepiness was observed only in 17.3% of cases. Although apnea-related EEG arousals are less common in children, subcortical arousals and subtle disturbances in sleep architecture occur frequently.⁶ These factors may contribute to neurobehavioral and autonomic complications. Gozal et al have demonstrated that students of grade I in lowest 10th percentile of their class academically had an amazingly high proportion (18%) of home studies suggestive of sleep-disordered breathing, reflecting the effect of sleep-disordered breathing on intellectual function.⁷ In the present study too, neurocognitive symptoms were seen in 34.7% cases.

In the present study, craniofacial abnormality (52.1%) was the commonest cause for pediatric OSA, followed by skeletal (17.3%), adenotonsillar hypertrophy (8.6%) and bilateral vocal cord palsy (4.3%). 13% cases had OSA associated with multisystemic disorders like achondroplasia, Albright's syndrome (pseudohypoparathyroidism with insulin resistance diabetes mellitus) and Laurence-Moon-Bardet-Biedl syndrome. Only one case was detected to have a very rare and unusual form of SDB, diagnosed as late onset central hypoventilation. The vast majority of cases of OSA in children reported in literature are associated with adenotonsillar hypertrophy, however in the present study the leading cause was craniofacial abnormality. This is perhaps because our dental hospital is a referral center for corrective surgery of craniofacial abnormality and hence awareness regarding associated SDB is high. TM joint ankylosis, retrognathia or micrognathia can cause OSA due to either congenital or post-traumatic anatomical defect leading to difficult mouth opening and upper airway narrowing because of reduced inter-incisal distance. Thoracic kyphoscoliosis is often associated with sleep apnea; the 'Quasimodo's syndrome' named after the legendary hunchback of Notre Dame. There is no upper airway obstruction in cases of Quasimodo's syndrome, however, the deformed and stiff chest wall causes reduced chest wall expansion leading to alveolar hypoventilation, which gets aggravated during sleep resulting in apneas. These patients also may have an abnormal central drive for respiration causing cessation of breathing. Although childhood OSA is associated with adenotonsillar hypertrophy, large tonsils and adenoids alone do not cause it. This

is explained by the fact that these patients do not obstruct during wakefulness. Studies have failed to show a correlation between upper airway or adenotonsillar size and OSA and a small percentage of children with adenotonsillar hypertrophy with OSA is not cured by TAR. Guilleminault and colleagues reported a cohort of children who were cured of their OSA by adenotonsillectomy, but developed a recurrence during adolescence.⁸ Thus; it appears that childhood OSA is a dynamic process resulting from a combination of structural and neuromotor abnormalities, rather than from structural abnormalities alone.

Untreated OSA can result in serious morbidity. Early reports documented complications such as failure to thrive, cor pulmonale, and mental retardation.⁹ These severe sequelae are less common now, due to earlier diagnosis and treatment. Even though failure to thrive is an exception these days, children with OSA still tend to have a growth spurt following TAR. A recent study found an increase in insulin-like growth factor-I following TAR, suggesting that endocrine factors play a role in postoperative spurt in growth.¹⁰ Cor pulmonale with heart failure used to be a common mode of presentation for children with OSA but is now rare. Tal and coworkers showed a reduced right ventricular ejection fraction in 37% of children with clinically diagnosed OSA, although only 7% had clinical evidence of pulmonary hypertension.¹¹ In the present study only 1(4.3%) patient had pulmonary hypertension having OSA due to severe micrognathia. Cor pulmonale can be reversed on treatment of OSA. Systemic hypertension is a well-described complication of OSA in adults, and has been reported in a few pediatric case series. A systematic study showed elevated diastolic blood pressure in children with OSA, which could be predicted by AHI, body mass index, and age.¹² None of the cases had elevated blood pressure in the present study.

Craniofacial surgery is appropriate for some children with craniofacial anomalies. In the present study out of the 6 patients who had followed up after surgical correction for craniofacial abnormalities, improvement in sleep symptoms and AHI was seen in all (100%) cases. In a study done for the role of distraction osteogenesis in the correction of micrognathia with OSA in 28 patients, all patients were shown to have improvement following surgery with a complete curative effect in 82.1% cases.¹³ Children suffering from tonsilloadenoid hypertrophy with OSA have both symptomatic and polysomnographic improvement following TAR.¹⁴ Similarly in the present study both patients showed complete resolution of symptoms and AHI following TAR. Nasal continuous positive airway pressure (CPAP) is the most widely used and perhaps the most effective treatment for adult OSA. Positive pressure to the upper airway acts like a pneumatic splint to maintain airway patency thereby increasing lung volume, which may improve oxygenation. However limiting factors for CPAP therapy in children include lack of adequate pediatric interfaces, inappropriate behavioral techniques and need for other equipment designs for children. Young or weak children frequently do not trigger bilevel ventilators. Children may also develop central apneas or hypoventilation at higher-pressure levels.¹⁵ This is presumably due to activation of the Hering-Breuer reflex by stimulating pulmonary stretch receptors. It can be remedied by placing the patient on bilevel ventilation with a backup rate. There is also concern among pediatric practitioners that the current nasal masks can cause midfacial depression when used in very young patients. Nasal deformities have also been noted in premature infants receiving CPAP via nasal prongs.

Sleep study with continuous positive airway pressure (CPAP) ventilation improved symptoms and AHI in bilateral vocal cord palsy, thoracic scoliosis and systemic disorders associated with OSA. Also, therapeutic trial of bilevel PAP ventilation in LOCHS showed significant clinical improvement in the present study. However, patients could not be persuaded to take long-term treatment with these devices because of technical difficulties and their cost.

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Oxygen Therapy Prevents Ventricular Arrhythmias in Patients with Congestive Heart Failure and Sleep Apnea

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BACKGROUND

Although ventricular arrhythmia is critical for the prognosis of patients with severe congestive heart failure (CHF), it is difficult to control the arrhythmia using conservative therapies. However, many CHF patients also have sleep apnea syndrome (SAS) and oxygen supply improves their prognosis. The beneficial effects of oxygen treatment for ventricular arrhythmia have not yet been clarified, so the present study was designed to evaluate the effects of oxygen treatment for premature ventricular contraction (PVC).

Methods and Results: Patients with CHF and SAS were divided into 3 groups: (1) the "PVC declined" group that included patients who had frequent PVCs and oxygen treatment that suppressed the number of PVC; (2) the "PVC not affected" group that included patients who had frequent PVCs and oxygen treatment did not affect the number of PVC; and (3) the "few PVC" group that included patients who had no or few PVCs. The group 1 patients showed higher apnea-hypopnea index, standard deviation of all R-R intervals, left ventricular ejection fraction, and brain natriuretic peptide levels than the patients in group 2. Oxygen treatment in group 3 did not affect the PVC frequency.

Conclusions: Oxygen treatment may be useful for preventing ventricular arrhythmia in selected patients with CHF and SAS.

Congestive heart failure (CHF) is a highly prevalent disorder that is associated with repeated hospitalization, high morbidity and mortality. Because ventricular arrhythmia is one of the major causes of poor prognosis in CHF patients,¹ it is associated with excess mortality.

Sleep-related periodic breathing with recurrent episodes of apnea is known to occur in patients with CHF.²⁻⁵ This breathing disorder may be associated with arterial oxyhemoglobin desaturation and excessive arousals, resulting in sympathetic activation and arrhythmias.^{6,7} Because sleep-disordered breathing is also observed in patients with idiopathic cardiomyopathy,⁸ the pathophysiological consequences of sleep apnea may further contribute to the mortality of CHF patients with ventricular arrhythmias. Although home oxygen therapy⁹ and bi-level positive airway pressure treatment^{10,11} improve the clinical condition of sleep apnea syndrome (SAS) in CHF patients, few studies of SAS in CHF with ventricular arrhythmias have been reported and detailed findings and laboratory examinations for arrhythmia in SAS and CHF are needed.

In this study, we studied patients with stable CHF to determine (1) the clinical characteristics and the prevalence of premature ventricular contraction (PVC) in patients with CHF and SAS, (2) the clinical features of the CHF with SAS patients with or without frequent PVCs, (3) the effects of nasal oxygen therapy for prevention of PVCs in patients with CHF and SAS, and (4) the clinical features of patients with CHF and SAS who are effectively treated with oxygen.

METHODS

Subjects: We recruited 50 patients with CHF admitted to the Department of Cardiovascular Medicine of the Tokyo Medical and Dental University Hospital. Patients <80 years of age were eligible if they met the following criteria: at least 1 episode of cardiac decompensation; and stable condition while receiving cardiac medication. Exclusion criteria were: myocardial infarction within 1 year of study entry; significant obstructive lung disease; unstable angina; unstable heart failure; acute pulmonary edema; congenital heart disease; severe renal and liver disorders; untreated hypothyroidism; and use of morphine derivatives, benzodiazepine, or theophylline. This study was approved by the ethics committee of Tokyo Medical and Dental University. Written informed consent was given by all participants. Medication (eg, diuretics, angiotensin-converting

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Table 1 CHF Patients With or Without Frequent PVCs

	Group 1	Group 2	p value
PVCs	>30/h	<30/h	
Number	15	22	
Sex (M/F)	9/6	19/3	
Age (years)	67.4±3.5	66.4±2.1	NS
BNP (pg/ml)	668±185	420±162	NS
CTR in X-p (%)	60.0±2.3	56.0±1.7	NS
EF in UCG (%)	40.9±5.1	52.6±5.0	NS
LAD in UCG (mm)	47.3±2.5	45.1±3.1	NS
LVDd in UCG (mm)	62.2±3.7	50.2±2.9	NS
Cause of CHF			
DCM	6	9	
Ischemic	6	8	
Valve	3	5	
β-blocker Tx.	9/15	11/22	NS
Morpheus (per 8 h)			
Total PVC	1,970±721	9.8±2.9	<0.05
Isolated PVCs	1,316±435	8.7±2.8	<0.05
Av. HR	76.1±2.5	68.5±2.3	NS
AHI	20±5	19±4	NS
Av. SpO ₂	93±1.3	96±0.5	<0.05
SDNN	136±50	121±17	NS
Asleep LF/HF	1.6±0.5	1.4±0.3	NS

CHF, congestive heart failure; PVCs, premature ventricular contractions; BNP, brain natriuretic peptide; CTR, cardiothoracic ratio; X-p, X-ray; EF, ejection fraction; UCG, echocardiography; LAD, left atrial diameter; LVDd, left ventricular diastolic diameter; DCM, dilated cardiomyopathy; Tx., treatment; HR, heart rate; AHI, apnea-hypopnea index; SDNN, standard deviation of all R-R intervals; LF/HF, low-frequency/high-frequency.

enzyme inhibitors (ACE), angiotensin II receptor antagonists (ARBs), β-blockers, digoxin, isosorbide dinitrates) dosages had been adjusted on the basis of the hemodynamic and clinical status of each patient and had not been changed within the previous 2 weeks. The etiologies of heart failure were ischemic cardiomyopathy, idiopathic cardiomyopathy, and valvular diseases.

At the time of the recruitment, no information was sought about symptoms or risk factors for SAS and arrhythmia. The patients were admitted to the hospital for at least 2 consecutive nights for this study. Caffeinated products were avoided during hospitalization. On the first day, a detailed history was obtained and physical examination was performed. The following tests were also carried out: complete blood count, serum electrolytes, blood urea nitrogen, serum creatinine, brain natriuretic peptide (BNP), echocardiography (UCG), and chest X-ray (X-p).

Sleep Study: Holter electrocardiogram (ECG) and respiratory monitoring were performed using the Morpheus C system (Teijin Pharma Co, Tokyo, Japan) consisting of a flow sensor for nasal and oral breath flows, a 3-channel electrocardiograph, and 1 stress-sensitive belt each for the thorax and the abdomen.^{12,13} For each subject, the overnight sleep study was recorded between 21.30 h and 05.30 h. On the first night, the respiratory and Holter monitoring was performed without nasal oxygen treatment; the same monitoring with nasal oxygen therapy (3 L/min) was performed on the second night. The data were stored on a computer which automatically calculated the apnea hypopnea index (AHI), the apnea index (AI), and the oxygen desaturation index (ODI). The ODI was defined as the number of events per hour of sleep in which oxygen saturation decreased by 4% or more. Apnea was diagnosed in patients in whom respiratory flow was reduced to <20% of normal for at least 10 s. The AI was defined as the number of episodes of obstructive apnea per hour of sleep. The AHI was defined as the

Table 2 Patients With Frequent PVCs in CHF (Group 1) With or Without an Oxygen Therapy

Oxygen	No	3 L/min	p value
CHF	(+)	(+)	
PVCs	>30/h	>30/h	
Morpheus (per 8 h)			
Av. HR	76.1±2.5	73.7±4.5	<0.05
Av. SpO ₂	93±2.0	98±0.3	<0.05
AHI	20±5.0	6.4±2.1	<0.05
Total PVCs	1,970±721	1,559±420	NS
Isolated PVCs	1,316±435	1,104±320	NS
SDNN	136±50	178±56	NS

Abbreviations see in Table 1.

number of episodes of apnea and hypopnea per hour of sleep; patients who had a score of 5 or more for AHI were diagnosed as having SAS.^{14,15}

Holter Monitoring: All patients and control subjects underwent Holter recording with 3-channel real-time recorders. For each patient, the total number of PVCs, ventricular couplets, and episodes of ventricular tachycardia (defined as ≥3 consecutive PVC with a rate ≥100 beats/min) were recorded. Heart rate variability (HRV) was assessed, both in time and frequency domains, on the Holter recordings after full revision of the ECG and editing of beats where indicated. During the analysis, only normal beats were measured, and all artifacts were eliminated. Time-domain HRV variables included the mean of all R-R intervals for the entire recording; the standard deviation of all R-R intervals (SDNN) was measured. In the frequency domain, HRV was assessed in the range of frequencies of 0–0.4 Hz by a fast-Fourier transform spectral analysis algorithm, with a spectral resolution of 0.0005 Hz, with the use of the aforementioned Brentwood software. The amplitude of the following frequency-domain HRV variables was obtained: low-frequency (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.40 Hz), and the low-frequency/high-frequency (LF/HF) ratio. The amplitude values of LF, HF, and LF/HF ratio were also obtained for each hour of the day.^{12–15}

Other Studies: Left ventricular ejection fraction (LVEF) was calculated from the echocardiogram by standard techniques. Chest X-p and arterial blood samples were obtained according to strict criteria as previously reported.^{16,17}

Statistical Analysis: We used the Wilcoxon rank-sum test to assess significant differences between the groups, because the data were not normally distributed. A value of p<0.05 was considered significant. Values are reported as mean±SD.

RESULTS

Frequent PVC Group: In this study, 37 of 50 patients were diagnosed with SAS and CHF, and we analyzed arrhythmia in all 37 patients. According to our defined thresholds, there were 15 patients (group 1, frequent PVCs) who had frequent PVCs (>30 PVCs/h) and the mean (±SD) number of total PVCs was 1,970±721 per 8 h. The remaining 22 patients (group 2, few PVCs) had fewer PVCs (<30 PVCs/h) and the mean was 9.8±2.9 per 8 h. Between the 2 groups, average SpO₂ levels were statistically different: group 1 showed a lower level (93±1.3%) than group 2 (96±0.5%, p<0.05 vs group 1). All other factors, including background diseases and β-blocker treatment, were statistically comparable between the 2 groups (Table 1).

Case 1, 79-year-old male

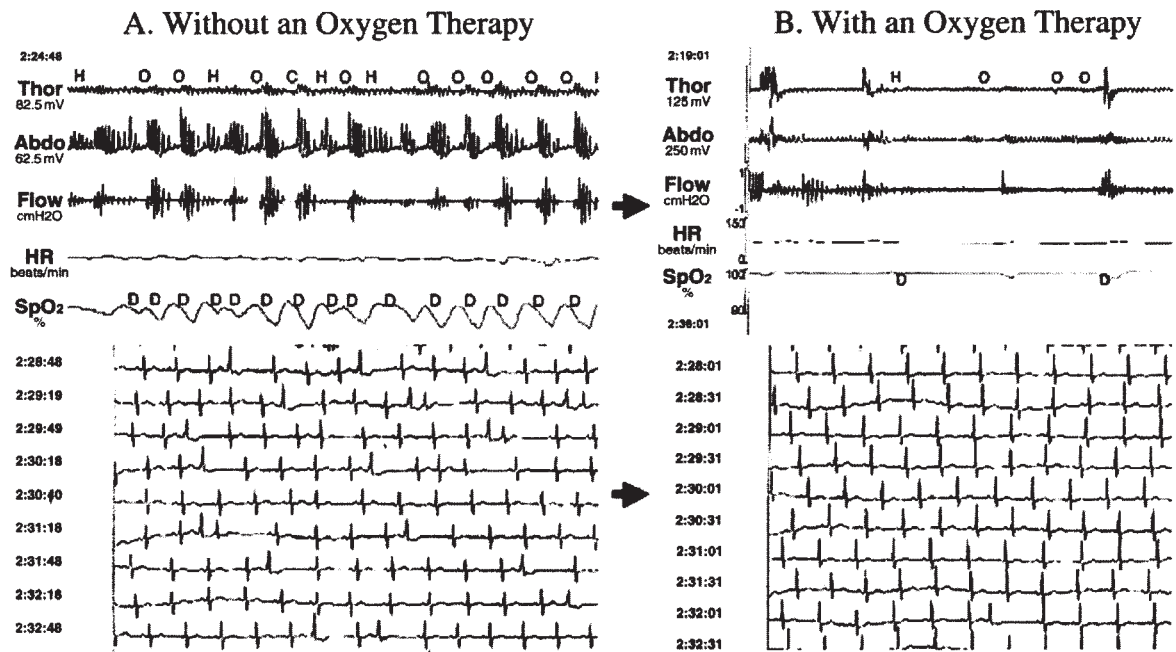


Fig 1. Representative case from the 'PVC declined' group. Representative Holter and saturation results without (A) and with (B) the oxygen treatment are shown. Frequent PVCs (8,770/8 h without oxygen vs 4,162/8 h with oxygen) and sleep apnea (AHI: 71.9 without oxygen vs 13.7 with oxygen) with desaturation (average SpO₂: 90% without oxygen vs 98% with oxygen) was significantly improved by the oxygen therapy. H, hypopnea; O, obstructive apnea; D, desaturation; PVC, premature ventricular contraction; AHI, apnea hypopnea index; HR, heart rate.

Case 2, 73-year-old male

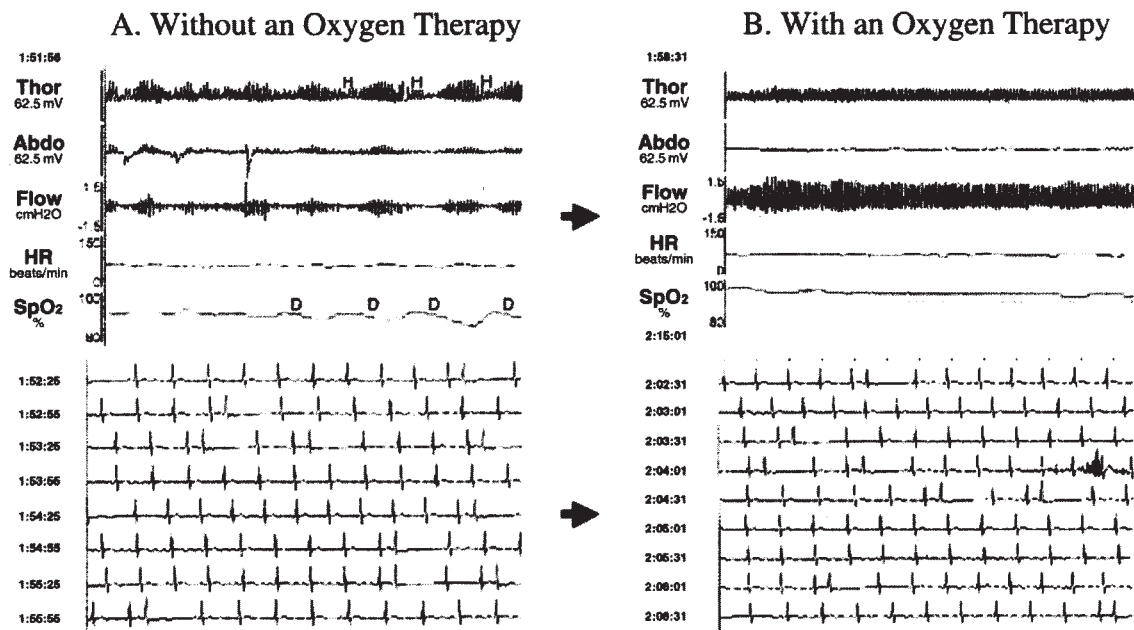


Fig 2. Representative case from the 'PVC not affected' group. Representative Holter and saturation results without (A) and with (B) the oxygen treatment are shown. Although sleep apnea (AHI: 22.2 without oxygen vs 14.5 with oxygen) with desaturation (average SpO₂: 92% without oxygen vs 96% with oxygen) was improved by the oxygen therapy, frequent PVCs were not suppressed (4,244/8 h without oxygen vs 4,599/8 h with oxygen) by the treatment. H, hypopnea; D, desaturation; PVC, premature ventricular contraction; AHI, apnea hypopnea index.

Effect of Oxygen Treatment on Number of PVCs: Because the only significant factor was the average SpO₂ level, we tried to clarify the effects of oxygen therapy (3 L/min nasal O₂ supply) on the number of PVCs in this group. Although average heart rate, SpO₂ level and AHI improved with the oxygen treatment, PVC numbers before (1,970±721) and after (1,559±420) treatment were not statistically different. SDNN was also comparable before and after the treatment (Table 2).

Mechanism of Effect of Oxygen Therapy on PVCs in CHF:

The 15 patients in group 1 (frequent PVCs) were further subdivided into 2 groups: "PVC declined" (n=6) group had patients who had frequent PVCs and oxygen treatment suppressed (>50% decline) the number of PVC, and "PVC not affected" (n=9) group which was those who had frequent PVCs and oxygen treatment did not affect (<50% decline) the number of PVC.

A representative from case group 1 (Fig 1) was a 79-year-old male who had dilated cardiomyopathy and was suffering from leg edema and dyspnea. His height was 166 cm and weight was 83 kg; blood pressure was 130/80mmHg and pulse was 72 beats/min regular. His blood examination showed anemia (hemoglobin (Hb) 9.1 mg/dl), renal dysfunction (creatinine 1.56 mg/dl) and a high BNP level (953.4 pg/ml). The ECG showed frequent PVCs with sinus rhythm. Chest X-p showed enlarged cardiothoracic ratio (62%), and pulmonary edema with enlarged pulmonary arteries. Echocardiogram showed good ejection fraction (EF) (62%), and enlarged left atrial diameter (56 mm). Frequency of PVCs (8,770 /8 h without oxygen vs 4,162 /8h with oxygen) and sleep apnea (AHI: 71.9 without oxygen vs 13.7 with oxygen) with desaturation (average SpO₂: 90% without oxygen vs 98% with oxygen) were both significantly improved by the oxygen therapy.

A representative case from group 2 (Fig 2) was a 73-year-old male who had a valve disease and was suffering from dyspnea. His height was 163 cm and weight was 66 kg; blood pressure was 130/80 mmHg and pulse was 72 beats/min regular. His blood examination showed mild anemia (Hb 12.6 mg/dl), renal dysfunction (creatinine 0.88 mg/dl) and BNP elevation (90.6 pg/ml). The ECG showed frequent PVCs with sinus rhythm. Chest X-p showed normal cardiothoracic ratio (51%), and enlarged pulmonary arteries. Echocardiogram showed borderline EF (53%), enlarged left atrial diameter (51 mm) and severe tricuspid regurgitation. Although sleep apnea (AHI: 22.2 without oxygen vs 14.5 with oxygen) with desaturation (average SpO₂: 92% without oxygen vs 96% with oxygen) was improved by the oxygen therapy, the number of PVCs was not suppressed (4,244/8h without oxygen vs 4,599/8h with oxygen) by the treatment.

Characteristics of Group 1: Statistically, higher serum BNP levels (780±233 vs 236±96, p<0.05), greater LVEF in UCG (49.0±8.1 vs 32.7±5.0, p<0.05), more PVCs before the oxygen treatment (3,341±1,576 vs 1,056±471, p<0.05), higher AHI (29±1.3 vs 15±4, p<0.05), and higher SDNN (215±121 vs 84±13, p<0.05) were observed in group 1. All other factors, including New York Heart Association grading, background diseases, β-blocker treatment, and ODI, were statistically comparable between the 2 groups (Table 3).

DISCUSSION

The pathophysiology of ventricular arrhythmia in CHF patients

Table 3 CHF Patients With Frequent PVCs With or Without Effective Oxygen Therapy

	PVC declined	PVC not affected	p value
CHF	(+)	(+)	
PVCs	>30/h	>30/h	
Number	6	9	
Sex (M/F)	4/2	5/4	
Age (years)	71.0±3.4	64.3±5.8	NS
NYHA	2.5±0.5	2.7±0.7	NS
BNP (pg/ml)	780±233	236±96	<0.05
CTR in X-p (%)	60.5±4.0	59.6±3.0	NS
LVEF in UCG (%)	49.0±8.1	32.7±5.0	<0.05
LAD in UCG (mm)	49.6±5.8	45.7±1.9	NS
LVDd in UCG (mm)	56.0±2.3	68.2±6.4	NS
<i>Causes of CHF</i>			
DCM	3	4	
Ischemic	2	3	
Valve	1	2	
β-blocker Tx.	4/6	5/9	NS
<i>Morpheus (per 8h)</i>			
Total PVC	3,341±1,576	1,056±471	<0.05
Isolated PVCs	2,040±926	834±350	<0.05
Av. HR	71.2±3.4	79.3±3.1	NS
AHI	29±1.3	15±4.0	<0.05
Av. SpO ₂	94±1.3	92±2.0	NS
SDNN	215±121	84±13	<0.05
Asleep LF/HF	1.9±1.2	1.4±0.3	NS
ODI 3%	30.7±10.7	20.3±3.4	NS

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index. Other abbreviations see in Table 1.

with SAS is complex and not completely understood. The individual apneic events have a considerable hemodynamic impact that is mediated by a complicated sequence of pathophysiologic events, such as vascular endothelial dysfunction¹⁸ and altered central chemosensitivity.¹⁹ Several important regulatory mechanisms in cardiovascular homeostasis seem to influence the number of PVCs in CHF. In this study, patients with frequent PVCs with CHF and SAS showed less average SpO₂ levels than patients with less frequent PVCs. Oxygen therapy was used to suppress the number of PVCs in the CHF and SAS patients, but we could not reveal any effects statistically because there was a large standard deviation among the patients. Therefore, we tried to reveal which factors are critical in the beneficial effect of oxygen therapy suppressing PVCs.

In the present study, patients with CHF and SAS who had frequent PVCs were further subdivided into 2 groups: the oxygen effective group and oxygen non-effective group. It has been shown that the frequency and severity of arrhythmia can increase in SAS patients.²⁰⁻²² We confirmed that oxygen treatment for prevention of PVCs is effective in patients with higher BNP levels, greater LVEF, and higher SDNN, which suggests that the oxygen therapy can affect both the physiological disorder and the impaired cardiac autonomic function that produce the PVCs.

First, the impairment of cardiac autonomic function in CHF patients with SAS can be a trigger for ventricular arrhythmia and nasal oxygen therapy may suppress the ventricular arrhythmia through the improvement of cardiac autonomic function. An altered autonomic balance has been suggested as a possible pathogenetic factor, and autonomic dysfunction is implicated in the subsequent development of cardiovascular diseases in CHF patients with SAS.²³⁻²⁹ Time-domain and

spectral HRV analysis are powerful tools for investigating arrhythmia in CHF patients with SAS. Spectral analysis of the HRV is a commonly used method for evaluating the autonomic modulation of the heart rate and arrhythmia. It gives selective information on parasympathetic and sympathetic function and moreover, because the method is noninvasive, it is appropriate for clinical studies. Spectral analysis is reproducible and has a better sensitivity and specificity than do the previously used time domain methods in short-term studies of cardiovascular reflex.^{30,31} In another variation from previous studies, our recording system using Morpheus C provided information for both spectral and time domain analyses. In this study, we could not clarify the difference of SDNN before and after the oxygen therapy because the time protocol was too short to detect the change. However, SDNN may change after a longer observation, so further study of the effects on SDNN using long-term observation is needed. From our results, nasal oxygen therapy may be effective for suppressing PVCs in CHF patients with SAS when the patient has impaired autonomic function.

Second, we also revealed that the oxygen-effective group had higher BNP levels and greater LVEF than the noneffective group. Recently, it was reported that plasma BNP level and cardiac autonomic function are closely related to prognosis in patients with heart failure. Plasma BNP levels are also known to be a strong predictor for mortality in heart failure patients and the BNP levels are statistically related to cardiac sympathetic nerve innervation.³² Another study indicated that increased plasma BNP levels were related to cardiac reflex parasympathetic dysfunction in type 2 diabetic patients.³³ In the present study, higher BNP levels and LVEF could be the result of insufficient treatment with conservative therapies, including β -blockers and other medicines. It is well known that conservative treatment of CHF using β -blockers, ACE inhibitors, and ARBs improves the prognosis of CHF patients. However, these drugs are not able to be used in some cases because of hypotension, bradycardia, and/or systemic adverse effects, which was the situation in the present study, and oxygen therapy should be used in CHF patients with such conditions as an alternative treatment for CHF. At present, the detailed relationship between oxygen treatment and BNP levels is not understood, but patients with high BNP may be good candidates for oxygen treatment for the suppression of PVCs.

We conclude that (1) desaturation and cardiac autonomic activity is altered in some CHF patients, (2) this alteration may be one of the causes of ventricular arrhythmia, and (3) oxygen therapy may be effective for suppression of PVCs when the CHF patient has desaturation, high BNP and/or impaired autonomic function.

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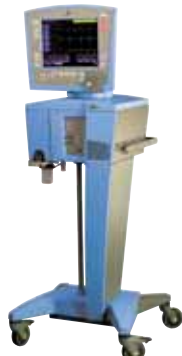
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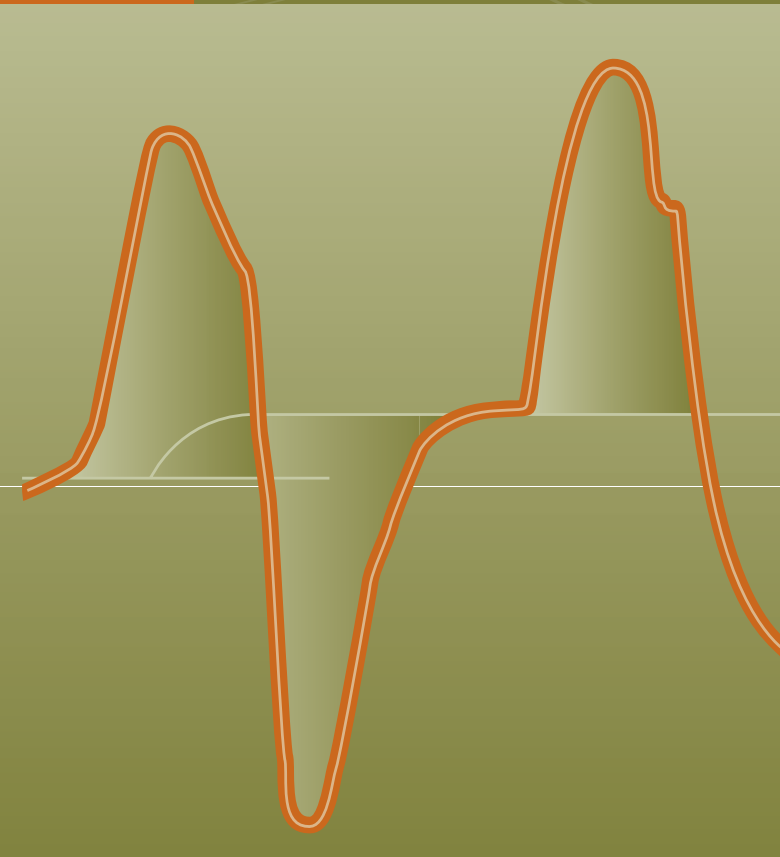


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