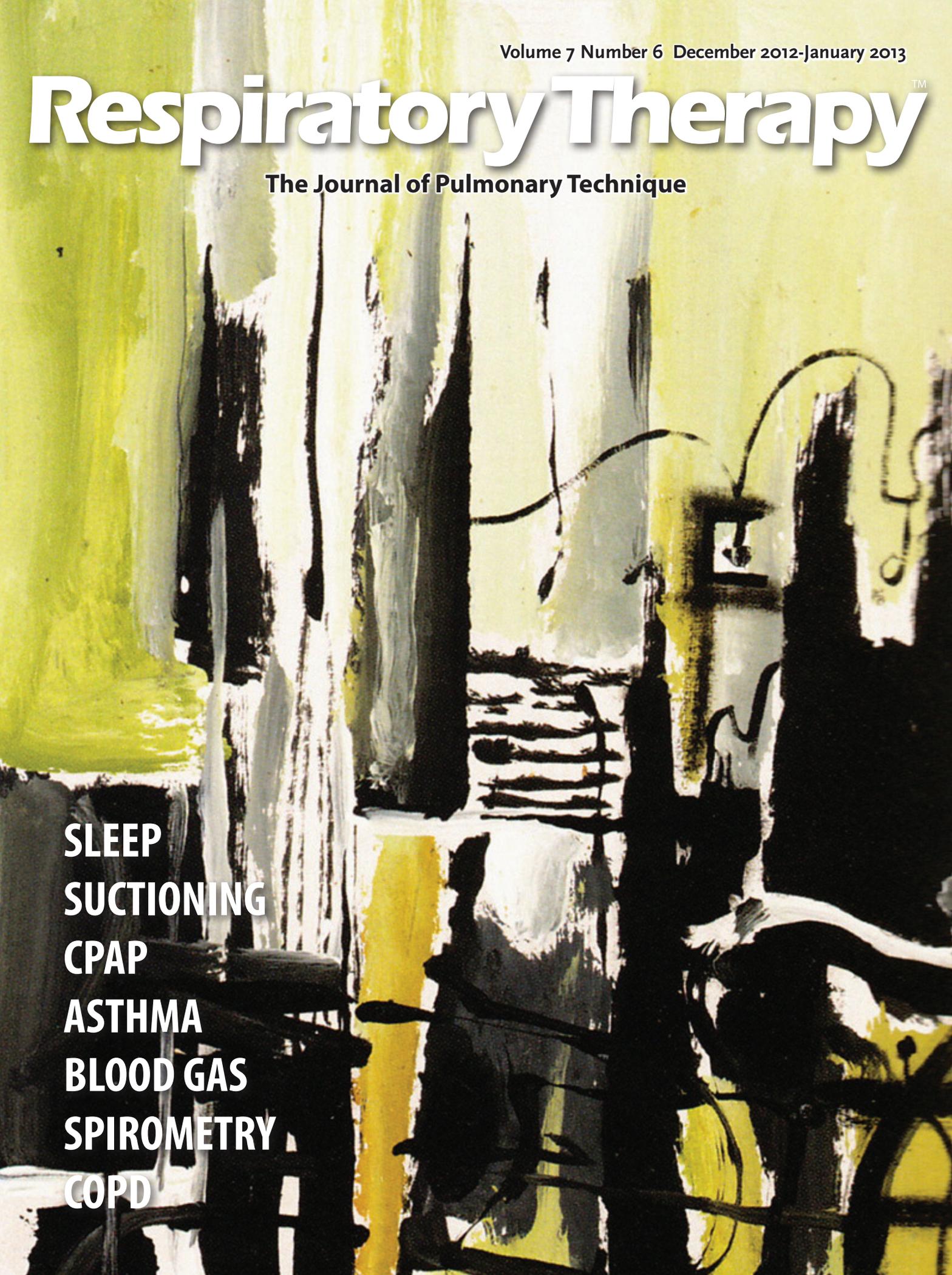


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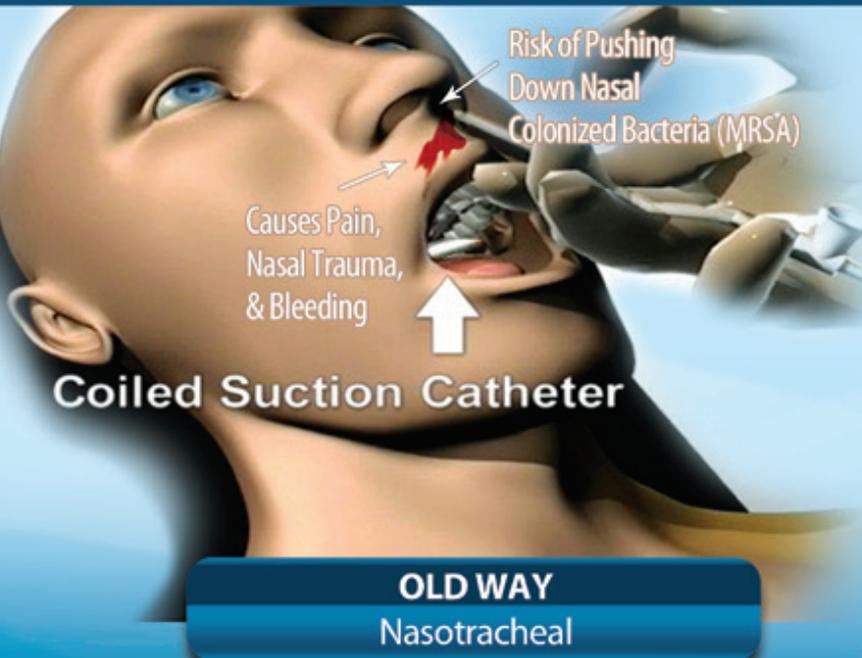


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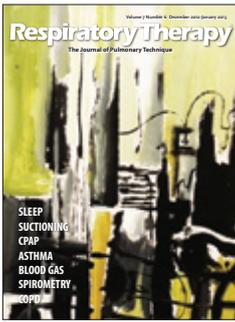
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Editorial

Hacked and App'd

Here's some interesting items in the news regarding medical devices and information technology: Torie Bosch reports via Slate.com that the GAO has asked the FDA to develop a strategy to address information security risks for medical devices. This comes after hackers demonstrated the vulnerability of such devices by hacking into an insulin pump. According to the GAO report, "A denial-of-service attack could be launched using computer worms or viruses that overwhelm a device by excessive communication attempts, making the device unusable by either slowing or blocking functionality or draining a device's battery." Medical data generated by the devices could be wiped or stolen and therapies could be altered. The Slate article noted that most medical devices don't require passwords, likely because a good security system could slow down medical treatment in case of an emergency.

The website PopSci reported that a computer expert at a security conference demonstrated the hacking of a pacemaker, sending 800 volts of electricity across 30 feet. He also showed how a virus could be passed into the pacemaker that could spread and infect other pacemakers nearby.

In related news, a bill has been proposed that would establish an Office of Mobile Health under the auspices of the FDA that would evaluate apps that claim to provide healthcare info. Jennie Gold reports in Kaiser Health News that "it can be hard to know which [apps] deliver on their health claims and provide accurate information." The KHN article points out, however, that apps are being developed at such a fast pace, it would be hard for the FDA to keep up.

Gold writes: "The Healthcare Innovation and Marketplace Technologies Act (HIMTA) would establish a special Office of Mobile Health at the FDA to provide recommendations on mobile health app issues and create a mobile health developer support program at the Department of Health and Human Services to help app developers make sure they are operating within privacy regulations, including the federal law HIPAA that sets privacy standards." The proposed bill has met opposition, with app developers protesting that typical governmental regulatory protocols are too hard to navigate, and hoped that a dedicated FDA office for mobile health would streamline the process.

The agency has already begun to regulate a handful of medical apps, but developers are complaining that the typical six to 20 month approval process is too slow, and would kill off innovation. The FDA's Safety and Innovation Act, currently signed into law, has been charged with setting up a strategy for mobile app regulation, but the report on its work won't be due until the spring of 2013. It's estimated that by 2015, 500 million smartphone users will be using medical apps.

Les Plesko, Editor



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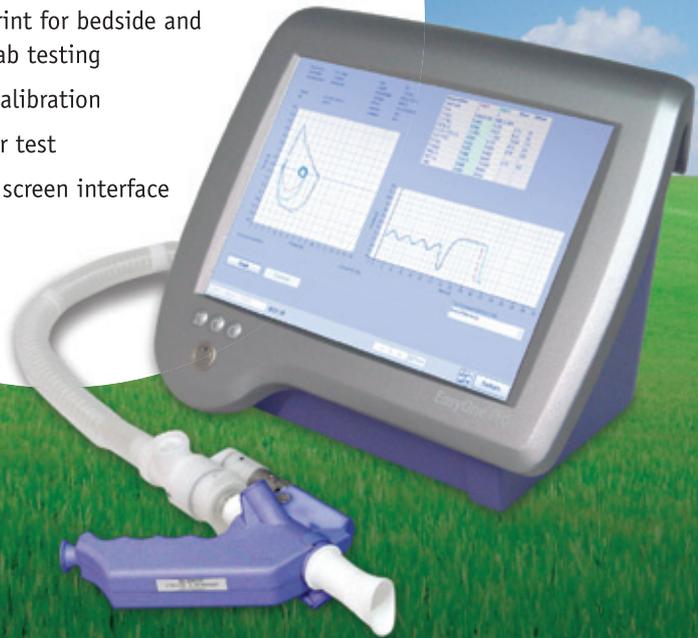
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News

□ December 2012-January 2013

SPIROMETRY BENCHMARK

New research has established the first global benchmarks using lung growth charts for assessing lung function across the entire life span. Previously, a number of different charts have been used across the world to help doctors interpret spirometry results. The international Global Lung Function research group collected data from 74,187 healthy non-smokers aged 3-95 years and derived new continuous “all-age” multi-ethnic lung growth charts. Previously, lung function charts were often only applicable to white subjects of European descent, but the new charts include the black population, those of Asian/Chinese descent and those of mixed ethnic origins.

NOT BLOWING SMOKE

Researchers at the University of Athens have found evidence that electronic cigarettes aren't so safe. The study included 8

people who had never smoked and 24 smokers, 11 with normal lung function and 13 with either COPD or asthma. Each person used an electronic cigarette for 10 minutes. The researchers then measured their airway resistance using a number of tests, including spirometry. The results showed that for all people included in the study, the e-cigarette caused an immediate increase in airway resistance, lasting for 10 minutes. In healthy subjects (never smokers) there was a statistically significant increase in airway resistance from a mean average of 182% to 206%. In smokers with normal spirometry there was a statistically significant increase from a mean average of 176% to 220%. In COPD and asthma patients the use of one e-cigarette seemed to have no immediate effect on airway resistance.

KEEP AWAY

Exposure to school-age children raises the odds that a person with lung disease who catches a cold will suffer symptoms like a runny nose, sore throat and cough, according to researchers at the University of Rochester, NY. They studied 1,000 samples of sputum and nasal secretions from people with COPD. Contact with school-age children was the only risk factor found, and it increased both the risk of infection and also the risk of suffering symptoms once a cold's been caught. Infected people were twice as likely to have had contact with school-age children as people whose infections did not become symptomatic. The study also found that adults who were on home oxygen use were somewhat protected against the added risk posed by schoolchildren.

POOR AND ASTHMATIC

Children living in low-income urban areas are especially prone to developing asthma, possibly related to infections they acquire

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early in life, according to researchers at the University of Wisconsin. To document patterns of respiratory viruses in infants living in urban and suburban locations, the researchers collected nasal secretions from 500 infants from four inner-city areas in Boston, Baltimore, New York City, and St Louis and 285 infants from suburban Madison, WI. Nasal secretions were sampled during periods when the babies had respiratory illnesses and when they were healthy. The inner-city infants had lower rates of viral detection overall. This may suggest that other factors, such as bacteria or allergic reactions to pollutions or toxic exposures, contribute significantly to respiratory illness. Sick urban infants had lower rates of HRV and RSV and higher rates of adenovirus infections. In the urban babies, 4.8% of nasal washes tested positive for only adenovirus, while just 0.7% of samples from suburban babies were positive for only adenovirus.

PLUGGED UP

Researchers at UC San Francisco, Johns Hopkins and Duke have demonstrated that a specific calcium-activated chloride channel holds clues to reducing two biological processes that contribute to the severity of asthma. These channels regulate airway secretions and smooth muscle contraction. Asthma sufferers have an elevated number of these cells in the lining of the tubes that lead to the lungs. Asthmatics also have an abnormal amount of smooth muscle surrounding the airway tubes. The researchers focused on a calcium-activated chloride channel called TMEM16A, which regulates a significant number of biological processes such as neuron firing, gastrointestinal activity and the secretion of sweat and tears, and wanted to prove that the channel was present in asthma. They studied human lung samples and looked for the mRNA and compared

protein levels in asthmatic and non-asthmatic patients. They found that the level of this channel was increased in the mucus producing cells of asthmatics compared to non-asthmatics. Then they tested the ability of these chemicals to inhibit TMEM16A and other channels, and found that they specifically blocked TMEM16A. Subsequently, the researchers simulated asthma in a dish and blocked the channel to observe whether it affected mucus production and found that mucus produced by these cells wasn't secreted as efficiently. Blocking TMEM16A also inhibited contraction of airway smooth muscles.

THALIDOMIDE!

Researchers at Johns Hopkins found that thalidomide reduced cough among those with idiopathic pulmonary fibrosis. Up to 80% of people with IPF have a dry, nagging cough, for which no effective treatment is available. Yes, this is the thalidomide taken off the market in 1961 after it was shown to cause severe birth defects. It is currently used to treat multiple myeloma and kidney cancer, and hasn't been studied as a treatment for lung disease so far. The researchers performed a randomized, double-blind, placebo-controlled trial and found that a low-dose of thalidomide significantly reduced cough and also improved the patients' quality of life. Patients either took low-dose thalidomide pills or a placebo for three months, followed by a two-week wash out period, followed by another three months when the thalidomide and placebo patients were switched. Patients often noticed the difference within two weeks of taking the thalidomide. When they stopped the drug, their cough came back. On average, the patients reported that the frequency of their coughing decreased about 63% while they were taking thalidomide, and their respiratory-specific quality of life, such as the ability to



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do daily activities, improved about 20%. Side effects, such as constipation, dizziness and malaise were reported by 74% of the participants while they were taking thalidomide, and by 22% of those who were on a placebo.

GENE-IUS

The COPD Foundation announced that the National Heart, Lung and Blood Institute will fund the second phase (2012-2017) of the COPDGene project as R01 grants to National Jewish Health and the Brigham and Women's Hospital. The grant enables scientists to build on the first phase of the COPDGene Study in analyzing the human genome comprehensively to find additional genetic predispositions to developing COPD. By understanding the biological mechanisms causing COPD, the study could lead to specific treatments that would prevent further progression of the disease. The COPDGene cohort of 10,171 subjects was created by medical centers across the US and is composed of subjects with a background of heavy smoking and who either have COPD or are at risk for developing this disease. In the second phase of this project, follow-up visits at a five-year interval from the initial visit will be done on all available COPDGene subjects in order to determine longitudinal changes in disease development and progression.

THEY'RE EVERYWHERE

Children exposed to diethyl phthalate (DEP) and butylbenzyl phthalate (BBzP)-phthalate chemicals found in personal care and plastic products have elevated risk of asthma-related airway inflammation, according to researchers at the Columbia Center for Children's Environmental Health. Of the 244 children aged 5 to 9 in the study, all had detectable levels of phthalates in

their urine. Higher levels of both phthalates were associated with higher levels of nitric oxide in exhaled breath, a biological marker of airway inflammation. The association between BBzP exposure and airway inflammation was especially strong among children who had recently reported wheeze. The researchers looked at children enrolled in the CCCEH Mothers and Newborns study, who lived in Northern Manhattan and the South Bronx where asthma prevalence is high. This study was the first to use exhaled nitric oxide in a study of phthalate exposure in children, which meant researchers didn't have to wait for patients to have an asthma exacerbation. Phthalates are used widely in plastics, vinyl flooring, and personal care products and enter the body through ingestion, inhalation, and absorption through the skin. Several phthalates are known to disrupt the endocrine system and early-life exposure and have been linked not only to asthma but also to adverse neurobehavioral and reproductive effects.

SOUP'S ON

A new study at the University of Aberdeen aims to reveal whether soups enhanced with food that contains vitamin E may help reduce the chance of childhood asthma. The intention of the researchers is to increase the amount of vitamin E pregnant women are consuming. The Scottish national average is currently 8mg per day, and the experts say 15mg per day would be more beneficial. The soups are made with foods that contain high levels of vitamin E, including beans, lentils, wheat-germ, sunflower oil and sun-dried tomatoes. Placebo soups have also been made to look and taste similar to the real ones, but do not contain intensified levels of vitamin E. Studies have shown that low vitamin E diets for pregnant women tend to result in

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babies being born with a higher chance of asthma by the time they reach 5 years old. Information is from Medical News Today, written by Christine Kearney, copyright Medical News Today.

TAMED

High doses of the vitamin D can help people with tuberculosis recover more quickly, according to researchers at the University of London. Researchers gave patients high doses of vitamin D alongside their normal antibiotic treatment and found that these patients recovered much more quickly. The researchers posited that when high doses of vitamin D are administered to TB patients, the body's inflammatory response to infection is dampened down, which results in less damage to the lungs and faster recovery. Ninety-five patients with TB were selected into two groups, one receiving vitamin D, and the other, a placebo. In the vitamin D group, it took 23 days for bacteria to clear the sputum, and 36 days for the placebo group. Information is from an article in Medical News Today, written by Christian Nordqvist, copyright Medical News Today

SKIN CREAMS FOR EASIER BREATHING

A study by researchers at Boston University has shown that a compound used in some skin creams may halt the progression of emphysema and reverse some of the damage caused by the disease. When the compound Gly-His-Lys (GHK) was applied to lung cells from patients with emphysema, normal gene activity in altered cells was restored and damaged aspects of cellular function were repaired. Researchers took cells from lungs donated by patients undergoing double lung transplants and found 127 genes had changes in activity as disease severity increased within the lung. The genes that showed increased activity included several that are associated with inflammation, such as those involved in signalling to B-cells that make antibodies. In contrast, the genes involved in maintaining cellular structure and normal cellular function, along with the growth factors TGF and VEGF, were down-regulated and showed decreased activity. Genes that control the ability of the cells to stick together produce the protein matrix that normally surrounds the cells and promote the normal association between lung cells and blood vessels were among the genes in this category. Using genomic technologies and computational methods, the researchers identified genetic activity defects that occur as emphysema progresses and matched these defects with compounds that could reverse the damage. The researchers knew that GHK can accelerate wound repair, so they tested it on cells from the damaged lungs and saw an improvement in the structure of their actin cytoskeleton and in cell adhesion, especially to collagen. GHK also restored the ability of cells to reorganize themselves to repair wounds and construct the contractile filaments essential for alveolar tissue repair. GHK is a natural peptide found in human plasma, but the amount decreases with age.

COMING UP SHORT

Children who use inhaled steroids for asthma wind up shorter as adults than kids who don't, according to researchers at Washington University School of Medicine in St Louis. The study involved more than 1,000 children ages 5-12 who were treated for mild to moderate asthma as part of the Childhood Asthma Management Program (CAMP) clinical trial. They received treatment for more than four years at eight centers and were divided into three groups: one received twice-daily budesonide, a second group received nedocromil, and a third group received a placebo. All children received albuterol and oral corticosteroids as needed. The researchers followed 943

participants at regular intervals until they reached adult height, which was 18 for women and 20 for men. The mean adult height was about one-half inch, or 1.2 centimeters, shorter in the group that received budesonide than in the patients who received nedocromil or placebo. The patients who experienced the slower growth were primarily between 5-11 years old when they began using budesonide. The slower growth took place only in the first two years of the four-year study. As the study progressed, the children who took the budesonide remained one-half inch shorter through adulthood than the children who did not use the drug. It made no difference if they were boys or girls or how long they had had asthma, or any other factors, including the height of the parents.

UNBALANCED

Asthma patients could be at a higher risk of worsening symptoms due to problems with their balance, according to new research which aimed to assess the link between asthma, anxiety and balance. Anxiety and imbalance are closely related. The researchers measured levels of anxiety in 30 people with persistent controlled asthma and a control group without asthma. They also assessed balance control using dynamic posturography, which tests a person's control of their posture in different positions. The results confirmed previous findings showing that asthmatics regularly suffer with anxiety problems. Eighty-eight percent of people in the asthma group had a moderate or intense anxiety level, compared with 46% in the control group. The asthmatic group frequently performed worse in the balance test, compared with the control group.

BULLY FOR YOU

New research has uncovered several factors which could explain why children with asthma are at an increased risk of being bullied. Researchers from the Derbyshire Children's Hospital used data from the large six-country "Room to Breathe" survey of childhood asthma to look at the factors associated with an increased risk of bullying. Parents and children aged 7 years and above were interviewed as part of the study. Data was collected from 943 questionnaires which asked about conditions at home, lifestyle of parents and children and their overall experience of their condition. Factors such as a reduced participation in sport and feelings of sadness were significantly associated with an increased risk of bullying. Additionally, factors that could be improved, such as poor asthma control, parental smoking and parents' on-going worries about their child's health, were also associated with bullying.

CALL ME MAYBE

Telemedicine is making it possible to bring sophisticated medical care and technology to patients and their caregivers. With the placement of faster fiber-optic networks in areas away from metropolitan hubs, high-speed bandwidth is making it possible for physicians, physicians' assistants and nurses to offer a full range of treatment options and diagnostics to patients in rural or underserved areas. The North Country Telemedicine Project in upstate New York is such an example. Upon its completion, with the click of a mouse every healthcare facility throughout the North Country/Adirondacks will be able to connect with each other as well as with larger healthcare facilities in other regions. Tech Valley Communications is stringing more than 5,000 miles of cable in Saratoga County to that end at a cost in excess of \$1 million, creating a fiber optic network allowing medical professionals to communicate with one another in real-time for any medical purpose.

SLEEP NEWS

SLEEP AND TEENS

A study at the University of Pittsburgh says that increasing the amount of sleep that teenagers get could improve their insulin resistance and prevent the future onset of diabetes. The researchers found if teens who get six hours of sleep went for seven, they'd improve their insulin resistance by 9%. The study tracked the sleep duration and insulin resistance levels of 245 healthy high school students. Participants provided a fasting blood draw, and they kept a sleep log and wore a wrist actigraph for one week during the school year. Sleep duration based on actigraphy averaged 6.4 hours over the week, with school days significantly lower than weekends. The study did not say if teens who slept through the entire morning after a night of partying showed further resistance.

DO IT YOURSELF

Just over half of those taking sleeping pills diagnosed themselves, without consulting a medical professional, according to researchers at The Royal Pharmaceutical Society. The researchers also noted that 30% of those suffering from insomnia took a sleeping remedy for more than a month before seeing a doctor, while 14% waited six months, and 18% could not recall when they started taking a sleep remedy. Most long-term insomnia is linked to a medical condition. Seventy percent of those with insomnia minimized its relation to other health conditions or didn't think any health conditions were involved. Information from an article by Sarah Glynn in Medical News Today, copyright Medical News Today.

POORER SLEEP

Patients with COPD experience poorer sleep quality than people who don't have it, according to researchers at St Vincent's University Hospital in Dublin. The researchers also found a relationship between how well patients with COPD slept and the oxygen levels in their arterial blood. The study participants had an average age of over 66 years; 67% were male and all were current or former smokers. The study also found that daytime hypoxemia is associated with sleep efficiency, but airflow obstruction is not and that COPD patients took longer to fall asleep than the age-matched controls after the lights had been turned off (sleep latency) and spent less of their time in bed sleeping (sleep efficiency). They also experienced greater differences in the way they slept, with more sleep at the lightest level (stage one) and less at REM. Slow wave sleep (stages three and four) was reasonably well preserved.

OBESE + PREGNANT + OSA

The newborns of obese pregnant women suffering from OSA are more likely to be admitted to the neonatal intensive care unit than those born to obese mothers without OSA, according to researchers at the University of South Florida. The researchers analyzed data for 175 obese pregnant women enrolled in a prospective observational study, which screened prenatal patients for sleep-related breathing disorders. The women were tested using an in-home portable device. Perinatal and newborn outcomes for 158 live births, including indications for NICU admissions such as respiratory complications, prematurity and congenital defects, were also reviewed. The prevalence of sleep apnea among study participants was 15.4%. Compared to the women with no sleep apnea (control group), the group with sleep apnea was heavier and experienced more chronic high blood pressure. The women with sleep apnea were more likely

than the control group to undergo a cesarean and to develop preeclampsia. Despite having similar rates of preterm births, the women with sleep apnea delivered offspring more likely to be admitted to the NICU than did their counterparts without sleep apnea. Many of these admissions were due to respiratory distress. Approximately one in five women are obese when they become pregnant.

MAN (& WOMAN) UP

Slow-wave sleep is intimately involved in the complex control of the onset of puberty, according to researchers at Mass General and Boston Children's Hospital. Researchers examined pulses of luteinizing hormone (LH) secretion in relation to specific sleep stages in children ages 9-15. LH is essential for reproduction and triggers ovulation in females and stimulates the production of testosterone in males. Researchers found that the majority of LH pulses that occur after sleep are preceded by deep sleep, suggesting that deep sleep is intimately involved in pubertal onset.

OSA IN WOMEN UNDIAGNOSED

Half of all women age 20 to 70 have some obstructive sleep apnea, with 20% showing moderate symptoms, and 6% showing severe symptoms, according to researchers at Umea and Uppsala universities in Sweden. It has long been held that sleep apnea effects mostly men. Researchers gathered data on 400 out of 10,000 women. Participants were given questionnaires and underwent overnight polysomnography. Fifty percent of the women had obstructive sleep apnea. Researchers found a link between sleep apnea and the women's blood pressure, body weight and age. The older, heavier and more hypertensive they were, the more likely the women were to suffer from it. An apnea-hypopnea index of 30 or more affected 14% of the women aged 55-plus. Thirty-one percent of the women who were obese and 50 years or older had severe sleep apnea.

OSA TREATMENT

Ben-Gurion University of the Negev researchers revealed that a majority of children suffering from OSA treated with montelukast showed significant improvement in respiratory disturbance and adenoid size. In the double-blind, randomized, placebo-controlled trial, 23 children were given placebos and 23 were given montelukast. After a 12-week treatment, children experienced reduced severity of OSA and showed significant improvement in respiratory disturbance, adenoid size and children's symptoms. The obstructive apnea index was decreased by over 50% in 65% of treated children.

DON'T LOOK IT UP

Fifty-nine percent of the US population in 2010 used internet searchers for health info, and parents looking up info about their kids topped the searchers. According to researchers at Children's National Medical Center in DC, Google internet searches related to infant sleep safety often do not reflect American Academy of Pediatrics recommendations. Seventy-two percent of adults thought that they could believe most or all of the health information on the internet, and 70% of adults said that information that they found on the internet impacted their health or their actions pertaining to their health or the health of their children. Researchers at the University of South Carolina School of Medicine, Children's National Medical Center, and George Washington University checked the accuracy of information on infant sleep safety available on the internet, using Google. Thirteen key phrases were created to reflect specific AAP

recommendations for infant sleep safety, and the first 100 search engine websites were analyzed for each phrase. Of 1,300 website results, 43.5% provided accurate information, 28.1% provided inaccurate information, and 28.4% provided information that was not relevant to infant sleep safety. When the websites that were not relevant were excluded, 60.8% of the websites provided accurate information. The key search phrases with the highest percentage of accurate information were “infant cigarette smoking,” “infant sleep position,” and “infant sleep surface.” Those with the highest percentage of inaccurate information were “pacifier infant,” “infant home monitor,” and “infant co-sleeping.” The most common types of websites resulting from the key search phrases were company/interest groups, retail product reviews, and educational websites. Government and organizational websites had the highest percentage of accurate information (80.1% and 72.5%, respectively). Blogs, retail product reviews, and individuals’ websites had the highest percentage of inaccurate information regarding infant sleep safety (30.9%, 36.2%, and 45.5%, respectively). News websites were accurate only half the time.

PRODUCTS

GET IT RETAIL

AG Industries, a domestic manufacturer of CPAP, oxygen therapy, aspirator and nebulizer filters, accessories and replacement parts for over 25 years, is introducing a new line of retail CPAP products for HMEs and their patients. Items including filters, chinstraps, tubing, and cleaners are now attractively packaged for the convenience of both providers and patients. AG’s CPAP products for the retail market not only help HMEs increase their range of offerings to current customers, but create a whole new source of cash revenue, independent of private insurance and mandates. Contact agindustries.com.

DRIVERS SEAT

Drive Medical announced that it has commenced the manufacturing and distribution of the Evo / Global Medical respiratory and SmartDose product lines. Evo / Global Medical has been a leading manufacturer of respiratory products, including suction canisters, nebulizers, 50 PSI compressors, aerosol products, along with its technologically advanced patented SmartDose line of oxygen conserving devices. The transition of the manufacturing and distribution of these products will be seamless to all customers. The company is continuing its respiratory grown strategy, which we began last year with the acquisition of Inovo / CHAD Therapeutics. The SmartDose oxygen conserving devices and certain Evo / Global Medical respiratory products will continue to be manufactured in the US through Inovo / CHAD Therapeutics, a division of Drive, in its ISO certified facilities located in Naples, Florida. Contact drivemedical.com.

A LITTLE BIRD

Fisher & Paykel announced: A little bird told us to make it small, light, fast and clever. The F&P Pilairo Nasal Pillow Mask is light on the patient, is big on performance, and is our lightest nasal pillows mask (1.83 ounces). The Pilairo integrates a new self-inflating AirPillow Seal and minimalist Stetchwise Headgear. As a result, the patient experiences freedom of movement coupled with stability they can trust. The design of the F&P Pilairo was inspired by the aerodynamic flight of the world’s lightest little bird – the hummingbird. The hummingbird can rotate its fine wings in a circle; it is the only bird able to fly forwards,

backwards, up, down and sideways and can hover in midair. This drove the design of a mask seal which self-inflates around the nares in a “hover-like way” while providing total freedom of movement. Experience easier therapy with F&P Pilairo. • One convenient size. • Quick and easy to fit. • No more messy straps and no complicated headgear adjustments necessary. • Only three simple parts to clean. Contact fphcare.com.

ANALYZERS

Radiometer offers its ABL80 Flex analyzer series. Time is of the essence in the cardiac cath lab. You need to make decisions quickly, based on the most accurate and up-to-the-minute data possible. Rapid, accurate and frequent updates of oxygen saturation let you make the best assessment of your patient’s status. To do this, you need an analyzer that is intuitively easy to use, always ready, and requires nothing more from you than to run the sample. The ABL80 Flex is Radiometer’s renowned oximetry technology in a compact, point-of care analyzer. It offers 50-second time to results, easy, cartridge-based operation – no sample preparation or cuvette handling, and complete data capture. There are five different models to fit your needs, all with a large color touch screen, customizable interface and manager control settings, portability and fully operational battery, full LIS/HIS connectivity, and an integrated barcode reader. The ABL80 FLEX and ABL80 FLEX CO-OX offer automatic QC. On the ABL80 FLEX analyzer series, sensor cassettes are available with several parameter panels and multiple test volumes to match your diagnostic needs. Contact radiometeramerica.com.

CRITICAL

The GEM Premier 4000, now with Plus Technology critical care analyzer, measures pH, blood gases, electrolytes, metabolites, Total Bilirubin and CO-Oximetry (integrated). The analyzer features Intelligent Quality Management (iQM) for continuous, real-time quality control, delivering the lab-quality results to any point-of-care location: ICU, NICU, CVOR, and ED. Exceptionally easy to use, the GEM Premier 4000 is virtually maintenance-free and features the only single-component, multi-use cartridge on the market. GEMweb Plus Custom Connectivity allows remote control of all GEM Premier analyzers in the network for total connectivity, regardless of location, optimizing point-of-care flexibility. Plus Technology offers faster touchscreen response, wireless communication to HIS/LIS, and remote service capabilities. Contact Instrumentation Laboratory, ilus.com.

DETECTION

The current “gold standard” test for detecting viral diseases such as the flu is based on polymerase chain reaction (PCR) technology. This test can’t be done at the patient’s bedside, however – the sample must be sent to a central laboratory for processing, which causes delays in diagnosis and treatment. In 2008 a consortium was created in North East England to devise a solution to this problem, led by UK nano-biotechnology firm Orla Protein Technologies. The £1.1m project has successfully developed biosensors for three of the main viral culprits – the Influenza A and B viruses and Respiratory Syncytial Virus (RSV). It has also resulted in the creation of a new company, OJ-Bio Ltd, to commercialize the technology. The Health Protection Agency collected nasal secretions, nose/throat swabs and nasal aspirates from patients and used these samples to test the consortium’s technology, Surface Acoustic Wave (SAW) biosensors, against the current benchmark PCR method, as well as another commercially available test. The results showed that the new SAW biosensors gave results in around 10 minutes, had good

levels of diagnostic sensitivity for the three test viruses and did not give false positives. They demonstrated 100% specificity even when other viral analytes were present. The SAW biosensors have the potential to communicate the results via wireless networks or a smart phone connection. The VIRASENS project has found a way to coat SAW chips with proteins oriented on the device surface to give highly specific responses when they come into contact with samples containing the disease concerned. The reaction that takes place is turned into an electronic signal which can be combined with a small reader to transmit and receive data. The company formed to commercialize the technology is Newcastle-based OJ-Bio, a joint venture involving global electronics company Japan Radio Company (JRC) who provide the SAW chip expertise and Orla Protein Technologies, the UK company that provides the protein surface technology. Contact www.oj-bio.com.

EFFECTIVE

Discovery Laboratories, Inc presented neonatal AFECTAIR data at the 11th European Congress on Pediatric and Neonatal Ventilation held June 6-9, 2012 in Montreux, Switzerland. Though initially presented in the US, these data presentations marked the first introduction of the AFECTAIR neonatal device through scientific exchange to a European pediatric critical care audience. The AFECTAIR neonatal device has been developed by Discovery Labs to simplify the delivery of inhaled medications for critical care patients requiring ventilatory support and was cleared for marketing in the US in early 2012. The AFECTAIR neonatal device will be commercially available in the US and EU in late 2012. Highlights from the two data presentations included: Utilization of iNO Using a Novel Ventilator Circuit Connector versus Standard of Care Under Simulated Neonatal Mechanical Ventilation Conditions – An In Vitro Study, by Mazela, et al. The Standard of Care (SoC) for ventilator delivery of inhaled nitric oxide (iNO) in pulmonary hypertension allows for potential iNO dilution, gas loss and environmental contamination. According to this study, which simulated neonatal mechanical ventilation conditions using an in vitro model, use of the AFECTAIR neonatal device resulted in the achievement of target nitric oxide concentrations using less nitric oxide when compared to the SoC delivery apparatus. Another study was: In Vitro Assessment of a Novel Aerosol Delivery System under Simulated Conditions, by Mazela, et al. According to this study conducted in an in vitro model of neonatal mechanical ventilation conditions, when compared with a conventional wye connector, use of the AFECTAIR neonatal device resulted in improved delivery of aerosolized albuterol sulfate, including a nine-fold increase in delivered dose under simulated CPAP conditions, a 14-fold increase in delivered dose under simulated mechanical ventilation conditions, and a smaller difference in particle size distribution between aerosol output from the nebulizer and aerosol output from the patient interface. Contact discoverylabs.com.

HIGH OCTANE

OCTANe, the Orange County startup accelerator dedicated to connecting people and ideas with capital and resources to fuel technology growth, hosted their seventh annual Medical Device & Investor Forum (MDIF) at the Hyatt Regency in Irvine, CA. The two-day event featured general sessions covering a broad range of pertinent industry topics ranging from a venture capital panel discussion, working with the FDA following the Medical Device User Fee Amendments of 2012 and a profile of Covidien. Rep Erik Paulsen shared his perspective as the co-chair of

the Congressional Medical Technology Caucus, highlighting upcoming legislative issues that could affect the industry. Each year, OCTANe programs and Signature Events attract more than 7,000 entrepreneurs, venture capitalists and major players from the regional technology industries. It is supported by nearly 50 major high tech companies, two major research universities and thousands of high tech professionals. The organization has helped over 120 companies receive more than \$217 million in investment and equity exits, enabled over 500 companies to connect via the LaunchPad accelerator, and annually welcomes more than 7,000 people to its programs and events. Over 2,000 business leaders throughout the Orange County region are OCTANe members. Contact octaneoc.org.

MERGED

Sunovion Pharmaceuticals Inc (Sunovion) announced that it has completed the company's acquisition, by merger, of Elevation Pharmaceuticals, Inc (Elevation). Elevation is now a wholly-owned subsidiary of Sunovion and has been renamed Sunovion Respiratory Development Inc. The terms of the acquisition include Elevation's EP-101 product, an inhalation solution of a long-acting muscarinic antagonist (LAMA) bronchodilator that is in Phase 2b clinical trials for the treatment of patients with moderate to severe COPD. EP-101 is a proprietary solution formulation of glycopyrrolate, developed to optimize medication delivery and allow ease of use. It was designed for patients who are not well controlled on current standard of care or who prefer a nebulizer. The delivery system was designed to offer reduced time for administration for patients (<2 min vs 5-10 min for standard jet nebulizer) and a more portable size, with a reduced noise level. Contact sunovion.com.

PERCUSSION POWER

The G5 Freedom System from General Physiotherapy, Inc generates High Frequency Chest Wall Percussion for airway clearance. The G5 is comfortable, lightweight and safe, and eliminates the need for manual CPT. A hand-held control module conforms to a wide range of body types and sizes. The Easy Start feature eases patients into the treatment with a graduated start-up cycle. Comfortable Directional-Stroking Action results in exceptionally high patient compliance. The G5 Freedom system is quiet and doesn't interfere with electronic appliances. With the ability to select from 1 to 8 individual Percussion Pods to be activated over select lung segments, combined with the ability to select the oscillation or cycle per second speed range of each Percussion Pod, the customized treatment combinations are endless. HFCWP oscillation in the 15-30 cycle range is produced over specific lung segments to mechanically dislodge and mobilize mucus toward larger airways for clearance. There are no positioning restrictions with the G5. A custom-designed power pack enables the G5 to be powered by a 110-240 volt outlet and steps the power down to 12 volts; hence, it can be used anywhere in the world. Contact G5.com.

NEW PLATFORM

Philips Respiroics introduced its new InnoSpire compressor nebulizer platform at Medtrade 2012. InnoSpire consolidates the company's current compressor offerings into three basic lines, Essence, Elegance and Deluxe. InnoSpire provides three basic compressors with variants to accommodate international use. This streamlined family of products is built to the same high-quality and reliability standards as its predecessor products, the OptionHome and Inspiration Elite, and continues the company's focus on high performance and fast treatment

times. The InnoSpire Essence compressor nebulizer system is compact, lightweight and economically priced. Coupled with proven SideStream aerosol technology, it provides fast, efficient drug delivery and a clear alternative when cost is a consideration. Combined with more sophisticated SideStream technology, InnoSpire Elegance partners with the SideStream reusable nebulizer or the SideStream Plus breath-enhanced reusable nebulizer. SideStream Plus incorporates an easy-action inspiratory valve that opens on inspiration to help boost medication delivery and closes on exhalation, reducing medication waste. InnoSpire Deluxe, anticipated to launch later in 2013, will include built-in conveniences that will make it an ideal choice for encouraging adherence to aerosol medication treatment plans. Built to provide the same sophistication and efficient SideStream medication delivery as Essence and Elegance, the unit will be sized to fit most school bags or luggage and can hold extra medicine or nebulizer supplies inside its storage compartment. An attached power cord tucks neatly into the storage area of the unit and a sturdy handle will make it easy to carry, even by small hands. Contact philips.com.

TB TREATMENT

Janssen Research & Development, LLC (Janssen) announced that the FDA has granted Priority Review to the New Drug Application (NDA) for bedaquiline (TMC207) to treat pulmonary, multi-drug resistant tuberculosis (MDR-TB) in adults as part of combination therapy. The FDA grants priority review to medicines that may offer major advances in care or provide a treatment option where no adequate therapy exists. If approved, bedaquiline would offer the first in a new class of anti-tuberculosis drugs. The regulatory submission was supported by 24-week data from the Phase II clinical development program, which includes an open-label study and a controlled, randomized trial that evaluated the safety and efficacy of bedaquiline versus placebo in the treatment of patients with pulmonary MDR-TB in combination with a background regimen. Bedaquiline is a diarylquinoline discovered by scientists at Janssen. Contact janssenrmd.com.

LAUNCHED

CareFusion announced the launch of the next generation product line, Jaeger Vyntus, together with the latest release of SentrySuite. The first products in this new range are Vyntus Spiro, Vyntus Pneumo, Vyntus APS and Vyntus IOS. These new Pulmonary Function Testing instruments are fully integrated into the SentrySuite Diagnostic Data Management Platform for system integration, virtual reporting stations, laboratory workflow solutions, and data management. With the launch of the first Vyntus products, and the new release of SentrySuite, CareFusion completed the implementation of the key pulmonary diagnostic measurement applications. This now allows for optimization of laboratory efficiencies, as users can migrate to the new SentrySuite world, taking immediate advantage of the latest features of the SentrySuite platform. SentrySuite's solutions for laboratory workflow, data management and system integration allow this modern platform to offer the efficiencies the changing healthcare environment. The platform has been expanded with new clinical assessment tools for Body Plethysmographic data, as well as added sophisticated data quality management tools, parameter linked animations, and clear patient and operator guidance. These new releases will improve laboratory efficiency and clinical outcomes. With unique features such as Sentry.NET, facilitating virtual reporting stations through the web, and the tablet wireless Patient Questionnaire,

Sentry Q, CareFusion continues to increase accessibility and ease of use. The new Jaeger Vyntus product range, with the new release of SentrySuite, became available in Europe in November. Countries outside of Europe will follow as soon as the necessary regulatory approvals are obtained. Contact carefusion.com.

INHALE

Boehringer Ingelheim Pharmaceuticals, Inc announced that COMBIVENT RESPIMAT is now available by prescription in the US. COMBIVENT RESPIMAT is a unique, propellant-free inhaler that uses a slow-moving mist to deliver the same active ingredients as COMBIVENT Inhalation Aerosol, which is delivered in a metered dose inhaler (COMBIVENT MDI). It is indicated for use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. COMBIVENT RESPIMAT requires one inhalation per dose as compared to COMBIVENT MDI, which requires two inhalations per dose. It offers a dose indicator to inform patients of the amount of remaining medication in the inhaler, and the device locks when all of the medication has been used. When used as directed, each COMBIVENT RESPIMAT delivers 30 days worth of treatment compared to 25 days worth of treatment in each COMBIVENT MDI, so COMBIVENT RESPIMAT patients may require two less inhalers over the course of a year. In a 12-week, randomized, double-blind, placebo- and active-controlled clinical trial, COMBIVENT RESPIMAT was shown to be clinically comparable to COMBIVENT MDI, in terms of FEV1. Contact boehringer-ingelheim.com.

REBRANDING

MGC Diagnostics Corporation announced its new trading symbol. The company's common stock has been assigned a new CUSIP number 552768103 in connection with the name change. Outstanding stock certificates are not affected by the name change and will not need to be exchanged. As part of a Company-wide rebranding initiative, MGC Diagnostics has launched a new corporate website and logo (www.MGCDiagnostics.com). The new identity is meant better communicate to customers and stakeholders what the company brings to market – leading-edge CardioRespiratory Diagnostic Technology, a renewed dedication to product innovation, unmatched customer service and support, and an eye toward anticipating and solving unmet needs. In the cardio-respiratory business, the company was known as MEDGRAPHICS. Contact mgcdiagnostics.com.

RESUSCITATE

LIFE offers its "612" oxygen regulator for its LIFE Emergency Oxygen Unit. Its Viton (fluorocarbon) regulator inlet seal is an elastomer recommended by NASA. The oxygen flow is encapsulated in brass. It has a compact lightweight design, with a one-piece body. The flame arrestor inlet fitting is designed to keep flames from entering the regulator. The unit has a low profile knob retainer and maintains precision flow settings from full to empty. The Life "612" provides the FDA minimum at 6 LPM and the AHA recommended 100% inspired O₂ at 12 LPM but is labeled "norm" for general emergencies and "high" for extreme emergencies. It is the only oxygen regulator with 6 and 12 LPM flow rates. The "612" regulator is available in all LIFE Emergency Oxygen units. Contact lifecorporation.com.

CLEARED AND APPROVED

Covidien announced FDA 510(k) clearance and European Economic Area (EEA) CE Mark approval for the Covidien

Nellcor Bedside Respiratory Patient Monitoring system. This new system provides continuous monitoring of blood oxygenation (SpO₂) and pulse rate, along with trend data to help clinicians detect and respond to dangerous respiratory events sooner. The new Nellcor Bedside Respiratory Patient Monitoring system is upgradable onsite to accommodate new parameters and features, including Nellcor Respiration Rate software, thereby reducing service disruptions and costs for hospitals. The new system features a color touch-screen graphical user interface and provides a variety of wired and wireless connectivity options to meet the various needs found in different hospital settings. It can connect to the Nellcor OxiNet III Remote Respiratory Monitoring system, enabling clinicians to monitor multiple patients from a central monitoring station on the general care floor. A SatSeconds alarm management feature helps clinicians differentiate between serious and minor events, reducing clinically insignificant desaturation alarms and alarm fatigue. The monitoring system also features a Saturation Pattern Detection alert for automated, real-time detection of patterns of desaturation that indicate repetitive reductions in airflow. Contact covidien.com.

TAKE A POWDER

The Anti-Infective Drugs Advisory Committee (AIDAC) to the FDA voted 13 to 1 that there was adequate evidence of efficacy and safety to support the use of tobramycin inhalation powder (TIP), by Novartis Pharmaceuticals, for the management of cystic fibrosis patients whose lungs contain the bacteria *Pseudomonas aeruginosa*. TIP is intended for use in CF patients aged six years and older whose lung function is within FEV₁ between 25% and 80% predicted. The AIDAC based its recommendation on three Phase III clinical studies involving more than 650 CF patients aged six years and older, of whom 425 patients received at least one dose of TIP. The studies found that treatment with TIP resulted in improved lung function. TIP could reduce the treatment burden because of its shorter administration time and greater portability compared to nebulized tobramycin. Investigational TIP is a new inhaled formulation of tobramycin consisting of dry powder in capsules delivered via a dry powder inhaler. The new formulation was developed using proprietary Novartis PulmoSphere technology, which enabled the creation of hollow porous particles of tobramycin that can be delivered as a dry powder. In the above trial, patients treated with TIP showed improved lung function. TIP also demonstrated comparable efficacy to nebulized tobramycin, with a reduction in administration time of approximately 70%, saving about 13 hours per treatment cycle. Contact novartis.com.

INTEGRATION

Hamilton Medical AG and Masimo announced a purchasing and licensing agreement, and associated international launch of the integration of Masimo's blood oxygenation (SpO₂) measurement technology with Hamilton Medical's fully closed-loop mechanical ventilation systems. INTELLiVENT-ASV is the world's first fully closed-loop ventilation solution, automating ventilation and oxygenation in one system. With the integration of Masimo SET extended measurement options, Hamilton Medical enhances its ventilation support options for the innovative Hamilton-S1 and Hamilton-G5 ventilators. This offers clinicians the choice of using an SpO₂ technology that they are used to working with. Masimo SET has been proven to provide accurate SpO₂ values under real-world challenging conditions, including patient motion, patient transport, and low perfusion. The integration of

Masimo SET with Hamilton Medical ventilators expands the options for SpO₂ technologies. SpO₂ measurements are used by INTELLiVENT-ASV, and are also available separately as monitored parameters. Hamilton Medical increases the ease of use with a dedicated sensor adapter for Masimo. The adapter mounts easily on all standard rails and includes a storage position for CAPNOSTAT CO₂ sensors. It also offers the ability to manage the SpO₂ and CO₂ sensor cables to avoid cable entanglements. Contact hamilton-medical.com and masimo.com.

FREE KNOWLEDGE

HealthTap brings research to patients in an easy to understand form, available through any mobile device and on the web. Anyone can find and connect with doctors across the country in its One Million Doctor Directory. This expansive directory highlights, in one place, all of a doctor's medical expertise and credentials, as well as biographical and other relevant information. HealthTap is private, safe, and secure. When patients ask questions or look up topics on HealthTap they'll discover free answers from over 15,000 US-licensed physicians, rated by other doctors, the latest peer-reviewed research, together with interactive feedback from experts who make it easy to understand, and listings of relevant doctors. Contact healthtap.com.

HIGHLIGHTS

Philips Respironics highlighted several products and services at Medtrade. Fit for Life, a comprehensive mask and service program, gives providers a way to offer their patients easy and reliable access to important replacement masks, supplies and resources they need to benefit from their OSA therapy. It also offers simple ways for homecare providers to monitor and document compliance with major commercial and public insurance providers' eligibility requirements and the recently released Centers for Medicare and Medicaid Services' (CMS) resupply policy clarification. Available late this year is the Wisp minimal contact nasal mask, a hybrid nasal/pillow mask that offers comfort, ease of use, visual appeal and the ability to fit a wide range of patients. The modular frame comes in two styles that patients can switch between: a reversible fabric and clear silicon. This allows patients to watch television or read a book before going to bed. Coming soon from Philips: the SleepMapper self-management system allows patients using Philips Respironics' CPAP devices to access their sleep performance data and obtain feedback quickly and easily through a smartphone, tablet or computer. Also added to its portfolio of respiratory solutions in early 2012, Philips Respironics' SimplyGo is a light, portable solution that meets the needs of nearly all oxygen users. SimplyGo is the only portable oxygen concentrator (POC) to offer continuous flow (up to two liters per minute) and pulse-dose delivery in a single device weighing 10 pounds or less. Contact philips.com.

IT'S A GAS

Ceretec, Inc announced that it has introduced an FDA-listed nitric oxide gas product (NO-Diff Nitric Oxide 800 ppm Lung Diffusion Mixture) for use in membrane diffusing capacity (DLNO) testing in pulmonary function laboratories in the US. Ceretec's NO-Diff is a gas product classified by the FDA as a Class 1 medical device; however, it will be produced for Ceretec by its medical gas partner in a pharmaceutical GMP facility. Alex Stenzler, Ceretec's Vice President,

explained, "Use of nitric oxide gas for diffusing capacity testing offers new insights into the structure of the alveolar-capillary membrane, which is important for understanding the progression of diseases that affect the lungs such as interstitial pulmonary fibrosis." He added, "We will be offering this gas only to institutions who have approval to perform this diagnostic pulmonary function measurement so as to not induce infringement of patents held by Ikaria Corporation that expire in January 2013." Ceretec anticipates a generic pharmaceutical nitric oxide product will enter the US market after regulatory approval for distribution and following the expiration of the relevant Ikaria patents. Contact ceretecinc.com.

SLEEP PRODUCTS

RELIEF

SensAwake Responsive Pressure Relief is now available with the F&P ICON Auto and Premo models. SensAwake promotes better overall sleep. We all experience subconscious waking through the night – at which time pressure intolerance is likely to occur. SensAwake responsive pressure relief detects wakefulness, promptly relieves pressure and eases the return to sleep. Whereas other pressure relief technologies provide partial relief during expiration, SensAwake provides a prompt and significant relief in pressure to the lowest most comfortable level upon waking. This eases the return to sleep and allows effective treatment to resume. Let your patients experience a great first night experience with the combination of F&P ICON with SensAwake and the new F&P Pilairo nasal pillows mask. To find out more, contact your local Fisher & Paykel Healthcare representative or go to fphcare.com.

PERFECTED

Dymedix Corporation announced that the American Academy of Sleep Medicine (AASM) has approved its PVDF technology for use in respiratory effort belts for sleep studies. Prior to this, the AASM had recognized respiratory inductance plethysmography (RIP) as the only recommended modality for measuring a patient's respiratory effort. Dymedix developed its Perfect Fit Effort Belts working in cooperation with an internationally recognized US medical teaching university. The company noted that previously many sleep labs were hesitant to use a non AASM recommended effort belt. However, the many sleep labs that have purchased the Dymedix Perfect Fit belts have given them excellent reviews. The belts stay in place for the sleep technician, thus avoiding the need to adjust the belts during the night's study. Many of Dymedix' customers state they have never seen such a clear pencil sharp tracing of breathing effort. Because of the rising awareness of the serious co-morbidities associated with sleep apnea, Dymedix is poised to experience significant and continual growth. Dymedix Corporation is a Shoreview, MN, privately held company that designs, manufactures and distributes a variety of sleep sensors and electrodes for sleep studies. Contact (888) 212-1100, dymedix.com.

MONITORING SOLUTIONS

Umbian, Inc announced a suite of new features and enhancements to U-Sleep, its universal CPAP monitoring solution. U-Sleep monitors CPAP devices from leading manufacturers and provides a number of interactive follow-up services for health care providers. The company has now expanded U-Sleep's functionality to offer even greater value to its customers. Several new features

have been added with the newest iteration of U-Sleep. It now integrates with ResMed's EasyCare Online data management solution for streamlined data management and versatility. New reports to fit a wider array of business needs are now available, including a population compliance report and a patient metric comparison report. Additionally, U-Sleep can now store a number of new manually-entered health indicator metrics, including body measurements, blood pressure, blood glucose and sleep test results. Third party health care software providers will also benefit from the addition of three powerful U-Sleep application programming interfaces (APIs). These include the Participant Boarding API, the Get Participant Information API and the Get Participant Usage Report API. These APIs, the first of a series to be released for U-Sleep, enable third parties to streamline their patient onboarding process and incorporate valuable patient and compliance information within their application. In addition to the new features, many detailed improvements have been made to the current interface, including a simplified user activation process; the ability for customers to confirm patient details on a patient's behalf; enhancements to reporting views; and the addition of baseline apnea-hypopnea index (AHI), the measure of how many apneas or hypopneas a user experiences, to the patient usage summary. Contact u-sleep.com.

IN PRINT

ImThera Medical, Inc announced that results from the first single-center study of targeted hypoglossal neurostimulation (THN) for obstructive sleep apnea (OSA) is appearing in a print edition of the European Respiratory Journal. The study, conducted at Université Catholique de Louvain (UCL) in Belgium and sponsored by ImThera, followed thirteen patients with moderate to severe OSA who were implanted with the ImThera aura6000 System for at least one year. It was found that the aura6000 improved the conditions of patients with obstructive sleep apnea and it was neither painful nor did it awaken patients. The primary objective of the study was to demonstrate a statistically significant improvement in the polysomnographically measured apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) at three months, and to maintain that improvement at 12 months. Thirteen out of 14 operated patients were successfully implanted with a six electrode cuff around the main trunk of the hypoglossal nerve, and a pulse generator (IPG) in a subcutaneous pocket in the upper chest. The mean surgical time was 100 minutes. Surgical complications were generally mild, and all resolved without sequelae. Stimulation was initiated three to four weeks after surgery. Seventy-six percent of patients (10 of 13) responded to therapy, defined as realizing at least a 50% reduction in AHI or 50% improvement in ODI. Two patients enrolled in the study did not meet inclusion criteria – one had central sleep apnea, and one had a very large and long uvula. Among responders, the mean AHI improved from 41.5 ± 13.1 to 14.3 ± 8.8 (66%) at 3 months and 13.2 ± 5.5 (68%) at 12 months; and ODI improved from 23.1 ± 10.2 to 7.6 ± 4.1 (67%) at 3 months and 7.8 ± 5.3 (66%) at 12 months. In a related announcement, ImThera also announced that a paper titled, "Targeted Hypoglossal Nerve Stimulation for OSA Treatment" is now available online in the Volume 15, Issue 4 edition of *Neuromodulation: Technology at the Neural Interface*. The paper describes the anatomy, physiology and mechanisms of actions of hypoglossal nerve stimulation. The result of this ImThera Medical-sponsored basic research guided the specification, design and development of the aura6000 THN Sleep Therapy System. (The auro6000 is not for sale in the US.) Contact imtheramedical.com.

SPOTLIGHT ON BLOOD GAS

DOWNTIME MINIMIZED

Analyzer downtime due to pack failure and blood clots and controlling costs with existing devices are major issues for respiratory managers requiring a near patient blood gas analyzer. The cobas b 123 POC system is Roche Diagnostics' next generation blood gas technology uniquely designed to provide optimal reliability. The cobas b 123 POC system features an unparalleled four levels of clot detection and prevention that detects and removes virtually all clots before they ever reach the analyzer system, minimizing a significant source of downtime. In addition, the cobas b 123 POC system consumables – fluid pack, sensor, AutoQC Pack and AutoCVC Pack – come equipped with smart chip technology allowing them to be transferred between analyzers, optimizing reagent use. The analyzer also has a broad assay menu including lactate and fast sample processing time for laboratory-class results. For high-volume blood gas testing locations, the cobas b 221 system offers dependable, reliable, and virtually uninterrupted performance that you can count on. The cobas b 221 system features a robust assay menu, 42-day onboard stability, "load-and-go" reagents stored at room temperature and zero maintenance sensors. Contact roche-diagnostics.us.

STAND CORRECTED

A new app from Radiometer for healthcare providers, "Avoid Errors," meets the most prominent needs for safety by identifying and enabling correction of errors. The new app is aimed at wards performing blood gas analysis and is specifically designed to provide users with a handbook describing how to avoid preanalytical errors, a guide for troubleshooting errors and a skill test. With this app Radiometer is providing the answer to an increasing need for e-learning and process optimization among healthcare providers. A key feature in the new app is the handbook section. It contains videos showing how to properly collect a blood gas sample by arterial puncture, through an arterial line or by capillary sampling. Exceptionally high or low values of a given parameter may be due to one or several types of preanalytical errors. In the troubleshooting section, the app easily guides you through the errors that might have caused a high or low test value. Finally, the app includes a skill test. It's an excellent way of refreshing your knowledge about how to avoid preanalytical errors and enables you to repeat the test whenever needed and compare results to previous tests. The iPhone version of the "Avoid Errors" is available at the App Store, and there are Android and Windows phone versions as well. The app's content is also available at avoidpreanalyticalerrors.com. Contact radiometer.com.

POINT OF CARE

The RAPIDPoint 500 Blood Gas System is the latest cartridge-based point-of-care analyzer for critical care testing available from Siemens Healthcare Diagnostics. With results in approximately 60 seconds, the RAPIDPoint 500 analyzer offers a comprehensive menu of critical-care tests for pH and blood gases, electrolytes, glucose and lactate and full CO-oximetry, including neonatal total bilirubin and total hemoglobin, all from a single, whole-blood sample. Additionally, the measurement cartridges last up to 28 days and contain a full complement of tests, which reduces downtime. Equipped with fully automated calibration and quality control (QC), the RAPIDPoint 500 system is also designed to help POC professionals satisfy organizational and regulatory compliance requirements. Plus, the self-contained

Automatic Quality Control (AQC) cartridge operates without manual intervention, helping reduce POC staff's administrative tasks. An integrated bar code reader – conveniently located on the front of the system – offers a wide scanning area to accommodate patient and operator identification to ensure overall data entry integrity. Also, the RAPIDPoint 500 analyzer can be integrated with the Siemens RAPIDComm Data Management System, which offers centralized management of multiple Siemens blood gas, urine chemistry, and hBa1c diabetes care analyzers and operators. For more information visit usa.siemens.com/rp500.

COMPREHENSIVE

Stat Profile pHox Ultra blood gas/critical care analyzers from Nova Biomedical provide a comprehensive broad 20-test menu of blood gases, electrolytes, chemistry, hematology, and co-oximetry for critical care testing. pHox Ultra requires just 2-3 drops of whole blood, features simple one-button operation, is self-calibrating, and provides results in 2 minutes or less. In addition to the pHox Ultra's robust test menu, the analyzer comes with built-in networking at no extra cost. Multiple pHox Ultra analyzers can be networked together into a single, common database. A supervisor or authorized operator can access all patient results, QC results and reports from all analyzers. No other blood gas/critical care analyzer can match the clinical value of pHox Ultra to effectively manage high acuity, critically ill patients. Individual tests include pH, PCO₂, PO₂, SO₂%, hematocrit, hemoglobin, sodium, potassium, chloride, ionized calcium, ionized magnesium, glucose, BUN, creatinine, lactate, and bilirubin. Contact novabiomedical.com.

SPOTLIGHT ON SPIROMETRY

COMPUTER-BASED

MGC Diagnostics, St Paul, MN, offers the CPFS/D USB computer-based spirometer. From simple spirometry to complete bronchial provocation, the CPFS/D device offers various testing capabilities and meets or exceeds all current ATS/ERS recommendations for accuracy and performance. The proprietary preVent flow sensor provides accurate measurement and superior infection control. Its snap-in design allows for replacement between patients. Combined with BreezeSuite diagnostic software, the CPFS/D spirometer delivers efficient testing, resulting in faster patient turn-around. For more information, please contact (800) 950-5597, mgcdiagnostics.com.

50 YEAR HISTORY

Vitalograph is a leading manufacturer of cardio-respiratory testing devices for use in physician clinics as well as in support of pharmaceutical clinical development. In 2013, Vitalograph celebrates a 50 year history of producing high quality medical instrumentation for diagnosing and monitoring cardio-respiratory diseases. Vitalograph also supports pharmaceutical development by providing an integrated solution to collect, centralize and report both site generated and patient reported outcomes for clinical trials. Vitalograph's new Compact Expert offers a portable, flexible and comprehensive cardio-respiratory testing workstation with the capability to support Centralized Spirometry, Challenge Testing, Centralized ECG, e-PRO, Blood Pressure, Pulse Oximetry and others. Our In2itive e-Diary provides the research marketplace with the only integrated e-Diary/Spirometer allowing for collection of patient generated data and data transfer directly from the subject's home to a central server. Vitalograph offer independent quality over-read

services by industry experts that review the collected information in accordance with industry standards. Reviewers provide constant feedback to research sites leading to improvements in test performance and test quality, thereby increasing data integrity. Whether you need a clinic based workstation or standardized systems to support a clinical trial, Vitalograph is a name synonymous with quality cardio-respiratory products and services. Let Vitalograph be your respiratory partner. For information on our products and services contact Vitalograph at (913) 888-4221 or visit our website at vitalograph.com.

SETTING STANDARDS

ndd Medical Technologies is setting new standards in pulmonary function testing by offering innovative products for the management of lung disease. The EasyOne Plus series of portable spirometers are based on our TrueFlow technology, are easy to use, reliable and accurate. ndd TrueFlow is absolute flow and is not influenced by contamination, humidity or temperature. Using 2 AA standard batteries, there is no recharging or downtime. For PC-based spirometry, the Easy On-PC offers real time curves, trending and pediatric incentives. The EasyOne Pro Pulmonary Function Analyzer allows for on the spot diagnosis of lung disease according to ATS guidelines. With our maintenance free and automatic calibration technology, ndd offers complete lung function in 1 square foot. By adding 5 minutes to your spirometry testing the EasyOne Pro gives instant results, differentiates COPD from asthma for accurate diagnosis and allows for immediate treatment. ndd's single use Spirette offers hygienically safe, precise, maintenance-free measurement for all of our products, while the Barriette for the EasyOne Pro is a virtual filter validated for optimum hygienic separation of spirette/patient from the analyzer. Contact nddmed.com.

SLEEP ROUNDTABLE

Philips Respironics

Philips Respironics offers its System One family of products, providing quality and durability with enhanced patient comfort, flexibility, and compliance. As Allies in Better Sleep and Breathing, we at Philips Respironics approach product development with your needs in mind. As a result, the enhanced System One sleep therapy system does even more to deliver exceptional therapy, increase patient comfort, and provide essential compliance tools that you need in today's challenging sleep environment.

The System One family of solutions offers both patient comfort and appeal. Our Flex Family technologies enhance patient comfort with proven pressure relief, while System One humidity control maintains constant and optimum humidity levels throughout the night. The Heated Tube humidification option provides increased flexibility and patient comfort. All of these features are found in an attractive, sophisticated external design that is 25% quieter than its closest competitor.

This System One solution also provides compliance tools integrating our exclusive CPAP-Check and Auto-Trial modes to enhance patient compliance, while increasing operational efficiencies. EncoreAnywhere patient compliance management provides real-time data access and the ability to report patients' changing therapy needs with System One's Advanced Event Detection.

With System One REMstar Pro and REMstar Auto, you now have the ability to assess your home sleep testing patients' CPAP prescriptions. The Auto-Trial mode was designed to optimize pressure settings at home, while providing the long-term benefits of fixed CPAP therapy. This therapy uniquely adjusts to your patients' CPAP pressure needs over time through the system's CPAP-Check mode. EncoreAnywhere gives you the ability to remotely monitor AHI, leak, and many other advanced events recorded by your patients' REMstar Pro and Auto devices. It is flexible technology designed to simplify and enhance patient management.

Philips Respironics offers on-line support tools to help health-care providers. Our Partners in Training (www.philips.com/partnersintraining) and Partners in Compliance (www.sleepapnea.com/picm/) web sites offer comprehensive resources to help improve patient compliance and increase business efficiencies.

Finding success in today's Sleep and Respiratory industries requires more than advanced technology; it takes the collaboration of experts. That's why Philips Respironics remains committed to working as Allies in Better Sleep and Breathing in harmony with the care team to produce solutions that can lead to healthier patients, healthier practices, and healthier businesses. At a time when caregivers and patients alike need a true ally, count on Philips Respironics.

SleepImage

Tell us about your sleep products.

SleepImage offers the only simple and objective measure of sleep quality. SleepImage is the first Sleep Quality recorder that gives the ultimate in flexibility and convenience for the patient and the physician. The SleepImage system consists of two parts – an easy to use website and an automatic lightweight sleep recorder that sits on the patient's chest. The small recording device called the M1, records the patient's heart rate, body position, actigraphy and snoring. The simple web interface allows the physician complete flexibility to manage the system and review studies from any computer. At the core of our lightweight, ultra-convenient solution is the proprietary Cardiopulmonary Coupling (CPC) technology. This innovative solution measures sleep quality through breathing and heart rate patterns known to control stable, healthy sleep versus unstable, unhealthy sleep.

Discuss the range of applications for your sleep product.

Healthcare providers and payers constantly demand increasing healthcare efficiencies. The SleepImage patient-centered screening device, the M1, meets those needs with the first simple tool for objectively measuring sleep quality. Unlike most home sleep tests that only test for sleep apnea, SleepImage allows physicians to keep patients informed about their sleep health with a data-driven scale called the Sleep Quality Index (SQI). Since the SleepImage system is completely independent of the sleep disorder it is the first FDA cleared tool available for objectively assessing complete sleep quality. Applications range from screening patient populations with diabetes, Post Traumatic Stress Syndrome (PTSD), depression, sleep breathing disorders (like apnea), limb movement disorders and more. Additionally, the SleepImage system offers the only cost effective way to track treatment outcomes. SleepImage can be used as a screening and tracking tool for monitoring therapy effectiveness for sleep or non-sleep related disorders.

Tell us about how your product can be used in the sleep lab, home, or hospital.

Because the SleepImage system is independent of the sleep disorder, easy to use and has a very low cost, it has many potential uses. Sleep labs can use it with their primary care referral sources to identify more patients with sleep disorders. Sleep labs can also use the SleepImage system to check patients with CPAP to ensure they are sleeping well – not just that their CPAP is working, which is the only information from the CPAP download. We know that diabetes is negatively impacted by sleep so SleepImage can be used by diabetic educators to identify their patients with poor sleep. Psychologists can use SleepImage to help monitor their patients with insomnia and track the effectiveness of behavioral treatments and/or medication. Occupational health specialists can use it to assess sleep quality among shift and transportation workers. With the prevalence of sleep apnea, it is often forgotten that these workers may suffer from many types of sleep disorder and any one of them will create sub-optimal performance and can cause accidents in the work place, costing the community unnecessary injuries and death. The low cost and easy to use SleepImage system is the ultimate answer to knowing how your patient slept without the interference of cables, wires, belts and tubes.

Discuss any relevant reimbursement issues regarding your product.

Currently the SleepImage is not reimbursed. However the cost per test of around \$20 makes it comparable to an insurance co-pay. Currently, clinicians are faced with the decision of whether to send a patient to a sleep lab, have the choice between complicated home apnea testers that will only look at breathing disorders or a full blown sleep test that can cost hundreds or thousands of dollars. Now they can use the SleepImage system to screen and then track their patients sleep to evaluate the effectiveness of treatment.

What training and support do you offer to the various users of your product?

The SleepImage is a very simple and easy to use system. For the patient, the M1 is simply placed on the chest before bed using two ECG electrodes. The M1 will start automatically and can be used for multiple nights without uploading or replacing the two small coin cell batteries. In the morning the M1 is removed, the electrodes discarded and the data uploaded. The M1 can then be used again on another patient. For the physician the system is as simple as registering the patient into the system, configuring the M1 and then passing it to the patient. There are no complicated belts, tubes or straps to train the patient how to put on and that undoubtedly disrupt sleep. The interpretation of the SleepImage system is equally simple, with clear diagrams and a simple representation of sleep differentiating Stable, Non-REM sleep, Unstable Non-REM sleep, REM and wakefulness. A CPC Clinical Atlas and video tutorials are also available together with clinical assistance from the SleepImage support team.

Ventus Medical

Tell us about the sleep products your company offers.

Ventus Medical is a privately-held medical device company dedicated to providing non-invasive medical solutions for people with sleep-disordered breathing. Based on its innovative

MicroValve Technology and patented designs, Ventus has developed a unique line of clinically proven medical devices to address the continuum of sleep disorders from severe obstructive sleep apnea (OSA) to mild snoring. Provent Sleep Apnea Therapy is an easy-to-use, disposable treatment that works across mild, moderate and severe OSA. And, Theravent Advanced Nightly Snore Therapy is an over-the-counter device for the treatment of snoring in the US. Provent Therapy is cleared by the US Food and Drug Administration (FDA) and numerous peer-reviewed published studies have demonstrated that Provent Therapy improves sleep apnea and oxygenation. The device works through a proprietary MicroValve Technology that uses the patient's own breathing to create expiratory positive airway pressure (EPAP) to keep the airway open during sleep. The Provent devices attach over the nostrils with a hypoallergenic adhesive. Provent Sleep Apnea Therapy is clinically proven to reduce AHI, ODI, improves daytime sleepiness and is a good option for sleep apnea sufferers looking for an alternative treatment to CPAP.

How does your product enhance patient compliance and ease of use?

Most patients with OSA are prescribed a CPAP machine. CPAP is extremely effective at treating OSA if worn as directed. However, more than half of all patients stop treatment with CPAP due to its cumbersome nature. Provent Therapy was developed to help patients who do not use CPAP regularly and who can benefit from a non-invasive and clinically effective treatment alternative. Provent Therapy offers a good treatment option for patients who refuse, fail or are not compliant with CPAP therapy. Most patients find Provent Therapy easy to use. Provent Therapy requires no mask, tubes, or machine; just a pair of two small devices worn over the nostrils. The devices are disposable and portable, making it easy for every night use as well as travel. In a 30 day at-home clinical study, subjects reported using the device all night during 94% of possible nights. In a market research study with current Provent Therapy users, satisfaction and intent to continue therapy was very high. Nearly 8 in 10 current Provent Therapy users were highly satisfied, and 9 in 10 current Provent users claimed they planned to continue therapy.

What training and education do you offer in the use of your product for healthcare providers?

Patient education is important to adherence and compliance with Provent Therapy, and many educational and support materials are provided to healthcare providers and suppliers: Detailed patient information is included in each Provent Therapy package. This includes steps and visuals on how to apply Provent Therapy, what to expect, and tips to acclimate. A comprehensive training video that provides application instructions instructs patients on the proper application method, expectations and acclimation tips. Comprehensive information is available at the Provent Therapy website, www.proventtherapy.com, including a detailed patient video, downloadable tip sheet and instructions. A Provent Therapy product specialist is available through a toll-free number to patients who have questions about how to apply and get adjusted to using Provent. A patient acclimation guide is provided to physicians and Provent Therapy suppliers. This acclimation guide contains steps and tips for successful acclimation to Provent Therapy and is a helpful at-home resource.

Continued on page 31...

Applying Transpulmonary Pressure in the ICU

Tom Piraino, RRT

Introduction

Mechanical ventilation in the intensive care unit (ICU) is usually guided by arterial blood gases, and the parameters used to maintain these blood gases are limited by standards for lung protective ventilation.¹ Airway pressures and tidal volume are minimized for lung protection despite evidence that they may be inadequate surrogates for lung stress and strain.² Transpulmonary pressure represents true lung pressure, and physiologically is ≥ 0 cmH₂O at end-exhalation.

Transpulmonary pressure < 0 cmH₂O results in a lower FRC, lower compliance, and airways are prone to collapse on exhalation.³ The respiratory therapists hypothesized that a patient admitted to St Joseph's Healthcare ICU from an external facility was being ventilated with insufficient positive end-expiratory pressure (PEEP), causing a negative transpulmonary pressure.

Respiratory definitions: transpulmonary pressure (P_{tp}) = airway pressure - pleural pressure, Crs = respiratory system compliance
PC = Pressure control level above PEEP, PIP = peak inspiratory pressure

Patient case overview

A 65-year old morbidly obese male (BMI 55.5 kg/m²) with obesity hypoventilation and severe COPD was intubated for respiratory failure, secondary to pneumonia. He received a tracheostomy after 10 days of ventilation and was transferred on the 22nd day of invasive mechanical ventilation to St Joseph's Healthcare facility to utilize our bariatric CT scanner to rule out abdominal sepsis.

The patient was sedated and apneic on arrival with ventilation settings as follows: Positive end-expiratory pressure (PEEP) of 10 cmH₂O, pressure assist control of 20 cmH₂O above PEEP, respiratory rate of 20 bpm, inspiratory time of 1.0 seconds, FiO₂ of 1.0. Initial blood gas analysis was pH 7.16 PaCO₂ 50 mmHg PaO₂ 215 mmHg HCO₃ 17 mmHg SaO₂ 0.99. Hemodynamically, the patient was hypotensive and required norepinephrine to maintain an acceptable blood pressure.

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Initial patient management

The first 12 hours of ventilation at our facility were challenging. The patient's ventilation requirements had increased to the following: Pressure assist control of 32 cmH₂O above PEEP, respiratory rate was 30 bpm, inspiratory time of 1.0 seconds, PEEP of 12 cmH₂O and FiO₂ of 0.5. Blood gas analysis on these settings was pH 7.17 PaCO₂ 47 mmHg PaO₂ 63 mmHg HCO₃ 16 mmHg SaO₂ 0.9.

Method and management using esophageal pressure manometry

To determine transpulmonary pressure (P_{tp}), an esophageal balloon was inserted into the patient. It was suspected that the patient might not have had the PEEP level needed to achieve a normal end-expiratory transpulmonary pressure (P_{tp}PEEP > 0 cmH₂O). The esophageal balloon catheter was inserted to a depth of 60 cm and gentle compression of the abdomen was done to confirm placement. The catheter was then pulled back 40 cm and cardiac oscillations were present, and the waveform was clearly different than before. (Figure 1). With the patient sedated and paralyzed using a neuromuscular blockade, an expiratory hold was done to obtain a stable transpulmonary reading. The resulting P_{tp} value was -12 cmH₂O. To achieve a transpulmonary pressure close to what would be physiologically normal (P_{tp} ≥ 0 cmH₂O), the PEEP was increased from 12 cmH₂O to 24 cmH₂O.

Patient response

The 48-hour trend of PaO₂/FiO₂, respiratory system compliance and peak airway pressure are shown in Figure 2. The blood pH improved as a result of HCO₃ increasing to a normal level. The respiratory rate and peak airway decreased significantly despite the CO₂ level remaining 45-47 mmHg over 48 hours. The PaO₂/FiO₂ ratio increased significantly from 126 to 370 as PEEP was titrated, according to P_{tp}, from an initial increase to 24 cmH₂O, and then to 18 cmH₂O 48 hours later.

Improved outcome

The use of esophageal pressure manometry to determine P_{tp} and set PEEP in this patient resulted in an individualized lung protective strategy. The end-result was improved oxygenation, improved ventilation (lower minute ventilation required), improved respiratory system compliance and peak airway pressure below the limitations recommended by literature. The patient was returned to the sending facility 2 days later with a PEEP of 18 cmH₂O, FiO₂ of 0.30, PC of 12 cmH₂O and a respiratory rate set at 22 bpm.

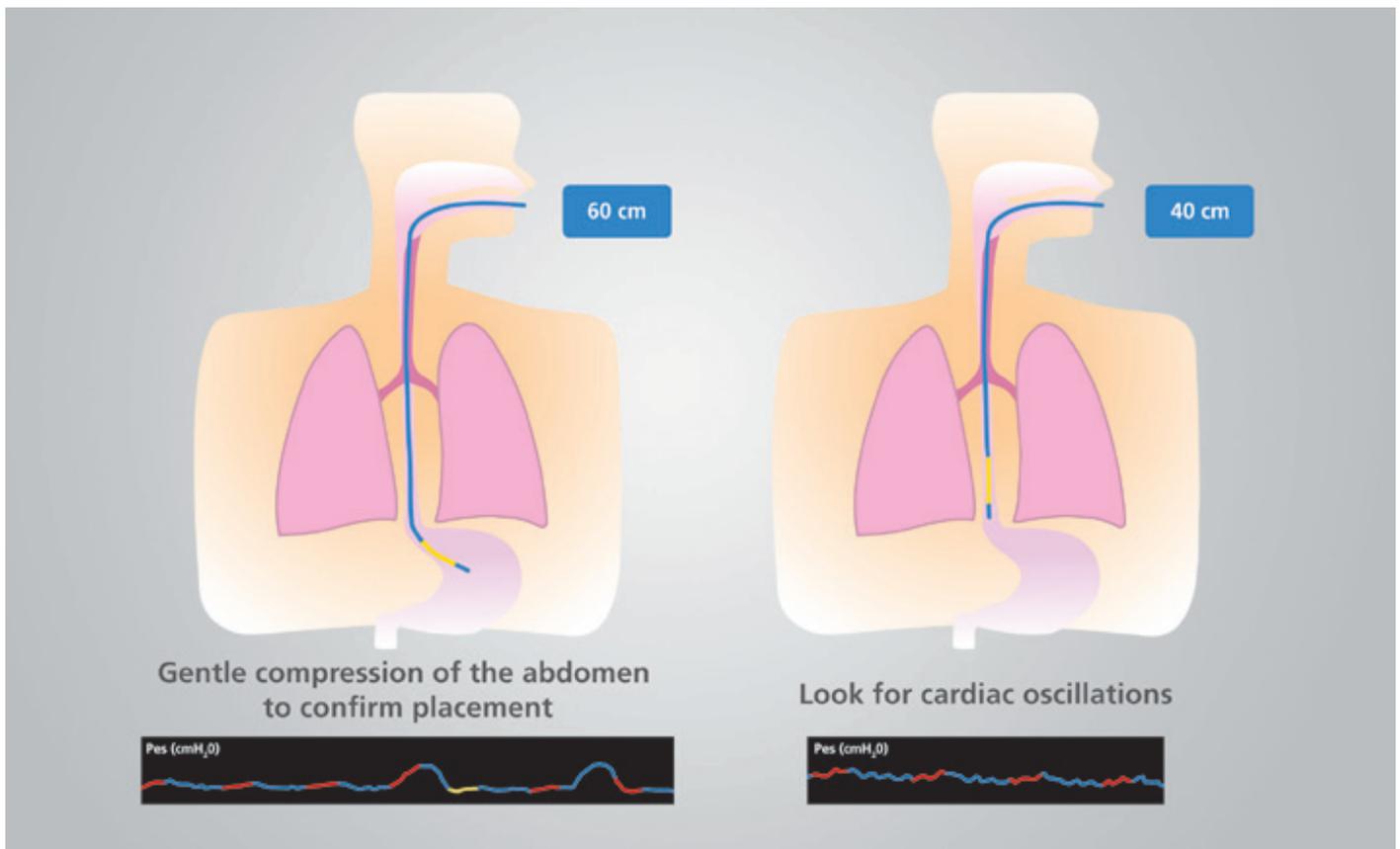


Figure 1. Insertion of the esophageal balloon.

Supporting research

A study by Behazin et al found that obese patients have higher pleural pressures than non-obese patients when sedated and paralyzed for surgery.³ This causes tidal breathing to occur at a lower FRC, lungs are less compliant and airways are prone to collapse during exhalation. It was also concluded that the pleural pressures were variable, and not predictable by BMI, making the measurement of Pes and Ptp a valuable clinical tool. The level of PEEP required to maintain a Ptp > 0 in this sedated patient was slightly higher than the normal range for surgical patients with BMI levels > 38. The cause of this patient's elevated pleural pressure may have been due to his fluid requirements secondary to hypotension caused by his sepsis. In my experience, I have seen clinicians be less concerned with elevated PIP in obese patients assuming that the size of the patient implies that they don't "feel" the pressure. This study helps demonstrate that when PEEP is set optimally, high PIP may not be necessary.

References

- 1 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *NEJM*, 2000, 342(18):1301-1308.
- 2 Chiumello, D et al. Lung Stress and Strain during Mechanical Ventilation for Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine*, 2008, 178(4):346-355.
- 3 Behazin N, Jones SB, Cohen RI and Loring SH. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. *Journal of Applied Physiology*, 2010, 108(1):212-218.

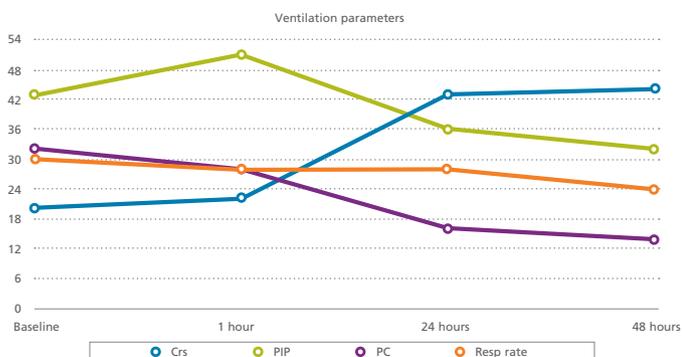


Figure 2. The 48 hour respiratory trend.

Sleep Apnea Diagnostics in the 21st Century

Richard A. Bonato, PhD, MA, RPSGT, RST

My first exposure to polysomnography and electroencephalography in a sleep laboratory was in 1986. Paper and ink oscillographs were the technology used to record electrophysiological data, a technique dating back to the 1930s. One night's recording resulted in about a quarter-mile of continuous fan-fold paper. The paper was heavy and became increasingly combustible as it aged. A few years later during the early 1990s a technological transition became widespread. With the introduction of low-cost, modern, digital computers there was a movement to replace ink and paper with a more efficient digital recording medium. For some, the change was easy; for others it took more time. Today, another change is taking place. This change involves the use of modern home sleep apnea recorders for the diagnosis of sleep disordered breathing and began in March 2008 when the Centers for Medicare and Medicaid Services approved home sleep apnea testing (HST).^{1,2} This watershed decision established a new standard by which many private payers began reimbursing HST. In fact, many payers now require preauthorization for laboratory based polysomnography (PSG) testing but not for HST. This welcome change in technology will improve patient convenience and comfort, and dramatically reduce costs. Rather than embrace HST as an opportunity to efficiently diagnose more patients, reduce time-to-treatment and expand business, many in the sleep disorders medicine field mistakenly view it as a threat. Sleep disorders laboratories will always have an important role in the management of sleep apnea, but their role is evolving to deal with the difficult to diagnose and the very sick.

Sleep apnea is defined as the cessation of breathing during sleep for a minimum duration of ten seconds frequently accompanied by an oxygen desaturation and terminated by an arousal from sleep. In the common, chronic form known as obstructive sleep apnea syndrome, it may be referred to as wake-up-gasping-choking-die-in-your-sleep disease. Sleep apnea is reported to occur in three to seven percent of the population.³ At the other end of the sleep disordered breathing spectrum is snoring, which is an alarm indicating something is wrong with breathing during sleep and occurs in 40 to 50 percent of the general population. The effect of sleep apnea on sleep quality, daytime performance, and overall health are widely known; however, upwards of 80 percent of sleep apnea sufferers remain undiagnosed. Ideally, home sleep apnea diagnostic devices record identical

physiological parameters in the home as recorded in the sleep laboratory, with the key difference being the lack of a technologist in attendance. However, studies have repeatedly found that when used properly home sleep apnea recorders have high sensitivity and specificity and are not inferior to laboratory based polysomnography.^{4,5,6}

Clinical standards have been published throughout North America for the appropriate use of home sleep apnea diagnostic recorders.^{7,8} Home recorders must record airflow, respiratory effort, blood oxygenation, and pulse rate or ECG and the recommended type of biosensors used to monitor these parameters in the home must be the same as those used for in-laboratory PSG. Patients suitable for HST are typically those with a high probability of sleep apnea who are otherwise healthy and do not present with any clinically significant comorbidities. Ideally, a clinical interview is performed by a medical doctor board certified in sleep medicine and, if available, a bedpartner is present during the interview. Supplemental paper and pencil questionnaires are administered and if sleep apnea is suspected a home sleep apnea test is administered. The respiratory therapist or sleep technologist should spend about ten minutes explaining the test to the patient with the actual device being applied and explained. If possible, it is recommended the patient's smartphone be used to take a photograph of the patient wearing the device. This is often valuable for subsequent patient reference. In certain circumstances, such clinical standards may be used to screen pediatric cases.

Recently, a home sleep apnea recording was performed in a four year old girl with observed snoring and apnea. In this case example, a four year old girl was observed by the parents to have continuous snoring during sleep. According to recent guidelines from the American Academy of Pediatrics, all children with observed snoring should undergo a sleep test.⁹ An examination of the oral cavity revealed a mallampati score of four and kissing tonsils were observed. The girl was otherwise healthy with no significant co-morbidities and the parents opted for a home sleep apnea test rather than wait for a laboratory PSG. A MediByte Type 3 HST recorder was used and the following parameters were used: oronasal airflow pressure, oronasal thermal airflow, thoracic ventilatory effort, abdominal ventilatory effort, SpO₂, pulse rate, body position, all-night audio recording, and snoring audio volume analysis. The home sleep apnea recording revealed an apnea + hypopnea index of 11.4 confirming the suspicion of sleep apnea (see Figure 1). The patient was referred to an otolaryngologist and scheduled for subsequent

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adenotonsillectomy. A consultation appointment with an orthodontist was also scheduled to discuss maxillary expansion.

The successful application of home sleep apnea testing will depend on the appropriate use of the tool. In the aforementioned case, it would have been ideal to include a measure of CO₂ when recording a child; however, the home test was able to confirm sleep apnea, resulting in faster access to treatment. The pediatric sleep laboratory resources remained available for more difficult to diagnose cases and for cases where co-morbidities precluded the use of a home test. Likewise, adult sleep laboratories can exploit the triage efficiencies of HST and use the cost-effectiveness, convenience, and comfort of home sleep testing to increase the occupancy rate of sleep laboratory facilities with patients who are unsuitable for HST or who require additional measures. Sleep laboratories will always be needed, but rather than view HST as a threat, successful sleep laboratories must include HST in their diagnostic armamentarium. Twenty years ago sleep medicine changed from paper polysomnography to paperless. Today, technological change permits a new home sleep testing opportunity which expands our diagnostic reach into the community.

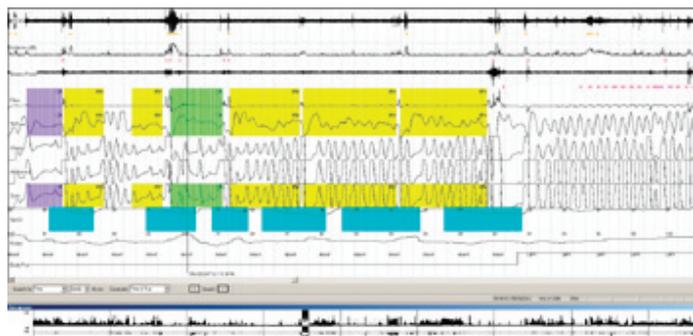


Figure 1. This five-minute sample of data is recorded from a four year old girl with high pre-test probability of sleep apnea. The timestamp is 0040 dated September 6, 2012. It shows various types of sleep disordered breathing events with numerous peripheral oxygen desaturations and microarousals from sleep. The software permits audio playback confirming the snoring sounds and events occurred during sleep. One eight percent desaturation is noted and is accompanied by an increase in heart rate to 115 bpm from a baseline of 77. Overall apnea + hypopnea index was 11.4 (an AHI ≥ 10 is severe in children). From top to bottom: Audio recording waveform, audio Volume in decibels, Snoring from oronasal cannula, Flow from oronasal cannula, Thermal airflow from oronasal thermistor, Chest respiratory effort, Abdomen respiratory effort, Sum derived from both Chest and Abdomen, SpO₂ and Pulse rate from a finger probe, and Body Position from the internal accelerometer.

References

- 1 Kryger, M. Sleep Medicine: The shot heard around the world. *Journal of Clinical Sleep Medicine*. 2012; 8(2):117-118.
- 2 Atwood, C. The Times They Are A Changin: Home Diagnosis of Sleep Apnea Has Arrived. *Sleep*. 2012; 35(6): 735-736.
- 3 Punjabi, N. The epidemiology of adult obstructive sleep apnea. *Proceeds of American Thoracic Society*. 2008; 5: 136-143.
- 4 Driver, H., Pereira, E., Bjerring, K., Toop, F., Stewart, S., Munt, P, Fitzpatrick, M. Validation of the MediByte® type 3 portable monitor compared with polysomnography for screening of obstructive sleep apnea. *Canadian Respiratory Journal*. 2011; 18(3): 137-43.
- 5 Pereira, E., Driver, H., Stewart, S., Fitzpatrick, M. Validated questionnaires and an ambulatory monitor in the diagnosis of obstructive sleep apnea. Paper presented at the World

Association of Sleep Medicine Conference, Quebec City, September 12, 2011.

- 6 Rosen, C., Auckley, D., Benca, R., Foldvary-Schaefer, N., Iber, C., Kapur, V., Rueschman, M., Zee, P., Redline, S. A Multisite Randomized Trial of Portable Sleep Studies and Positive Airway Pressure Autotitration Versus Laboratory-Based Polysomnography for the Diagnosis and Treatment of Obstructive Sleep Apnea: The HomePAP Study. *Sleep*. 2012; 35(6): 757-767.
- 7 Collop, N., Anderson, M., Boehlecke, B., Claman, D., Goldberg, R., Gottlieb, D., Hudgel, D., Sateia, M., Schwab, R. Portable Monitoring Task Force of the American Academy of Sleep Medicine. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine*. 2007; 3(7):737-47.
- 8 Blackman, A., McGregor, C., Dales, R., Driver, H., Dumov, I., Fleming, J., Fraser, K., George, C., Khullar, A., Mink, J., Moffat, M., Sullivan, G., Fleetham, J., Ayas, N., Bradley, D., Fitzpatrick, M., Kimoff, J., Morrison, D., Ryan, F., Skomro, R., Series, F., Tsai, W. Canadian Sleep Society/Canadian Thoracic Society position paper on the use of portable monitoring for the diagnosis of obstructive sleep apnea/hypopnea in adults. *Canadian Respiratory Journal*. 2010; 17(5): 229-32.
- 9 Marcus, C., Brooks, L., Draper, K., Gozal, D., Halbower, A., Jones, J., Schechter, M., Sheldon, S., Spruyt, K., Ward, S., Lehmann, C., Shiffmann, R. Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome. *Pediatrics*. 2012; 130(3): 576-584.

SleepImage – A New Way of Looking at Sleep

We have all heard about the huge number of people who have some form of sleep disorder. We know that the first step to treatment is diagnosis, and that the current options are limited. We also know that the problem is too big for in-lab polysomnography (PSG) to handle alone. PSG is expensive, time consuming and inconvenient. Looking at other countries, Europe was years ahead of the United States in accepting the role of home testing, but even with this model, the focus is almost exclusively on sleep apnea.

The Centers for Disease Control and Prevention (CDC) has been very clear that “Insufficient sleep is associated with a number of chronic diseases and conditions, such as diabetes, cardiovascular diseases, obesity, and depression. Sufficient sleep is increasingly being recognized as an essential aspect of chronic disease prevention and health promotion.” In short, sleep issues are not just about apnea. Sleep is finally being recognized as a key player in our overall health.

Why don't primary care physicians address sleep more aggressively? There are many reasons, including the time it takes to explain why a patient should spend the time, effort and cost of going to a sleep lab, putting the patient through the aggravation of a sleep test without being certain that it's required, and last but not least, explaining that they are expected to sleep normally in a strange environment, connected to a host of wires with a camera recording their every move. As a result, sleep becomes a last resort for busy primary care physicians.

In almost every other field of medicine, patients go through a triage of tests from simple to more complex and expensive. Sleep is one of the only conditions that moves from subjective questionnaires to the most complex, expensive test in one step.

If we are to have an impact on patients' sleep, and therefore their overall health, we need to simplify the way that sleep issues are identified and addressed by primary care physicians, in their office, on the patients' first visit, not their last.

So, what is “good” sleep? Sleep clinicians may answer that question by looking at multiple channels of data (EEG, EMG, ECG etc), and point out normal sleep architecture. Patients may answer that question by saying they feel refreshed and alert throughout the day. Because home sleep tests are complicated, intrusive and expensive, the most common way to screen patients for potential sleep issues has been through subjective questionnaires such as the Epworth, STOP-Bang, PSQI, SF39 and others. These questionnaires are severely restrained by their subjective nature, although not entirely a bad approach, but if a patient has not slept well for years, how can we expect them to tell us if they slept well last night? Patients may sleep better one

night over the next, but they may have slept very poorly both nights. Any answer is going to be subjective.

All of this speaks to the need for an objective, low cost sleep recorder that does not focus solely on one condition but on the quality of sleep in general.

This sleep recorder would not replace the sleep laboratory, but provide a tool that sleep specialists can use to engage all physicians who have patient populations suffering from health risks such as insomnia, depression, diabetes, apnea and others.

Such a sleep recorder now exists. It is called SleepImage, and it features a highly validated technology called Cardiopulmonary Coupling (CPC). CPC uses heart rate and breathing rate variability to distinguish “Stable” vs “Unstable” sleep and generates a simple Sleep Quality Index. The sleep recorder weighs less than one ounce, fits barely detectably on a patient's chest and records ECG, actigraphy, body position and snoring. It is fully integrated with a secure website and delivers an objective, easy to understand “image” of sleep.

There are many practical applications for the SleepImage system. Physicians can use the device as the initial objective screener for patients who complain of poor sleep or to monitor their patients' sleep over time and evaluate the effectiveness of behavioral interventions or medications on sleep. Clinicians dealing with patients with multiple conditions can use SleepImage to quickly screen for sleep disorders before other treatments are considered. Sleep specialists can use SleepImage to identify the type and severity of a patient's sleep disorder before PSG. For example, CPC can help identify Central or Complex Sleep Apnea before patients come to the lab. These are disorders that make conventional CPAPs unsuitable.

The beauty of this technology is that it is simple for the patient to put on, it is very small so the patient forgets they have it on, and it starts recording automatically. The analysis is automatic and the results are in the form of a graphic display that is easy to view.

The SleepImage system offers an objective measure of sleep quality that not only provides a picture of the patient's sleep architecture but, perhaps most importantly, can also assist the clinician in tracking sleep trends over time to give an objective measure of the effectiveness of a given therapeutic choice.

The next time your patient looks tired or complains of tiredness you now have the tool to get an objective answer and start managing the patient effectively.

You can find out more information about the SleepImage system at www.sleepimage.com.

This information was provided by SleepImage.

The No-Bite V: The New Standard of Care When Nasotracheal Suctioning is Contraindicated

(A Case Series of Three Patients)

Abstract

To understand The No-Bite V, one must understand some difficulties and contraindications to nasopharyngeal/nasotracheal suctioning:

- Occluded Nasal Passages/Deviated Septum¹
- Nasal Trauma/ Bleeding¹
- Recent Nasal Fractures/Sinus Surgery¹
- Elevated Coagulation Times from Blood Thinners¹
- Coagulopathy or Bleeding Disorders¹
- Frequent Coiling of Suction Catheters Upon Insertion¹
- Basal Skull Fracture/Transphenoidal Neurosurgery (absolute contraindications)¹

Question: When Nasotracheal Suctioning is either Difficult or Contraindicated, how would you suction your patient?

Answer: The No-Bite V.

This quick Q & A explains exactly why there is a national push for The No-Bite V. Clinicians are all too familiar with situations where a patient is in need of suctioning but the nasal passageways prove to be either difficult or even contraindicated. Never before did an alternative option exist to perform pharyngeal or tracheal suctioning while avoiding the nasal pathways. In the following report, we described three cases of successful suctioning experiences w/ The No-Bite V in patients where the nasal approach to suctioning was contraindicated and unable to be done.

Case #1

MICU, 30 y/o male, pmHx of Hepatitis C, encephalopathy, w/ actively bleeding esophageal varices, critical condition w/ hemoglobin=5, hematocrit=15, platelets=12, religion= Jehovah's Witness, where family was refusing blood transfusions d/t religious beliefs; severe generalized weakness, ineffective cough, thick secretions, moderate respiratory distress, in need of nasotracheal suctioning, but contraindicated, risk of nasal hemorrhage too great of a risk for nasotracheal suctioning approach, so The No-Bite V was successfully used by ICU RT & RN staff for oral tracheal suctioning for 3.5 days in conjunction with BiPAP therapy.

Conclusion: The patient avoided an almost certain intubation, and most importantly avoided nasal trauma & bleeding that may have ended his life. Patient transferred from ICU to step-

down unit 2.5 days later, patient seen sitting up in chair. The patient was followed an additional 5 days and no complications identified.

Case #2

Step-down unit, 80 y/o female, pmHx: Liver disease, currently w/ pneumonia, right lung "white out" on chest X-ray, generalized weakness, moderate respiratory distress. Patient w/ low platelets, elevated coagulation times d/t heparin drip, & low H & H. Moderate nasal bleeding noted as well as a substantial amount of suction catheter coiling d/t awake and alert nature of patient, patient coughing when nasal suctioning performed, therefore causing coiling of suction catheter in back of throat upon insertion. NJR Medical received special permission for No-Bite V use per RT & physician staff for oral tracheal suctioning in the middle of pilot study on different floor per hospital administration. Attending physician stated, "If not suctioned with No-Bite V, patient most likely would have been intubated for bronchoscopy and then re-admitted to MICU." Patient frequently suctioned deep oral tracheal with No-Bite V for 1 day and PRN for an additional 2 more days.

Conclusion: After day 1, chest X-ray remarkably better by AM rounds and subsequently; bronchoscopy/intubation/re-admit to MICU all avoided. The patient was followed an additional 5 days and no complications were identified.

Case #3

MICU, 78 y/o female, pmHx: CAD, DM, CA, currently w/ pneumonia, generalized weakness and respiratory failure that was recently extubated and not expectorating secretions properly. Patient developed a large amount of pharyngeal secretions d/t a weak cough and was also confused and uncooperative post extubation. Nasopharyngeal suctioning was attempted and unsuccessful due to complete blockage of the nasal passages. Oral pharyngeal suctioning was attempted, but the patient was biting on the suction catheter, therefore preventing suctioning altogether. The No-Bite V was used successfully per ICU RT and RN staff for 2.5 days.

Conclusion: After day 1 of suction assistance with The No-Bite V, secretions were less and patient was able to gain strength and expectorate more effectively, aspiration and re-intubation avoided. The patient was followed an additional 5 days and no complications were identified.

Discussion

Nasotracheal suctioning has been proven to prevent intubation in cases intended solely for secretion removal.²⁻⁶ In our opinion, when the nasotracheal suctioning approach proves to be difficult or contraindicated, an alternative method of suctioning with The No-Bite V, can also prove to prevent intubation. And if just one intubation can be prevented, an average additional hospital stay of 7 days and cost of \$29,200 can be avoided to a hospital.⁷⁻¹²

References

- 1 www.rcjournal.com/cpgs/pdf/09.04.1080.pdf
- 2 Burton GG, Hodgkin JE, Ward JJ, editors. Respiratory care: a guide to clinical practice, 4th ed. Philadelphia: JB Lippincott; 1997:600-607.
- 3 Fuchs PL. Streamlining your suctioning techniques. Part I. Nasotracheal suctioning. *Nursing* 1984;14(5):55-61.
- 4 Demers RR. Management of the airway in the perioperative period. *Respir Care* 1984;29(5):529-536; discussion, 536-539.
- 5 Vender JS, Shapiro BA. Essentials of artificial airway management in critical care. *Acute Care* 1987;13(1-2):97-124.
- 6 Garvey C. Respiratory therapy function and therapy. In: Nettina SM, editor. *The Lippincott manual of nursing practice*, 7th ed. Philadelphia: JB Lippincott; 2001:221-229.
- 7 Bouza, C., Garcia, E., Diaz, M., Segovia, E., & Rodriguez, I. (2007). Unplanned extubation in orally intubated medical patients in the ICU: a prospective cohort study. *Heart & Lung*, 36(4), 270-276.
- 8 Krivopal M., Shlobin O., & Schwartzstein R. (2003). Utility of daily routine portable chest radiographs in mechanically ventilated patients in the medical ICU. *Chest*, 123:1607-1614
- 9 De Lassence A., Alberti C., Azoulay E., et al. (2002). Impact of unplanned extubation and reintubation after weaning on nosocomial pneumonia risk in the intensive care unit. *Anesthesiology*, 97:148-156.
- 10 Epstein S, Nevins M, & Chung J. (2000). *American Journal of Respiratory and Critical Care Medicine*, 161:1912-1916.
- 11 Dasta J.F., McLaughlin T.P., Mody S.H., & Piech C.T. (2005). Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Critical Care Medicine*, Jun; 33(6):1266-1271.
- 12 Candrilli S. & Mauskopf J. (2006, May). How Much Does a Hospital Day Cost? Poster at 11th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Philadelphia, PA.

Sleep Roundtable...continued from page 24

SOMNOmedics

SOMNOmedics strives to keep its technology compatible with the latest developments in the sleep and neuro diagnostics field. We take pride in our technology by offering the practitioners and patients the flexibility, versatility and reliability in all our devices.

Our emphasis lies on the development of innovative solutions for ambulatory as well as lab-based sleep diagnostics, long-time EEG and motion analysis. Our devices are the smallest ones currently available on the market and can be used flexibly as Screener or complete PSG system with extended EEG recording.

Our full PSG system "SOMNOscreen plus" allows the practitioner to perform any level of sleep testing in any environment either attended or unattended. Here are some of the features of the SOMNOscreen plus:

- Real time and ambulatory
- Complete wireless real time data transfer
- Small and fully portable
- Continuous Impedance
- Up to 33 Channels
- Internal built in sensors: Body Position, Movement, Ambient light sensor, Effort, Patient marker, Pulse oximeter
- Reusable and non-reusable sensors
- Fully rechargeable battery – Up to 55 hours of continuous recording without memory effect
- Unlimited mobility for the patient and practitioner
- Wireless Video and Audio synchronization
- Active sensors technology
- Interchangeable miniaturized headboxes from 4 EEG channels for HST to PSG as well as 35 channels for 24 hours EEG
- All in one device: Type 1, 2, 3, 4 sleep studies can be performed
- Upgradeable at any time from a screening device to a full PSG device
- Rechargeable battery
- Additional features include: Systolic/Diastolic Blood Pressure – Limited EEG recording (for ambulatory testing) – Actigraphy
- 24 hours technical support
- Installation and training included.

Auto-titrating vs Fixed CPAP for the treatment of OSA

Stanley Ip, Carolyn D'Ambrosio, Kamal Patel, Ndidiamaka Obadan, Georgios D. Kitsios, Mei Chung, Ethan M. Balk

Abstract

Background: Obstructive sleep apnea is a relatively common disorder that can lead to lost productivity and cardiovascular disease. The form of positive airway treatment that should be offered is unclear. Methods: MEDLINE and the Cochrane Central Trials registry were searched for English language randomized controlled trials comparing auto-titrating positive airway pressure (APAP) with continuous positive airway pressure (CPAP) in adults with obstructive sleep apnea (inception through 9/2010). Six researchers extracted information on study design, potential bias, patient characteristics, interventions and outcomes. Data for each study were extracted by one reviewer and confirmed by another. Random effects model meta-analyses were performed for selected outcomes.

Results: Twenty-four randomized controlled trials met the inclusion criteria. In individual studies, APAP and fixed CPAP resulted in similar changes from baseline in the apnea-hypopnea index, most other sleep study measures and quality of life. By meta-analysis, APAP improved compliance by 11 minutes per night (95% CI, 3 to 19 minutes) and reduced sleepiness as measured by the Epworth Sleepiness Scale by 0.5 points (95% CI, 0.8 to 0.2 point reduction) compared with fixed CPAP. Fixed CPAP improved minimum oxygen saturation by 1.3% more than APAP (95% CI, 0.4 to 2.2%). Studies had relatively short follow-up and generally excluded patients with significant comorbidities. No study reported on objective clinical outcomes.

Conclusions: Statistically significant differences were found but clinical importance is unclear. Because the treatment effects are similar between APAP and CPAP, the therapy of choice may depend on other factors such as patient preference, specific reasons for non-compliance and cost.

Background

Obstructive sleep apnea (OSA) is a relatively common disorder in the US. The Wisconsin Sleep Cohort Study, a prospective natural history study, reported that about 10% of adults aged 30 to 60 years old had clear evidence of OSA in 1988, when the study began. A National Sleep Foundation poll in 2005 suggested that as many as one in four American adults are at high risk of OSA and could benefit from an evaluation for OSA.

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The defining characteristic of OSA is a partial or complete obstruction of the airway while sleeping. The most common first-line therapy is the use of continuous positive airway pressure (CPAP) devices during sleep. The CPAP machine directly relieves the airway obstruction by increasing luminal pressure, thereby splinting the airway open. When used properly and consistently, CPAP results in improved sleep patterns and quality of life due to decreased daytime somnolence. However, many patients refuse the offer of CPAP therapy, do not tolerate it or fail to use CPAP devices properly. Patients commonly did not fully comply with CPAP use, either using the device for only part of the night or only on some nights. This non-compliance has fueled the development of a number of technological solutions.

The most common variation on delivering positive airway pressure is the use of auto-titrating positive airway pressure (APAP) devices. Fixed CPAP provides continuous fixed pressure during the entire sleep period. In contrast, APAP varies the pressure delivered depending on changes in airflow resistance. Such changes in airflow resistance during sleep are dependent on many factors like posture and the degree of nasal congestion. Theoretically, varying the pressure delivered would promote an increase in breathing synchrony with the CPAP device and therefore could improve patient comfort with the device and thus enhance compliance. A 2009 Cochrane review comparing APAP with CPAP concluded that APAP was slightly more efficacious than CPAP in increasing patient compliance. We undertook the present review in the context of a larger review of all primary studies of treatments for OSA. We sought to update and expand upon the previous review. The aim of the present review is to evaluate the body of evidence regarding the comparative efficacy of APAP versus CPAP on clinical and sleep-related outcomes, quality of life, compliance and other outcomes.

Methods

[The methods employed have been considerably edited.] We followed standard systematic review methods as described in the Agency for Healthcare Research and Quality (AHRQ) Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. A full technical report describing these methods in detail, including literature search strategies, and presenting our findings in full (with evidence tables) is available elsewhere.

We searched the MEDLINE and Cochrane Central Trials Registry databases from study inception to September 2010 for English language studies examining adults (older than 16 years) with OSA. Our search, available in the full technical report, included terms for OSA, sleep apnea treatments and relevant research designs. The full literature search was performed for a range of key questions about OSA diagnosis, treatment with

any intervention and predictors of outcomes. Six reviewers independently screened the abstracts. We used a computerized screening program, *abstrackr*, to automate the screening of abstracts for the selection of eligible articles for full-text screening. The *abstrackr* software uses an active learning algorithm to screen for relevant articles... Using *abstrackr*, we reduced by 50% the number of abstracts we needed to manually screen prior to starting the subsequent steps of the systematic review. Later, all abstracts rejected by *abstrackr* were manually screened for confirmation and were eventually rejected. Full-text articles were rescreened for eligibility by the same six reviewers.

We included peer reviewed, randomized controlled trials (RCTs) that compared APAP with fixed CPAP in ≥ 10 patients per intervention with confirmed diagnoses of OSA, including a formal sleep study demonstrating an apnea-hypopnea index (AHI) ≥ 5 events/hour. We included studies of any duration, though CPAP had to be used by the patients at home. Outcomes of interest included: objective clinical outcomes (death, cardiovascular events, hypertension, non-insulin dependent diabetes, depression); sleep and wakefulness related clinical outcomes (quality of life, sleepiness measures, neurocognitive tests, accidents, productivity); sleep study measures (AHI, arousal index, deep sleep, sleep efficiency, minimum oxygen saturation); comorbidity intermediate outcomes (hemoglobin A1c, blood pressure); compliance; and adverse events or harms.

Extracted data included information on study and patient characteristics, details concerning the CPAP devices used, outcomes and study quality. For most outcomes, only data from the last reported time-point were included. The primary data extractor determined the study quality (rated with the letter grades A, B or C), and at least one other reviewer confirmed it. Quality A studies adhered most closely to the commonly held precepts of high quality, including clear descriptions of the population, setting, interventions, outcomes and design; no obvious reporting omissions or errors; fewer than 20% dropouts; and no obvious source of bias. Quality B studies had some deficiencies in these criteria that were, however, unlikely to engender a major bias. Quality C studies had inadequate descriptions of their studies or had substantial flaws in reporting or design, such that a major bias could not be excluded.

We performed random effects model meta-analyses of differences of selected continuous variables between interventions where there were at least three unique similar studies. We performed meta-analyses for the AHI, the Epworth Sleepiness Scale (ESS), arousal index (per hour frequency of arousals from sleep), minimum oxygen saturation (during sleep), the multiple sleep latency test (measurement of how quickly a subject will fall asleep during the day), the quality of life measure Functional Outcomes Sleep Questionnaire and compliance (measured as time per night using the device). Studies that compared two different forms of APAP to CPAP were treated as independent despite the common CPAP arm.

[A meta-analysis was used] to explore sources of heterogeneity in between-study findings.

We took into account the overall study quality, the consistency across studies, the applicability of the studies to the general population of patients treated for OSA, the magnitude and

precision of the treatment effects and the relative clinical importance of the different outcomes assessed. The overall strength of evidence was rated as high, moderate, or low - which each indicate the level of confidence that the evidence reflects the true effect - or insufficient.

Results

Our literature search yielded 15,816 citations, from which 861 articles were retrieved. We identified 24 RCTs that compared APAP with fixed CPAP treatment in patients with OSA. Three RCTs identified in prior meta-analyses were added after completion of our full technical report. Fifteen trials used a cross-over design and nine a parallel design. Studies generally failed to report complete data about outcomes. For 17 studies, the variance of the difference in baseline and final values was not reported and had to be estimated by making an assumption about the correlation between the values. Patients who were new to positive airway pressure treatments were enrolled in 21 of 24 studies (three did not provide this information). There was a broad range of OSA severity at baseline across studies; patients' mean baseline AHI ranged from 15 to 58 events/hour. In all studies, most patients were either overweight or obese (body mass index ranged from 29.9 to 42 kg/m²). None of the studies selectively focused on patients with other comorbidities. Study sample sizes ranged from 10 to 181 patients (total 1,017 across studies). Study durations ranged from three weeks to nine months, with the majority of studies lasting three months or less. Two trials were rated quality A, 12 were rated quality B and ten rated quality C. Primary methodological concerns included small sample sizes without statistical power calculations, incomplete data reporting, short follow-up durations and high dropout rates. Based primarily on the eligibility criteria and baseline characteristics of the trial, the outcomes are applicable mainly to newly diagnosed (previously untreated) OSA patients with AHI >15 events/hour and body mass index >30 kg/m².

Objective clinical outcomes: No trial evaluated clinical outcomes, including death; cardiovascular events such as myocardial infarction, heart failure or stroke; or diabetes or depression severity.

Compliance: All 24 included trials reported data on compliance. The number of hours used per night was derived from machine-recorded compliance data. No statistically significant differences were observed in device usage (hours used per night) between APAP and CPAP in 20 of the trials, while four reported a significant increase in the use of APAP compared with CPAP. Twenty-two trials provided sufficient data for meta-analysis, which showed a statistically significant difference of 11 minutes per night favoring APAP (difference = 0.18 hours; 95% CI, 0.05 to 0.31 minutes; $P = 0.006$), without statistical heterogeneity.

To test the a priori hypothesis that the relative effect on compliance may differ based on baseline severity, we performed subgroup meta-analyses stratified by minimum AHI threshold. By meta-regression, the subgroups had no significantly different effects from each other. Results were also similar in parallel and cross-over design studies.

Apnea-hypopnea index: Sixteen trials provided sufficient data for analysis of residual AHI while using treatment. None of the studies reported a statistically significant difference in AHI (events/hour) between APAP and CPAP. The mean net difference in individual studies ranged from -2.8 to 3.5 events/hour, where

negative values favor APAP. Meta-analysis across these studies indicated a non-significant difference between APAP and CPAP of 0.25 events/hour (95% CI, -0.16 to 0.66 events/hour; $P = 0.23$). No statistically significant heterogeneity was observed across studies, despite a broad range in the severity of OSA at baseline. Meta-regression stratified by different minimum AHI thresholds or by study design revealed no apparent differences across subgroups in the relative effects of APAP and CPAP.

Epworth Sleepiness Scale: Twenty-two trials reported ESS after treatment. No statistically significant differences in ESS were observed between APAP and CPAP in 20 trials, while two studies reported a significant decrease in ESS favoring APAP. The mean net difference in ESS across all studies ranged from -3.3 to 2.0, where negative values favor less sleepiness with APAP. Eighteen trials provided sufficient data for meta-analysis, which yielded a statistically significant difference between APAP and CPAP of -0.48 (95% CI, -0.81 to -0.15; $P = 0.005$), favoring APAP. Despite the broad range of severity of OSA across studies, there was no statistically significant heterogeneity within the overall meta-analysis. Meta-regression stratified by minimum AHI threshold or by study design revealed no apparent differences across subgroups in relative effects of APAP and CPAP.

Other sleep study measures: Meta-analysis of nine trials showed a non-significant difference in arousal index of -0.85 events/hour (95% CI, -2.2 to 0.5 events/hour; $P = 0.23$), favoring APAP (Figure 5). Meta-analysis of nine trials showed a statistically significant difference in minimum oxygen saturation of -1.3% (95% CI, -2.2 to -0.4%; $P = 0.003$), favoring CPAP (Figure 6). Neither meta-analysis had statistically significant heterogeneity. Meta-regression revealed no differences across AHI or study design subgroups.

The three trials reporting on sleep efficiency (percentage of time asleep while in bed) after a period of treatment did not find a statistically significant difference between APAP and CPAP for improvement in the percentage of time spent asleep. Nine trials reporting on percentage of time spent in REM sleep did not find statistically significant differences between groups. Seven of eight trials found no statistically significant difference in slow wave sleep (stages 3 or 4). The one outlier reported a statistically significant net mean increase of 7.8% (95% CI, 1.8 to 13.7%; $P < 0.01$); patients using APAP spent more time in slow wave sleep. No study reported effect on the multiple sleep latency test.

Quality of life: Nine trials evaluated quality of life measures. One trial that included the SF-36 (Short Form Health Survey) found a significant difference in the mental health (net difference of 5 points; 95% CI, 0.2 to 9.8 points; $P < 0.05$) and vitality (net difference of 7 points; 95% CI, 0.6 to 13.4 points; $P < 0.05$) components, favoring those who used APAP. No other significant differences in quality of life measures between APAP and CPAP were reported in this or the other eight trials. One trial reported on the Sleep Apnea Quality of Life Index and found no difference between groups. No study reported any effect on the Functional Outcomes Sleep Questionnaire. Due to the heterogeneity of specific quality of life outcome reported (13 among these studies, including the components of SF-36).

Blood pressure: Three trials reported changes in blood pressure. Two studies did not find significant differences in blood pressure changes between the APAP and CPAP groups. In the third study, based on reported data, we estimated a non-significant

greater reduction in systolic blood pressure (net difference = 6 mmHg; 95% CI, -1 to 13 mmHg; $P = 0.09$) and a significant greater reduction in diastolic blood pressure (net difference = 8 mmHg; 95% CI, 4 to 11 mmHg; $P < 0.001$) with CPAP compared to APAP.

Adverse effects: No trials reported any unexpected adverse effects with positive airway treatments. Seven trials reported quantitative comparisons of treatment-related side effects between groups. The side effects were dry mouth, air leakage, skin or nasal-oral irritation. No differences in side effects were reported in five trials. Two trials reported that the use of APAP was associated with significantly fewer treatment-related side effects.

Discussion

Despite the lack of evidence on objective clinical outcomes, given the largely similar magnitude of effects between APAP and CPAP on sleep measures and wakefulness assessment and the relatively small increase (even though statistically significant) in compliance of about 11 minutes with APAP, we concluded that the overall strength of evidence is moderate that APAP and CPAP result in largely similar treatment effects for patients with OSA.

The aim of this study was to systematically compare the treatment effects of APAP versus fixed CPAP. Twenty-four trials that included over 1,000 patients provided evidence that APAP reduces sleepiness as measured by ESS by approximately 0.5 points more than fixed CPAP. For compliance, there was a statistically significant difference of 11 minutes per night also favoring APAP compared to fixed CPAP. The clinical significance of these reported improvements in ESS and compliance, however, is unclear. The two types of devices were found to result in similar changes from baseline in AHI, quality of life and most other sleep study measures. However, there is also evidence that minimum oxygen saturation improves more with CPAP than with APAP by about 1%. Evidence is limited regarding the relative effect of fixed CPAP and APAP on blood pressure. There were no data on objective clinical outcomes.

The etiology and severity of OSA varies widely across patients, as do patients' symptoms and their ability to tolerate or consistently use treatments. CPAP, specifically, can be cumbersome and uncomfortable to use; therefore, it is of particular importance to identify which subgroups of patients may benefit most from which specific treatments to maximize the effectiveness of intervention. Our subgroup meta-analyses based on different minimum AHI thresholds to define OSA failed to demonstrate any difference in effectiveness between APAP and CPAP for all outcomes. Higher AHI is used as a marker for more severe disease and is associated with greater mortality; however, our power to find any differences based on baseline AHI was low, particularly since the study eligibility categories overlapped. Even if we had found a difference, it would at best be hypothesis-generating and would need to be confirmed in a primary study. But we found no study that directly analyzed any subgroup of patients who may particularly benefit from a given treatment. It should be noted that experts have opined that APAP may be used in the setting of failed fixed CPAP (CD, personal communication), although we are not aware of a study in such a setting.

Despite the addition of newer studies in our meta-analyses, our findings differed little from those of a Cochrane meta-analysis
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Abdominal Adiposity and Obstructive Airway Disease: testing insulin resistance and sleep disordered breathing mechanisms

Matthew T. Haren, Gary Misan, Tracey-Jayne Paterson, Richard E. Ruffin, Janet F. Grant, Jonathan D. Buckley, Peter R.C. Howe, Jonathan Newbury, Anne W. Taylor, Robyn A. McDermott

Abstract

Background: This study examined associations of abdominal adiposity with lung function, asthma symptoms and current doctor-diagnosed asthma and mediation by insulin resistance (IR) and sleep disordered breathing (SDB).

Methods: A random sample of 2500 households was drawn from the community of Whyalla, South Australia (The Whyalla Intergenerational Study of Health, WISH February 2008 - July 2009). Seven-hundred twenty-two randomly selected adults (≥ 18 years) completed clinical protocols (32.2% response rate). Lung function was measured by spirometry. Post-bronchodilator FEV1/FVC was used to measure airway obstruction and reversibility of FEV1 was calculated. Current asthma was defined by self-reported doctor-diagnosis and evidence of currently active asthma. Symptom scores for asthma (CASS) and SDB were calculated. Intra-abdominal fat (IAF) was estimated using dual-energy x-ray absorptiometry (DXA). IR was calculated from fasting glucose and insulin concentrations.

Results: The prevalence of current doctor-diagnosed asthma was 19.9% (95% CI 16.7 – 23.5%). The ratio of observed to expected cases given the age and sex distribution of the population was 2.4 (95%CI 2.1, 2.9). IAF was not associated with current doctor-diagnosed asthma, FEV1/FVC or FEV1 reversibility in men or women but was positively associated with CASS independent of IR and SDB in women. A 1% increase in IAF was associated with decreases of 12 mL and 20 mL in FEV1 and FVC respectively in men, and 4 mL and 7 mL respectively in women. SDB mediated 12% and 26% of these associations respectively in men but had minimal effects in women.

Conclusions: In this population with an excess of doctor-diagnosed asthma, IAF was not a major factor in airway obstruction or doctor-diagnosed asthma, although women with higher IAF perceived more severe asthma symptoms which did not correlate with lower FEV1. Higher IAF was significantly associated with lower FEV1 and FVC and in men SDB mechanisms may contribute up to one quarter of this association.

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Background

Obesity, as defined by body mass index (BMI) has been shown to be associated with a 2.5-fold increase in the risk of current doctor-diagnosed asthma in women but not in men¹ and the association appears to be specific to non-atopic asthma.^{2,3} Raviv et al⁴ showed that obesity was associated with asthma symptoms only in the least obstructed tertile, as measured by the ratio of FEV1 (forced expired volume in one second) to FVC (forced vital capacity). Together, these findings suggest that obesity may produce a mild obstructive airway phenotype distinct from that mediated by type 2 T-helper (Th2) cell inflammatory pathways.⁵ Moreover, in one of the first studies to explore the associations between spirometric lung function and adiposity using DXA-measured fat mass, Sutherland and colleagues demonstrated correlations of total, trunk and abdominal fat masses with FVC in men and women and with FEV1 in men only, using a small convenience sample. This study was unable to adjust for potential confounders or investigate potential mechanisms and thus could not provide accurate estimates of the direct and indirect associations between adiposity and lung function and did not include a measurement of airway obstruction.⁶

Proposed mechanisms for an obesity-induced obstructive airway phenotype include, amongst others, insulin resistance (IR)^{7,8} and sleep disordered breathing (SDB).⁵ The mechanisms by which SDB could increase asthma severity are not known, but potentially involve increased vagal tone, leading to bronchoconstriction; upper airway inflammation, leading to lower airway inflammation; and perturbations in central control of bronchomotor tone.⁵ The authors have previously reported strong positive associations between the frequency of SDB symptoms and expression of fat mass/hyperinsulinaemia, glycaemia and lipid/lean mass phenotypes in non-diabetics in the population under study which has a prevalence of abdominal obesity of 50%.⁹ Thus, this population appears suited to examine this hypothesis.

Research context: The industrial, outer regional city of Whyalla in South Australia has a complex mix of social and physical environmental exposures which may relate to excess asthma risk. Public perceptions about the causes of respiratory ill-health in this community may be dominated by the tangible evidence of the once visible “red dust” from the process of pelletizing iron ore for Steelmaking and uncovered exporting of iron ore in the city.¹⁰ An ecological study, using administrative data from 1977 to 2005 suggested that asthma, chronic lung disease, and lung cancer were in excess in Whyalla, but that the prevalence

Table 1 Respiratory, metabolic and socio-demographic characteristics, The Whyalla Intergenerational Study of Health (WISH, 2008–2009)

		Current Doctor-Diagnosed Asthma				Asthma x spirometry quality	
		No (n = 575)	Yes (n = 151)	F(df) or Chi2(df)	P	F(df) or Chi2(df)	P
Completion/	No test	77	21				
acceptability of spirometry	Unacceptable	51	15				
	Acceptable	447	115				
Outcomes, asthma symptoms							
CASS, range 0-8	No test	3.62 (3.26, 3.99)	5.33 (4.64, 6.27)	F(5,711) = 19.26	<0.001	F(2,711) = 1.16	0.32
	Unacceptable	3.28 (2.83, 3.72)	5.23 (4.35, 6.11)				
	Acceptable	3.28 (3.13, 3.43)	4.56 (4.26, 4.86)				
log CASS	No test	1.16 (1.05, 1.27)	1.63 (1.41, 1.84)	F(5,711) = 14.33	<0.001	F(2,711) = 0.55	0.58
	Unacceptable	1.09 (0.95, 1.22)	1.54 (1.27, 1.82)				
	Acceptable	1.07 (1.03, 1.12)	1.42 (1.33, 1.51)				
Outcomes, spirometry (acceptable tests only)							
FEV1 reversibility, L		0.11 (0.09, 0.12)	0.12 (0.09, 0.14)	F(1, 538) = 0.22	0.64		
FEV1 reversibility,%		3.88 (3.27, 4.49)	5.03 (3.83, 6.24)	F(1, 538) = 2.80	0.10		
post FEV1, L		3.01 (2.93, 3.10)	2.76 (2.60, 2.92)	F(1, 538) = 7.62	<0.01		
post FVC, L		3.80 (3.70, 3.90)	3.64 (3.44, 3.83)	F(1, 523) = 2.02	0.16		
post FEV1/FVC,%		79.46 (78.73, 80.19)	76.14 (74.70, 77.57)	F(1, 523) = 16.34	<0.001		
post PEF, L/s		7.83 (7.62, 8.03)	7.23 (6.83, 7.63)	F(1, 538) = 6.80	<0.01		
post FEF25%-75%, L/s		3.06 (2.94, 3.17)	2.55 (2.32, 2.78)	F(1, 538) = 15.16	<0.001		
FEV1, ppv†		90.34 (88.79, 91.88)	84.20 (81.16, 87.24)	F(1, 538) = 12.46	<0.001		
FVC, ppv†		93.90 (92.44, 95.35)	91.70 (88.81, 94.60)	F(1, 523) = 1.76	0.19		
FEV1/FVC, ppv†		96.66 (95.81, 97.50)	91.03 (89.35, 92.70)	F(1, 523) = 34.55	<0.001		
PEF, ppv†		97.24 (95.50, 98.98)	92.44 (89.02, 95.85)	F(1, 538) = 6.03	0.02		
FEF25%-75%, ppv†		84.55 (81.90, 87.20)	71.28 (66.07, 76.49)	F(1, 538) = 19.79	<0.001		
Independent variables							
Intra-abdominal fat,%	No test	39.58 (37.26, 41.90)	39.44 (34.92, 43.96)	F(5,692) = 1.16	0.33	F(2,692) = 1.71	0.18
	Unacceptable	38.81 (35.92, 41.70)	33.06 (27.66, 38.47)				
	Acceptable	39.55 (38.57, 40.52)	39.91 (37.99, 41.83)				
Mediator variables							
HOMA2-IR	No test	1.35 (1.09, 1.66)	2.01 (1.52, 2.52)	F(5,703) = 1.51	0.19	F(2,703) = 3.18	0.04
	Unacceptable	1.39 (1.06, 1.71)	1.71 (1.09, 2.34)				
	Acceptable	1.40 (1.30, 1.59)	1.32 (1.11, 1.54)				
SDB symptom score, range 0-12	No test	1.18 (0.63, 1.73)	1.87 (0.75, 2.98)	F(5,594) = 1.74	0.12	F(2,594) = 0.07	0.93
	Unacceptable	1.54 (0.83, 2.25)	2.09 (0.79, 3.40)				
	Acceptable	0.96 (0.74, 1.18)	1.39 (0.93, 1.85)				

A description of the outcome, independent and mediator variables, and covariates by current doctor-diagnosed asthma and spirometry completion and quality, The Whyalla Intergenerational Study of Health (WISH, 2008–2009)

Determination of 'unacceptable test' was based on either baseline and post-bronchodilator EasyOne™ system quality control (QC) grade of D or lower, or non-reproducible trials exceeding 3% variability. The analytical sample satisfied a QC grade of C or higher and reproducible trials within 3% variability. †Percentage of Predicted Value (PPV) was based on equations of Gore et al. (1995)[17]

of smoking was similar in Whyalla when compared with other 'dusty' regional South Australian cities.¹¹ This suggests that local environmental or population factors might be contributing to the excess of respiratory disorders in Whyalla.

This study aimed to test the hypotheses that abdominal adiposity, which has been shown to be at high prevalence in this community, is associated with poorer lung function, increased severity of asthma symptoms and a higher prevalence of current doctor-diagnosed asthma through mechanisms involving IR or SDB.

Methods Sampling and recruitment: The Whyalla Intergenerational Study of Health (WISH) cohort was established between February 2008 and July 2009. Whyalla households (n = 2500) were randomly selected from the residential housing database of the State Planning Authority. The strength of this sampling frame was the completeness, however approach and recruitment was a complex multi-stage process due to limited contact information in the databases (residential address only). This novel sampling frame was used instead of telephone listings (Electronic White Pages (EWPs)) due to a high proportion of households without landline telephone connections, which is

Table 2 Associations of intra-abdominal fat percentage with lung function and asthma outcomes, and hypothesised mediators (sleep disordered breathing score and insulin resistance) in men and women, The Whyalla Intergenerational Study of Health (WISH, 2008–2009).

	Men			Women		
	Coef. (bootstrap 95%CI)	P	R-squared	Coef. (bootstrap 95%CI)	P	R-squared
Current doctor-diagnosed asthma	1.002 (0.975, 1.029)	0.913		1.004 (0.983, 1.027)	0.686	
<i>Obs</i>	214			320		
log CASS	0.006 (0.000, 0.012)	0.045	0.148	0.009 (0.002, 0.016)	0.011	0.123
<i>Obs</i>	213			317		
rev FEV1	0.045 (−0.045, 0.135)	0.328	0.077	0.005 (−0.063, 0.073)	0.892	0.026
<i>Obs</i>	212			313		
post FEV1/FVC						
L/L	0.065 (−0.028, 0.158)	0.172	0.363	0.056 (−0.002, 0.113)	0.056	0.321
PPV (Gore et al. [17])	0.090 (−0.029, 0.209)	0.138	0.229	0.066 (−0.033, 0.165)	0.194	0.129
<i>Obs</i>	210			300		
SDB	0.055 (0.017, 0.094)	0.005	0.129	0.024 (0.002, 0.047)	0.034	0.083
<i>Obs</i>	178			273		
HOMA2-IR	0.059 (0.048, 0.071)	<0.001	0.272	0.052 (0.038, 0.065)	<0.001	0.286
<i>Obs</i>	214			318		

more common in rural than metropolitan South Australia.¹² Invitations to participate, addressed to “The Householder,” were mailed to randomly selected households, co-ordinated with a community-wide media campaign informed by a Community Advisory Group. Householders were invited to register online or by telephone, providing their telephone number and basic demographic information. One-hundred seventy-eight (7%) households responded to this approach. The second stage successfully matched 1183 of the randomly selected household addresses in the sample to names and telephone numbers in the EWPs. Thirdly, remaining unmatched randomly selected households were approached by door-knocking; a minimum of two attempts to contact were made and calling cards were left.

Once telephone numbers were obtained, Computer Assisted Telephone Interviewing (CATI) technology was used to recruit the adult (≥18 years) in each household who last had their birthday,¹³ and to collect demographic, health and risk factor data and schedule clinical assessments. Interviews were conducted by trained interviewers under established protocols.^{13,14} Participants provided written informed consent at the time of clinical assessment. Protocols and procedures were approved by the Human Research Ethics Committee of The University of South Australia and the Aboriginal Health Research Ethics Committee of South Australia.

Major outcome measures: Spirometry, including bronchodilator reversibility was performed in accordance with American Thoracic Society guidelines¹⁵ and manufacturer’s recommendations using portable ultrasonic sensor spirometers (nidd EasyOne) interfaced with EasyWare 2008 (nidd Medizintechnik AG, Zurich Switzerland) on laptop computers. This device has been demonstrated to maintain good stability during everyday use in Australian general practice and does not require daily calibration.¹⁶ Quality control was maintained by achieving a minimum of three trials with volumes within 3% and achieving the manufacturers recommended minimum system quality control grade. The primary spirometric outcome was airway obstruction measured by post-bronchodilator FEV1/FVC. The degree of reversibility in the FEV1 was calculated as: 100 x FEV1 (post-bronchodilator) – FEV1 (baseline) / FEV1 (baseline) FEV1/FVC. Secondary outcomes were post-bronchodilator FEV1; FVC; peak expiratory flow (PEF); and the average expired flow over the middle half of the FVC maneuver (FEF25-75%). These

variables were also referenced to South Australian-derived prediction equations of Gore et al.¹⁷ and expressed as the percentage of predicted value (PPV).

Self-reported “ever doctor-diagnosed asthma” was defined as answering yes to either: (1) Have you ever been told by a doctor that you have any of the following conditions? (option 2 = Asthma); or (2) have you ever been told by a doctor that you have asthma? “Current doctor-diagnosed asthma” was defined as “ever doctor-diagnosed asthma” plus evidence of currently active asthma defined by positive responses to any of the following questions: (1) During the past 12 months, did you have any symptoms of asthma? (2) During the past 12 months, did you take asthma medication that was prescribed or given to you by a doctor? (3) Do you still have asthma? The frequency of three asthma symptoms (wheeze, shortness of breath and cough; scored as never (0), occasionally (1), most days/every day (2) and the amount of phlegm produced during cough (none (0), a little (1), several tablespoons/day or more (2) over the past three months,¹⁸ were summed to produce a comprehensive asthma symptom score (CASS) ranging from zero indicating no asthma symptoms to eight indicating the highly frequent presence of all four symptoms.

Independent variables: Body composition was assessed using dual-energy x-ray absorptiometry (DXA, Lunar Prodigy, GE Medical Systems, Madison WI) with the manufacturer’s software (enCORE 2003 version 7.52). Scans were performed according

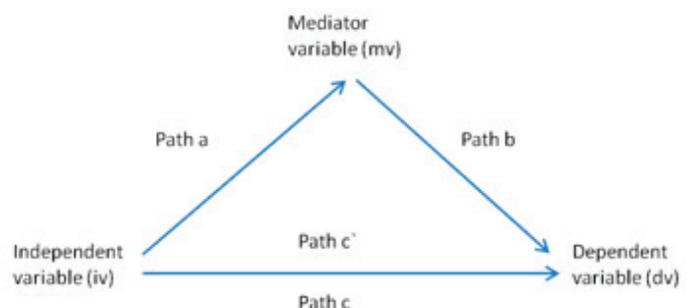


Figure 1 Regression Paths in Mediation Analysis. The mediation model of Baron & Kenny, 1986.²⁴ Criteria for mediation are: (1) significant path c association; (2) significant path a association; (3) significant path b association with a reduction in the path c coefficient (c).

Flowchart of adult participation in the Whyalla Intergenerational Study of Health (WISH)
February 2008 to June 2009

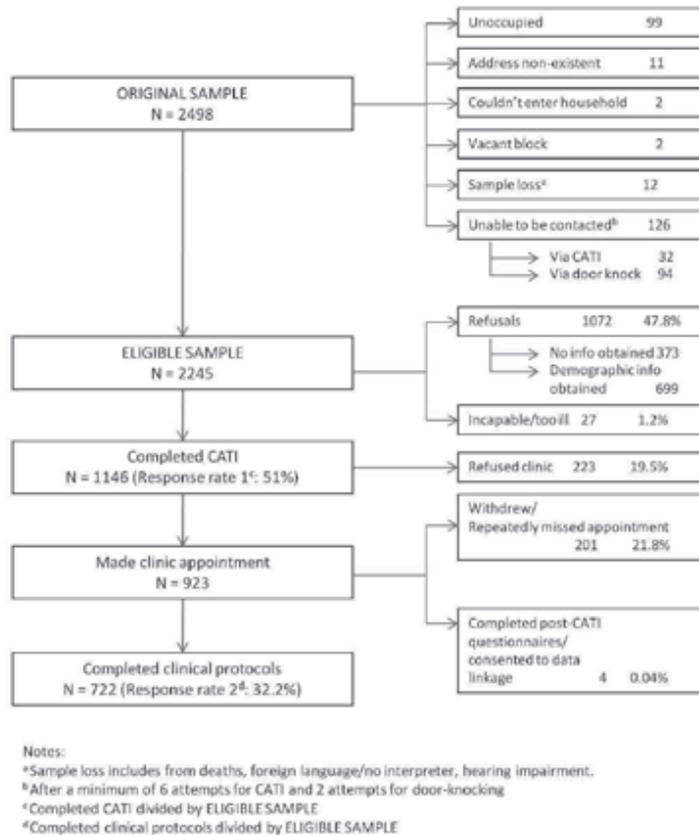


Figure 2. Flowchart of participation in the Whyalla Intergenerational Study of Health (WISH, 2008–2009).

to the manufacturer's protocols with participants supine. Total body fat mass (g) was determined automatically from the manufacturer's software. Total intra-abdominal fat (IAF) mass was estimated by defining a region of interest in the abdomen by drawing quadrilateral box with the base touching the top of the iliac crest, the upper margins touching the most inferior aspect of the ribs and the lateral borders extending to the inner border of the rib cage. IAF percentage was estimated as fat mass / (fat mass + lean mass + bone mineral content) * 100.

Fasting, morning venous blood samples were collected (approximately 40 mL) and assayed by a National Association of Testing Authorities accredited laboratory. Fasting plasma glucose concentrations were measured using a Chemistry analyser system (Olympus AU5400, Olympus Optical C Ltd, Japan) with inter-assay CVs of 2.41% at 3.41 mmol/L and 2.21% at 19.72 mmol/L. Fasting serum insulin concentrations were measured in serum collected, separated and frozen at -80°C within two hours of collection. Radioimmunoassay was performed on an Abbott Architect immunoassay analyzer (Abbott Park, IL USA) with inter-assay CVs of 7.81% at 8.44 mU/L, 5.87% at 57.44 mU/L and 8.53% at 97.90 mU/L. IR was estimated from these two concentrations using the Homeostasis Model Assessment (HOMA2) Microsoft Excel calculator from the University of Oxford Diabetes Trial Unit, which uses the equations of Levy and colleagues.¹⁹ A SDB symptom score (range 0–12) was computed as the sum of symptom frequency from zero (never) to four (>4 times per week) for three symptoms: snorting or gasping; loud snoring; and breathing cessation, choking or struggling for breath during sleep.²⁰

Covariates: Height was determined to within one millimeter using a wall stadiometer (Surgical and Medical Products No. 26SM, Mentone Education Supplies, Melbourne, Australia), body mass was measured to the nearest 100 g with an electronic scale (Tanita BF-681). Smoking status was defined as “never smoker,” “past smoker” and “current smoker.” Gross annual household income was collected in approximate 20,000 Australian Dollar (AUD) increments and reduced to three categories of 40,000 AUD increments for analysis. The number of people residing in the household was categorized as one, two, three, four, and five or more. Medication inventory was performed during clinical assessment and participants were asked if they had taken bronchodilators or any other respiratory medication in the previous 24 hours. Doctor-diagnosis of Obstructive Sleep Apnea Syndrome (OSAS) and management of OSAS with Continuous Positive Airway Pressure (CPAP) therapy was determined by questionnaire.

Statistical analysis: Data analysis was performed using Stata 11 for Windows (StataCorp, College Station TX USA). For prevalence estimates, data were weighted to the age and sex distribution of the Estimated Residential Population of Whyalla in 2007²¹ and the likelihood of being recruited into the study, as per the equation: $\text{weight} = \text{hhld_adult} * (\text{bnh}/\text{lnh}) * (\text{ln}/\text{bn})$; where hhld_adult is the number of people aged 18 and over (adults) residing in the household; bnh is the adult population size of Whyalla by sex and age-group; bn is the total adult population of Whyalla; lnh is the adult sample size of WISH by sex and age-group; and ln is the total adult sample size of the WISH cohort. To calculate the Australian standardized prevalence

ratio (SPR) for current doctor diagnosed asthma in Whyalla, the stratum-specific prevalence estimates from the national standard population data²² were used to calculate the expected number of cases in the study population (WISH). Expected cases were summed across strata, and compared with the number of observed cases, the SPR was calculated as the ratio of observed to expected cases. The same method was used to estimate the SPR's for current and past smoking using 2007–2008 Australian NHS data as the standard population.

Ordinary least squares regression was used to model the associations of IAF with: spirometric outcomes and log-CASS. Prevalence ratios (PR) for the association of IAF with current doctor diagnosed asthma were estimated using Generalized Linear Models with Poisson distribution, log-link function and robust estimation of confidence intervals as suggested by Wolkewitz et al 2007.²³ Formal mediation tests were conducted in Stata 11 using *sgmediation*, which uses bootstrap analyses to estimate the indirect effect of the independent variable on the dependent variable through the mediator variable, overcoming the assumption of a normal sampling distribution required for use of the classical Sobel test. Bootstrap analysis involves drawing a large number of samples, in this case 5000 (with replacement), from the data set, computing the indirect effect for each sample, and then generating an average indirect effect across all samples. Regression paths and criteria for mediation followed those outlined by Baron and Kenny²⁴ and summarized in Figure 1.

Results

Overall, 51% of eligible households participated in the CATI and 32.2% participated in the clinical study (Figure 2). The estimated population prevalence of current doctor-diagnosed asthma was 19.9% [95% CI 16.7 – 23.5%] which was 2.4 times higher than Australian national prevalence estimates after age- and sex-standardization [95%CI for the SPR 2.1 – 2.9]. The prevalence of both current (23% [95% CI 19.6 – 26.7%]; SPR 1.11 [95% CI 0.95 - 1.29]) and past smoking (28.6% [95% CI 25.1 – 32.4%]; SPR 0.96 [95% CI 0.83 - 1.10]) in Whyalla were similar to those of Australia overall.

Of the 726 adults who completed comprehensive questionnaires, 236 men and 348 women (n = 562, 78%) completed baseline and post-bronchodilator spirometric maneuvers of acceptable quality. In total, 98 participants did not complete spirometry tests for various reasons: opted out (n = 29); terminated spirometry protocols early (n = 66); excluded on the basis of illness, injury or doctor's advice (n = 3). Sixty-six participants completed spirometry, but breathing maneuvers were of unacceptable quality to provide valid and reliable data (n = 60) or technical malfunctions were experienced (n = 6).

Post-bronchodilator FEV1/FVC, FEV1, PEF and FEF25%-75% were all lower and there was a non-significant trend towards higher FEV1 reversibility in current doctor-diagnosed asthmatics when compared with non-asthmatics. CASS was higher in current doctor-diagnosed asthmatics when compared with non-asthmatics but it did not differ by spirometry completion or quality grade in either group (Table 1). Neither IR nor SDB symptom scores were higher in the current doctor-diagnosed asthmatics when compared with non-asthmatics, but within the doctor-diagnosed group, IR was higher in those who did not attempt or complete an acceptable spirometry test (Table 1).

Determination of “unacceptable test” was based on either baseline and post-bronchodilator EasyOne system quality control (QC) grade of D or lower, or non-reproducible trials exceeding 3% variability. The analytical sample satisfied a QC grade of C or higher and reproducible trials within 3% variability. †Percentage of Predicted Value (PPV) was based on equations of Gore et al. (1995)¹⁷

Obstructive sleep apnea syndrome (OSAS) had been doctor-diagnosed in 42 participants (5.9%) and 20 of these used CPAP to manage the condition. CPAP use was associated with a lower log CASS (1.18 ± 0.56 v 1.52 ± 0.40 , $p = 0.04$) but non-significant differences in current doctor diagnosed asthma prevalence, IAF, IR, SDB symptom score, post FEV1/FVC and reversibility of FEV1 (data not shown).

Table 2 shows the covariate-adjusted associations of IAF with current doctor-diagnosed asthma, CASS, spirometric outcomes, IR and SDB symptom frequency in men and women who completed acceptable spirometry tests. IAF was not associated with current doctor-diagnosed asthma, FEV1/FVC, FEV1 reversibility, FEF25-75% or PEF and in men or women. A one percent increase in IAF was associated with a significant >1 unit increase in CASS in both men and women (0.006 and 0.009 respectively on the log scale) although the association in men was of borderline significance and was not robust to repeated bootstrap analysis. The associations of CASS with both FEV1/FVC and FEV1 were different between men and women. For every log-unit increase in CASS FEV1/FVC declined by 4% ($p < 0.001$) and FEV1 by 295 mL in men ($p = 0.007$) but there were no associations in women.

Associations of intra-abdominal fat percentage with lung function and asthma outcomes, and hypothesized mediators (sleep disordered breathing score and insulin resistance) in men and women, The Whyalla Intergenerational Study of Health (WISH, 2008–2009). FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IR, insulin resistance (HOMA2); SDB, sleep-disordered breathing. Covariates included in all models were age, current and past smoking, gross annual household income and number of household residents. For lung function models height and respiratory medication in the previous 24 hours were included as covariates. A one percent increase in IAF was associated with a 12 ml and 20 mL decrease in FEV1 and FVC respectively in men and a 4 ml and 7 mL decrease respectively in women. This corresponded to reductions in the percentage of predicted value for FEV1 of 34% in men and 16% in women; and for FVC of 46% in men and 24% in women. IAF was positively associated with IR and SDB symptom frequency in both men and women, although the significance of the association at $p < 0.05$ between SDB and IAF in women was not robust to repeated bootstrap analysis.

The significant associations of IAF with CASS, FEV1 and FVC were tested for mediation by IR and SDB symptom frequency in men and women. After adjustment for IAF, IR was not associated with any of the three outcomes in men or women (path b, data not shown) and thus did not meet the necessary criteria for mediation. In men, after adjustment for IAF, SDB frequency was significantly associated with FEV1 and FVC (path b) and mediated between 12% and 26% of the associations with IAF (Table 3). The small total “effect” (association) between IAF and CASS in men did not reach significance during mediation analysis and thus the 65% mediation of that association is of

Table 3 Mediation by sleep-disordered breathing symptom frequency of associations of intra-abdominal fat with comprehensive asthma symptom score, FEV1 and FVC expressed as Litres and 'percentage of predicted values' (PPV) in men and women, The Whyalla Intergenerational Study of Health (WISH, 2008–2009).

Dependent variables (dv)	Path a mv regressed on IAF	Path b dv regressed on mv controlling for IAF	Total effect (Path c) dv regressed on IAF	Direct effect (Path c') dv regressed on IAF controlling for mv	Bootstrapped Indirect Effect	% Mediated
MEN						
log CASS, <i>n</i> = 178	0.060 (0.025, 0.094)	0.061 (0.027, 0.095)	0.006 (−0.002, 0.013)	0.002 (−0.006, 0.010)	0.004 (0.001, 0.007)	64.7
post FEV ₁ , <i>n</i> = 178						
Litres	0.060 (0.025, 0.094)	−0.047 (−0.080, −0.014)	−0.012 (−0.019, −0.005)	−0.009 (−0.017, −0.002)	−0.003 (−0.006, −0.001)	23.4
PPV (<i>Gore et al.</i> [17])	0.061 (0.026, 0.096)	−1.462 (−2.370, −0.555)	−0.344 (−0.553, −0.135)	−0.255 (−0.466, −0.045)	−0.087 (−0.187, −0.026)	25.8
post FVC, <i>n</i> = 176						
Litres	0.060 (0.026, 0.095)	−0.040 (−0.079, −0.002)	−0.020 (−0.029, −0.011)	−0.018 (−0.027, −0.009)	−0.002 (−0.006, −0.000)	12.1
PPV (<i>Gore et al.</i> [17])	0.061 (0.026, 0.096)	−1.271 (−2.104, −0.439)	−0.467 (−0.658, −0.275)	−0.389 (−0.583, −0.196)	−0.076 (−0.154, −0.025)	16.6
WOMEN						
log CASS, <i>n</i> = 271	0.024 (−0.001, 0.049)	0.054 (0.023, 0.085)	0.010 (0.003, 0.016)	0.008 (0.002, 0.015)	0.001 (0.000, 0.003)	13.7
post FEV ₁ , <i>n</i> = 267						
Litres	0.021 (−0.004, 0.047)	−0.018 (−0.044, 0.009)	−0.005 (−0.010, 0.001)	−0.004 (−0.010, 0.002)	−0.000 (−0.002, 0.000)	8.5
PPV (<i>Gore et al.</i> [17])	0.021 (−0.004, 0.047)	−0.821 (−1.810, 0.167)	−0.204 (−0.409, 0.001)	−0.186 (−0.392, 0.020)	−0.019 (−0.066, 0.001)	8.6
post FVC, <i>n</i> = 254						
Litres	0.022 (−0.005, 0.048)	−0.013 (−0.044, 0.019)	−0.008 (−0.014, −0.001)	−0.007 (−0.014, −0.001)	−0.000 (−0.002, 0.000)	3.7
PPV (<i>Gore et al.</i> [17])	0.021 (−0.005, 0.048)	−0.587 (−1.551, 0.377)	−0.263 (−0.461, −0.064)	−0.250 (−0.449, −0.051)	−0.013 (−0.065, 0.006)	4.8

little significance. In women, associations between the SDB and IAF were weak and of borderline significance corresponding to relatively minor indirect effects.

Mediation by sleep-disordered breathing symptom frequency of associations of intra-abdominal fat with comprehensive asthma symptom score, FEV1 and FVC expressed as volumes and 'percentage of predicted values' (PPV) in men and women, The Whyalla Intergenerational Study of Health (WISH, 2008–2009) CASS, comprehensive asthma symptom score; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PPV, Percentage of Predicted Value. Criteria for mediation are: (1) significant path c association; (2) significant path a association; (3) significant path b association with a reduction in the path c coefficient (c'). Covariates included in all models were age, current and past smoking, gross annual household income and number of household residents. For lung function models height and respiratory medication in the previous 24 hours were included as covariates.

Discussion

In this population there was little evidence to support the existence of an obesity-induced obstructive airway phenotype. These findings are inconsistent with the previously documented associations between central obesity and asthma, particularly mild non-atopic asthma phenotypes.^{1-3,25} This may suggest the dominance of other asthma-causing agents over obesity in this population. The only indication of a link between abdominal adiposity and asthma was the association between greater IAF and more frequent asthma symptoms, particularly in women where there was no relation to measured airway obstruction. Thus, this association may be partly explained by greater perceived exertion from daily physical tasks in more abdominally obese people rather than true airway obstruction.

The contribution of the high prevalence of abdominal obesity to the relative 2.4 case excess of current doctor-diagnosed asthma in this community would appear therefore to be low and instead be dominated by non-obesity induced phenotypes. Asthma symptoms were higher and post-bronchodilator lung function was poorer in those who reported a current doctor-diagnosis of asthma, but as previously noted asthma symptom scores were poorly correlated with measured airway obstruction in women,

who were significantly more likely than men to report a current doctor-diagnosis of asthma. Anecdotally, there is high awareness of respiratory disease in this city which may contribute to greater knowledge of respiratory symptoms, higher levels of help-seeking by those experiencing respiratory symptoms (which may be biased towards women) and more widespread asthma screening and diagnosis by general practitioners. In terms of other potentially contributing population factors, the city has a greater than twenty percent enrichment of blue-collar workers when compared with South Australia and Australia overall,²⁶ who are largely employed in the steel industry. This may confer significantly more occupational asthma on the population over and above the 15% of cases in working aged adults estimated to be either caused or aggravated by occupational exposures from previous research.²⁷ The degree to which occupational exposures, environmental dust exposure or other population factors such as asthma awareness (population and general practitioners) and vigilance in help-seeking contribute to the excess of, and gender difference in, current doctor-diagnosed asthma remains to be determined in this community which has implications for community interventions on asthma.

IAF was, however, associated with FEV1 and FVC in the Whyalla population. Based on age-related rates of decline in lung volumes from the US National Health and Nutrition Examination Survey (NHANES)²⁸ a five percent increase in IAF (adjusted for IR or SDB symptom frequency) was equivalent to two years of age-related decline in the FEV1 (60 ml) and more than three years of age-related decline in the FVC (100 ml) of men; the effects were up to three times smaller in women. These associations, including being three to four times weaker in women compared with men, were of similar magnitude to those of other studies,^{25,29-31} although the range of adiposity measures used make cross-study comparisons difficult.

We did not observe the inverse association between IR and expired lung volumes previously reported in cross-sectional studies of other populations.^{32,33} Prospective studies have shown that reduced lung function can precede the development of IR and diabetes³⁴⁻³⁹ possibly through microangiopathy of alveolar capillaries and pulmonary arterioles.^{40,41} Thus it is possible that the absence of a cross-sectional association between lung function and IR in this study may be due to healthy-participant

bias. If those with more advanced disease (reduced lung function) and IR, were less likely to participate due to poor health (or having died) than those with earlier stage reductions in lung function without IR, then the association between lung function and IR would be underestimated.

Associations between IAF and SDB symptom frequency were weaker in women than in men and had negligible mediating effects on FEV1, FVC or CASS. In men however, SDB symptom frequency mediated between 12% and 17% of the association of IAF with FVC and between 23% and 26% of the association with FEV1. This finding is inconsistent with two small studies ($n \leq 20$) that suggested six to eight weeks of continuous positive airway pressure treatment for sleep apnea was not effective in improve spirometric measures of lung function^{42,43} but improved asthma symptoms. These studies were unlikely to have been powered to detect meaningful changes in these outcomes, but they do raise caution about interpreting causal directions from these cross-sectional findings.

There is no universally applied clinical definition of asthma and case assignment in epidemiological studies is often defined by self-reported doctor-diagnosis, which has good sensitivity (91%), specificity (97%) and reasonable positive predictive value (60%) for indicating prevalent disease.⁴⁴ The combination of measured lung function, self-reported asthma symptom frequency and doctor-diagnosed current asthma as outcomes; and the specific focus on intra-abdominal fat estimated using DXA measurements as opposed to most other studies which have relied on BMI or waist girths as measures of adiposity are particular strengths of this study. Assessment of SDB was limited to self-reported symptom frequencies which have good sensitivity (85%) but poor specificity (55%) for identifying men with obstructive sleep apnea.²⁰

In terms of potential selection bias, this cohort was 10% under-represented by state-administered housing residents which, due to greater odds of current doctor-diagnosed asthma in lower-income households combined with greater odds of abdominal obesity and diabetes in households with gross annual income below 40,000 AUD in this community (unpublished observations), would theoretically result in an underestimate of the true abdominal adiposity-current doctor diagnosed asthma association. However, given the strength of the null finding it is unlikely that elimination of this potential bias would shift the association to a degree which would result in statistical or clinical significance. In Table 1, we showed that within the current doctor-diagnosed asthmatics, IR was higher in those who did not attempt or complete an acceptable spirometry test. As stated previously, if those asthmatics with more severe IR for which acceptable quality spirometric data were not available also had poorer lung function, than those without IR, then the association between lung function and IR would theoretically be underestimated. However, Table 1 also reveals evidence that CASS did not differ by spirometry completion or quality grade in either current doctor-diagnosed asthmatics or non-asthmatics which suggests non-completion of successful spirometry was not dependent on greater obstructive airway symptom severity indicating that this may in fact not be a source of bias.

Conclusions

In this population with a high prevalence of abdominal obesity and an excess of doctor-diagnosed asthma, IAF was not a major factor in doctor-diagnosed asthma or airway obstruction

although women with higher IAF perceived more severe asthma symptoms which did not correlate with lower FEV1. Higher IAF was significantly associated with lower FEV1 and FVC and in men SDB mechanisms may contribute up to one quarter of this association.

References

- 1 Chen Y, Rennie D, Cormier Y, Dosman J: Sex specificity of asthma associated with objectively measured body mass index and waist circumference: the Humboldt study. *Chest* 2005, 128:3048–3054.
- 2 Chen Y, Dales R, Jiang Y: The association between obesity and asthma is stronger in nonallergic than allergic adults. *Chest* 2006, 130:890–895.
- 3 Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE: Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol* 2006, 118:1284–1291.
- 4 Raviv S, Dixon AE, Kalhan R, Shade D, Smith LJ: Effect of obesity on asthma phenotype is dependent upon asthma severity. *J Asthma* 2011, 48:98–104.
- 5 Lugogo NL, Kraft M, Dixon AE: Does obesity produce a distinct asthma phenotype? *J Appl Physiol* 2010, 108:729–734.
- 6 Sutherland TJ, Goulding A, Grant AM, Cowan JO, Williamson A, Williams SM, Skinner MA, Taylor DR: The effect of adiposity measured by dual-energy X-ray absorptiometry on lung function. *Eur Respir J* 2008, 32:85–91.
- 7 Choi JH, Park S, Shin YH, Kim MY, Lee YJ: Sex differences in the relationship between metabolic syndrome and pulmonary function: The 2007 Korean National Health and Nutrition Examination Survey. *Endocr J* 2011, 58:459–65.
- 8 Hickson DA, Burchfiel CM, Liu J, Petrini MF, Harrison K, White WB, Sarpong DF: Diabetes, impaired glucose tolerance, and metabolic biomarkers in individuals with normal glucose tolerance are inversely associated with lung function: the Jackson Heart Study. *Lung* 2011, 189:311–321.
- 9 Haren MT, Misan G, Grant JF, Buckley JD, Howe PRC, Newbury J, Taylor AW, McDermott RA: Proximal correlates of metabolic phenotypes during 'at-risk' and 'case' stages of the metabolic disease continuum. *Nutrition and Diabetes* 2012, 2:e24.
- 10 Haren MT, Stokes A, Taylor J, McDermott RA: Community participation in the Whyalla Intergenerational Study of Health (WISH): looking back on the possible influences of knowledge, trust and power. *Public Health Bulletin SA* 2011, 8:41–48.
- 11 South Australian Department of Health: The Whyalla Health Impact Study. Adelaide: South Australian Department of Health; 2006.
- 12 Dal Grande E, Taylor AW: Sampling and coverage issues of telephone surveys used for collecting health information in Australia: results from a face-to-face survey from 1999 to 2008. *BMC Med Res Methodol* 2010, 10:77.
- 13 Dillman DA: Mail and telephone surveys: The total design method. New York: Wiley-Interscience (Wiley & Sons); 1978.
- 14 Grant JF, Chittleborough CR, Taylor AW, Dal Grande E, Wilson DH, Phillips PJ, Adams RJ, Cheek J, Price K, Gill T, Ruffin RE: The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort for selected chronic diseases. *Epidemiol Perspect Innov* 2006, 3:4.
- 15 American Thoracic Society: Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995, 152:1107–1136.
- 16 Walters JA, Wood-Baker R, Walls J, Johns DP: Stability of the EasyOne ultrasonic spirometer for use in general practice.

- Respirology 2006, 11:306–310.
- 17 Gore CJ, Crockett AJ, Pederson DG, Booth ML, Bauman A, Owen N: Spirometric standards for healthy adult lifetime nonsmokers in Australia. *Eur Respir J* 1995, 8:773–782.
 - 18 Australian Centre for Asthma Monitoring (ACAM): Survey questions for monitoring national asthma indicators. In *Survey questions for monitoring national asthma indicators* (Australian Institute of Health and Welfare ed.). Canberra; 2007.
 - 19 Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998, 21:2191–2192.
 - 20 Maislin G, Pack AI, Kribbs NB, Smith PL, Schwartz AR, Kline LR, Schwab RJ, Dinges DF: A survey screen for prediction of apnea. *Sleep* 1995, 18:158–166.
 - 21 Australian Bureau of Statistics: Population by age and sex South Australia (2007). Canberra: Commonwealth of Australia; 2008.
 - 22 Australian Centre for Asthma Monitoring (ACAM): Asthma in Australia 2008. (Australian Institute of Health and Welfare ed.). Canberra; 2008.
 - 23 Wolkewitz M, Bruckner T, Schumacher M: Accurate variance estimation for prevalence ratios. *Methods Inf Med* 2007, 46:567–571.
 - 24 Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986, 51:1173–1182.
 - 25 Chen Y, Rennie D, Cormier YF, Dosman J: Waist circumference is associated with pulmonary function in normal-weight, overweight, and obese subjects. *Am J Clin Nutr* 2007, 85:35–39.
 - 26 Australian Bureau of Statistics (ABS): Population and Housing Census: Basic Community Profile, 2006. In *Book Population and Housing Census: Basic Community Profile, 2006* (ABS ed.). Canberra: 2006.
 - 27 Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C: Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005, 62:290–299.
 - 28 Berclaz PY, Gao H, Tobian JA, Swanson DL, Webb DM, Crapo RO, Jensen RL: The impact of diabetes and age on pulmonary function: data from the National Health and Nutrition Examination Survey. *Diabetes Res Clin Pract* 2009, 83:e1–e3.
 - 29 Canoy D, Luben R, Welch A, Bingham S, Wareham N, Day N, Khaw KT: Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. *Am J Epidemiol* 2004, 159:1140–1149.
 - 30 Rossi A, Fantin F, Di Francesco V, Guariento S, Giuliano K, Fontana G, Micciolo R, Solerte SB, Bosello O, Zamboni M: Body composition and pulmonary function in the elderly: a 7-year longitudinal study. *Int J Obes (Lond)* 2008, 32:1423–1430.
 - 31 Rossi AP, Watson NL, Newman AB, Harris TB, Kritchevsky SB, Bauer DC, Satterfield S, Goodpaster BH, Zamboni M: Effects of body composition and adipose tissue distribution on respiratory function in elderly men and women: the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci* 2011, 66:801–808.
 - 32 McKeever TM, Weston PJ, Hubbard R, Fogarty A: Lung function and glucose metabolism: an analysis of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2005, 161:546–556.
 - 33 Lawlor DA, Ebrahim S, Smith GD: Associations of measures of lung function with insulin resistance and Type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004, 47:195–203.
 - 34 Engstrom G, Janzon L: Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* 2002, 19:167–170.
 - 35 Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L: Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Intern Med* 2003, 253:574–581.
 - 36 Lazarus R, Sparrow D, Weiss ST: Impaired ventilatory function and elevated insulin levels in nondiabetic males: the Normative Aging Study. *Eur Respir J* 1998, 12:635–640.
 - 37 Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ: Association between glycemic state and lung function: the Framingham Heart Study. *Am J Respir Crit Care Med* 2003, 167:911–916.
 - 38 Lange P, Parner J, Schnohr P, Jensen G: Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. *Eur Respir J* 2002, 20:1406–1412.
 - 39 Lazarus R, Sparrow D, Weiss ST: Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. *Eur Respir J* 1998, 12:641–645.
 - 40 Vracko R, Thorning D, Huang TW: Basal lamina of alveolar epithelium and capillaries: quantitative changes with aging and in diabetes mellitus. *Am Rev Respir Dis* 1979, 120:973–983.
 - 41 Klein OL, Krishnan JA, Glick S, Smith LJ: Systematic review of the association between lung function and Type 2 diabetes mellitus. *Diabet Med* 2010, 27:977–987.
 - 42 Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktas H: Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. *Respir Med* 2005, 99:529–534.
 - 43 Lafond C, Series F, Lemiere C: Impact of CPAP on asthmatic patients with obstructive sleep apnoea. *Eur Respir J* 2007, 29:307–311.
 - 44 Oksanen T, Kivimaki M, Pentti J, Virtanen M, Klaukka T, Vahtera J: Self-report as an indicator of incident disease. *Ann Epidemiol* 2010, 20:547–554.

Changes in Blood Hemoglobin and Blood Gases PaO₂ and PaCO₂ in Severe COPD over a Three-year Telemonitored Program of Long-term Oxygen Treatment

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Abstract

Background: Information on the effects of long-term oxygen treatment (LTOT) on blood hemoglobin (Hb) in severe COPD are limited. The aim was to assess blood Hb values in severe COPD, and investigate the time-course of both Hb and blood gas changes during a 3-year telemetric LTOT.

Methods: A cohort of 132 severe COPD patients (94 males; 71.4 years \pm 8.8 sd), newly admitted to the tele-LTOT program, was investigated. Subjects were divided according to their original blood Hb: group A: <13 g/dL; group B: $\geq 13 < 15$ g/dL; group C: $\geq 5 < 16$ g/dL; group D: ≥ 16 g/dL. Blood Hb (g/dL), PaO₂ and PaCO₂ (mmHg), SaO₂ (%), and BMI were measured at LTOT admission (t₀), and at least quarterly over three years (t₁-t₃). Wilcoxon test was used to compare t₀ vs t₁ values; linear regression to assess a possible Hb-BMI relationship; ANOVA to compare changes in Hb time-courses over the 3 years.

Results: LTOT induced a systematic increase of PaO₂, and changes were significant since the first year (from 52.1 mmHg \pm 6.6sd to 65.1 mmHg \pm 8.7 sd, $p < 0.001$). Changes in SaO₂ were quite similar. Comparable and equally significant trends were seen in all subgroups ($p < 0.001$). PaCO₂ dropped within the first year of LTOT (from 49.4 mmHg \pm 9.1sd to 45.9 mmHg \pm 7.5 sd, $p < 0.001$): the t₀-t₁ comparison proved significant ($p < 0.01$) only in subgroups with the highest basal Hb, who showed a further PaCO₂ decline over the remaining two years ($p < 0.001$). Hb tended to normalization during LTOT only in subgroups with basal Hb > 15 g/dl (ANOVA $p < 0.001$); anemic subjects (Hb < 13 g/dl) ameliorated not significantly in the same period (ANOVA = 0.5). Survival was independent of the original blood Hb. Anemia and polyglobulia are differently prevalent in COPD, the latter being the most represented in our cohort. LTOT affected both conditions, but to a different extent and according to different time-courses. The most striking Hb improvement was in polyglobulic patients in whom also PaO₂, PaCO₂ and SaO₂ dramatically improved. In anemic subjects effects were smaller and slower, oxygenation being equally ameliorated by LTOT.

Conclusions: LTOT effects on Hb and PaCO₂ are regulated by an Hb-dependent gradient which seems independent of the original impairment of blood gases and of effects on oxygenation.

Background

Chronic obstructive pulmonary disease (COPD) is currently defined as characterized by airflow limitation which is not fully reversible and able to produce systemic consequences (Global Initiative for Chronic Obstructive Lung Disease¹).

Besides its effect on lung function, the chronic impairment of the respiratory system due to COPD has long-term multi-organ consequences on the bone and liver metabolism, heart and cardiovascular system, brain, kidney, and skeletal muscles.

Many chronic diseases have been shown to affect hematopoiesis, and also COPD may be associated to this kind of disorder which represents further aspects of the multiple involvement of the disease.

Even though COPD had in the past been commonly regarded as a determinant of polyglobulia rather than of anemia,² it is currently thought that the latter condition occurs more frequently than expected (in 10-15% of severe COPD patients),³ and it is presumed to be associated with ongoing inflammation, altered erythropoietin function, and poor marrow production.⁴

There is still limited information concerning the distribution of blood hemoglobin (Hb) concentrations in the COPD population,^{3,5,6} although both the direct contribution of anemia in causing breathlessness and the tendency to a secondary polyglobulia have long been accepted in severe COPD.² On the other hand, limited information is available concerning the effects of long-term domiciliary oxygen treatment on Hb and concomitantly on blood gases in these circumstances.⁷

The present study aimed to assess the distribution of blood Hb values in a population of severe COPD patients with chronic respiratory failure, and to investigate the time course of both Hb and blood gas changes during a 3-year program of telemonitored long-term oxygen therapy (LTOT).

Methods

A cohort of 132 consecutive non-smoker (87.1% former smoker), severe COPD patients was studied (94 males; mean age 71.4 years \pm 8.8 sd). All patients had been admitted as first-time candidates to the domiciliary LTOT program over the last

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Table 1 Mean basal values ± sd for lung function, blood gases, Hb and BMI (n = 132) in the study group

	Whole sample (n = 132)	Males (n = 94)	Females (n = 38)
FEV ₁ % pred.	35.3 ± 11.8	36.6 ± 16.4	35.7 ± 14.1
FVC% pred.	60.2 ± 10.7	59.2 ± 13.5	62.5 ± 19.3
FEV ₁ /FVC%	58.3 ± 8.1	61.8 ± 7.9	57.1 ± 8.6
pH	7.41 ± 0.05	7.40 ± 0.05	7.41 ± 0.04
PaO ₂ mm Hg	52.1 ± 6.6	52.2 ± 6.5	51.8 ± 7.1
PaCO ₂ mm Hg	49.4 ± 9.1	48.9 ± 8.9	50.5 ± 9.5
HCO ₃ mmol/L	30.5 ± 4.5	30.0 ± 3.9	31.4 ± 5.5
SaO ₂ %	86.3 ± 5.7	86.5 ± 5.7	85.8 ± 6.0
Hb g/dL	15.1 ± 1.9	15.4 ± 2.0	14.5 ± 1.8
BMI	27.4 ± 6.8	27.8 ± 6.9	26.5 ± 6.8

BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Hb, Hemoglobin; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; SaO₂, oxyhemoglobin saturation.

three years (2008-2010) and were selected from the dedicated institutional database (ISO 9001-2000 certified since 1999).⁸ In order to avoid possible bias in the study, both the selection procedures and the subsequent creation and management of the data bank were outsourced to IT professionals employed by a third party, i.e. not working in the Lung Department. All COPD patients had a requirement of LTOT according to our regional guideline; they were managed according to daily telemonitoring of vital signs (such as heart rate, SAP, DAP, oxygen saturation (SaO₂), oxygen consumption) and compliance to oxygen therapy, by a program which has been operating in our Lung Department for a number of years (Contel System, Air Liquide – VitalAire SA, Paris, France).⁹ From the point of view of their basic pharmacological respiratory treatment (directly delivered by the Lung Department on a regular basis), 96.2% of patients (127/132) were daily assuming long-acting β₂-adrenergics (LABA) and long-acting anti-cholinergics (LAMA), and 91.7% (121/132) were also assuming inhaled corticosteroids (ICS). All patients were also using diuretics (furosemide) and were equally supplemented with vitamins and other nutritional supports (essential amino acids).¹⁰ Their adherence to both oxygen (an average consumption of 2.3 L/min liquid oxygen ± 0.8 sd, for at least 17 hours/day; range 0.5-3.0 L/min) and pharmacological treatments was assessed monthly by professional caregivers, and defined as very good (>75% of the prescribed doses in all subjects). The mean % patients' survival at three years and the mean prevalence/patient of comorbidities (e.g. due to cardiovascular, metabolic, renal, gastrointestinal and neurological causes) were also measured.

Blood Hb (g/dL), PaO₂ and PaCO₂ (mm Hg), SaO₂ (%), and BMI were measured in each patient at admission to the telmonitored

Table 2 Distribution of subjects in the four subgroups according to their basal hemoglobin (Hb) values, and corresponding mean Hb values ± sd

Subgroups	n (%)	Hb (mean ± sd)
A (< 13 g/dL)	15/132 (11.3%)	11.7 g/dL ± 0.9
B (≥ 13 < 15 g/dL)	42/132 (31.8%)	14.1 g/dL ± 0.5
C (≥ 15 < 16 g/dL)	41/132 (31.1%)	15.4 g/dL ± 0.3
D (≥ 16 g/dL)	34/132 (25.8%)	17.5 g/dL ± 1.3

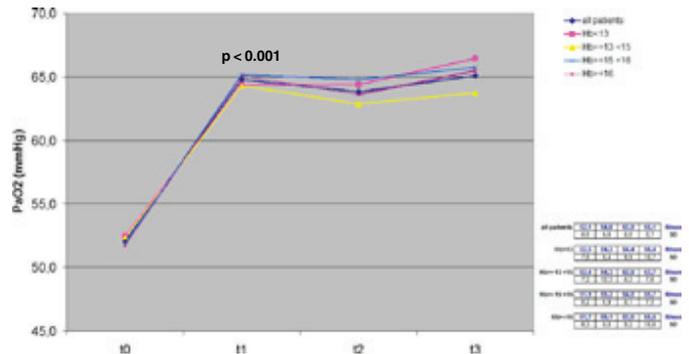


Figure 1. Time course of PaO₂ values in the whole cohort and in each subgroup: t test between t₀ and t₁. Hb, hemoglobin; PaO₂, partial pressure of arterial oxygen.

LTOT program (t₀), and at least three times/year over the following three years (t₁-t₃). Each variable was expressed yearly as mean ± sd of all measurements performed in the period.

The whole cohort was then divided into four subgroups, according to the subjects' original blood Hb: group A: < 13 g/dL; group B: ≥ 13<15 g/dL; group C: ≥ 15<16 g/dL; group D: ≥ 16 g/dL.

For statistical analysis the Wilcoxon test was used to compare t₀ vs. t₁ values of all variables, linear regression was used to compare Hb and BMI values, and ANOVA to compare changes in Hb time courses of the entire sample and of each subgroup over the 3-year period; p<0.05 was assumed as the minimum level of significance.

Results

Basal lung function, blood gases, and Hb measured in the whole population are reported in Table 1, while the distribution of patients within the four subgroups together with their corresponding mean blood Hb values are reported in Table 2. Mean basal Hb level was lower in females by 0.8 g/dL, and this difference was maintained during the entire survey (p = ns). In the entire cohort, 18.2% of patients (24/132; 15 males) had a mean BMI < 23 kg/m², while clearly pathological Hb levels were found in only 37.1% of patients (49/132), anemic subjects being less numerous than polyglobulic subjects (11.3% vs. 25.8%, respectively). No significant gender differences were found.

Trends for PaO₂, PaCO₂, SaO₂, BMI and Hb measured over the 3-year period in the whole cohort and in the four subgroups with different basal Hb levels are reported in Figures 1, 2, 3, 4, 5.

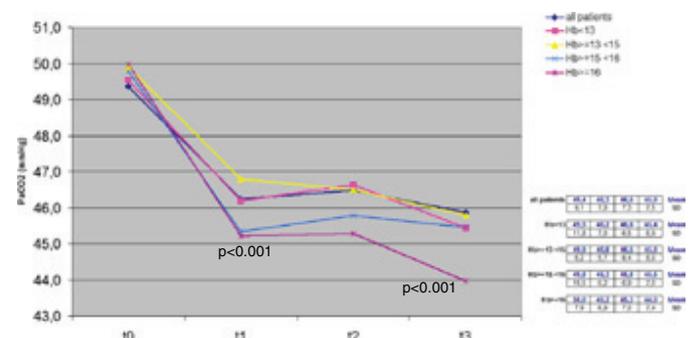


Figure 2 Time course of PaCO₂ values in the whole cohort and in each subgroup: t test between t₀ and t₁. Hb, hemoglobin; PaCO₂, partial pressure of arterial carbon dioxide.

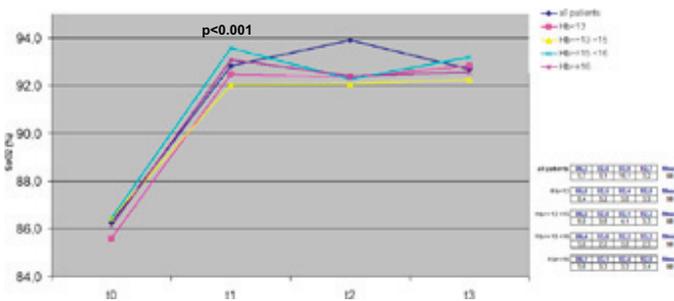


Figure 3. Time course of SaO₂ values in the whole cohort and in each subgroup: t test between t₀ and t₁. Hb, hemoglobin; SaO₂, oxyhemoglobin saturation.

LTOT induced a systematic increase of arterial PaO₂ in all patients, and changes proved highly significant already within the first year of LTOT (from 52.1 mm Hg ± 6.6 sd to 65.1 mm Hg ± 8.7 sd, $p < 0.001$); then PaO₂ values remained unchanged over the remaining two years. The corresponding trends in each subgroup were comparable to that of the whole cohort, and the comparison between t₀ and t₁ mean values was equally statistically significant in all subgroups ($p < 0.001$) (Figure 1). A quite similar time course was observed for SaO₂ (Figure 2).

Also the great proportion of changes of arterial PaCO₂ measured in the entire cohort of patients occurred within their first year of LTOT (from 49.4 mm Hg ± 9.1 sd to 45.9 mm Hg ± 7.5 sd, $p < 0.001$). In this case, the corresponding PaCO₂ trends in each subgroup were very similar to that of the entire cohort, but the comparison between t₀ and t₁ mean values proved statistically significant only in group C and D, such as in those with the highest original Hb values (from 49.8 mm Hg ± 10.5 sd to 45.3 mm Hg ± 6.2 sd; $p < 0.05$, and from 49.9 ± 7.9 sd to 45.2 mm Hg ± 6.9 sd; $p < 0.01$, respectively). Moreover, subgroup D (i.e. subjects with basal Hb > 16 g/dL) showed the highest drop in arterial PaCO₂ at t₁, and also showed a further progressive PaCO₂ decline towards normal values over the remaining two years of LTOT ($p < 0.001$) (Figure 3).

BMI proved significantly related to Hb values in basal condition ($p < 0.03$; $r = 0.23$). The general trends of BMI for the whole population and the four different subgroups persisted without any significant change over the total 3-year control period (Figure 4).

All changes measured in Hb values are summarized in Figure 5. Differently from the time course (absolutely flat) registered in the whole cohort, peculiar trends were measured in the four subgroups. In particular, Hb values tended to drop (ie to normalize) since the first year of LTOT in those subgroups originally characterized by the highest mean Hb values (ie > 15 g/dL) (ANOVA $p < 0.001$). On the other hand, the anemic subgroup

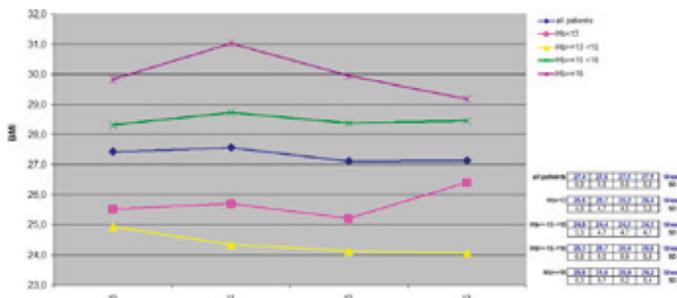


Figure 4. Time course of BMI values in the whole cohort and in each subgroup. BMI, body mass index; Hb, haemoglobin.

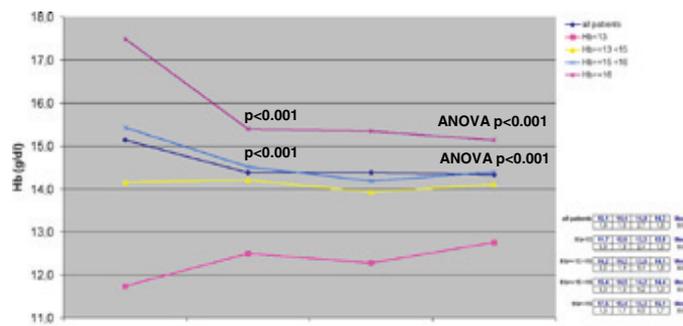


Figure 5. Time course of Hb values in the whole cohort and in each subgroup: t test between t₀ and t₁, and anova over time. Hb, haemoglobin.

(Hb < 13 g/dL) showed a progressive but not significant (ANOVA = 0.5) increase of Hb mean values over the 3-year period; the highest change occurred within the first year also in these subjects even though the variation never reached statistical significance ($p < 0.08$).

Finally, the overall survival was 73.4% at three years: 73.3% in group A; 71.4% in group B; 73.2% in group C, and 76.5% in group D ($p = ns$), while the overall prevalence of comorbidities was 2.0/patient in the cohort: 2.2/p in group A; 1.9/p in group B; 2.0/p in group C, and 2.1/p in group D, respectively.

Discussion

Lung function and blood hemoglobin have been investigated extensively in COPD, and continuous long-term oxygen treatment (>15 hours/day) is generally regarded as of significant benefit in hypoxic patients suffering from COPD.¹¹

Nevertheless, the true mechanisms underlying the improved clinical outcomes (eg hospitalization rate, QoL, or survival) during LTOT still have to be clarified, although it is well known since long ago that long-term oxygen decreases hematocrit values, pulmonary vascular resistances, and improves brain performance.^{12,13}

Anemia and polyglobulia are conditions differently represented in COPD, the latter being the most prevalent in our cohort. Several mechanisms have been suggested to explain the former condition, such as the shortening of red blood cell lifespan and sequestration of iron in macrophages, which can lead to the so-called “anemia of chronic disease” (ACD).^{14,15} ACD represents a further aspect of the multiple involvement of COPD and is presently regarded as an immune driven abnormality that occurs in many inflammatory diseases.³ It is a condition which is associated with increased morbidity and mortality in chronic renal failure,^{16,17} congestive heart failure,¹⁸⁻²⁰ HIV and hepatitis C infection,²¹⁻²³ digestive disease,^{3,24} and cancer.²⁵ Furthermore, anemia is also associated with disability, impaired physical performance, lower muscle strength in individuals over 65 yrs of age,⁶ and reduced health-related quality of life (HRQL). Recent reports suggest that anemia is highly prevalent in patients with COPD and associated with increased mortality.^{6,26}

Polyglobulia had been traditionally accepted as a secondary event due to chronic hypoxemia occurring in a great proportion of COPD patients;^{2,27} nevertheless, it has been supposed that the normal values found in the majority of COPD patients are the result of a balance between the trend towards a decreased red cell mass and an opposite trend towards an increased red cell

mass due to the erythropoietic effect of erythropoietin in these subjects.²⁸

Concerning the prevalence of these two conditions, the anemic condition was found in 11.3% while polyglobulia was found in 25.8% of patients of the present study, and these findings are in good agreement with the current literature.^{3,26,29,30}

LTOT proved to affect both conditions in our cohort, but to at different extent and according to different time courses. In particular, the most striking changes in Hb values were obtained in polyglobulic patients in whom >90% of the effect (ie a decrease) was seen within the first year of LTOT. In these patients, also PaO₂, PaCO₂ and SaO₂ dramatically improved in the same period; only PaCO₂ showed a further, progressive decrease compared to the original Hb values over the remaining two years of the survey.

On the contrary, the effect of LTOT on anemic subjects was smaller and much slower. Actually, these patients were originally characterized by a lower BMI (25.5 vs. 28.3 and 29.8 kg/m² of patients with Hb values >15 g/dL), and required a longer period (a further couple of years) for an improvement to be seen in both their Hb and BMI, thus emphasizing the crucial role of metabolic and nutritional aspects. On the other hand, the prognostic value of an improved nutritional status has been demonstrated in severe COPD to be mainly related to the increase in BMI and other related indices:³¹ BMI values proved directly related to Hb values in our population during LTOT, particularly in the anemic subgroup during the third year of the survey (Figures 4 and 5), thus emphasizing the possible role of LTOT in ameliorating the nutritional status (Hb included) of anemic subjects.

Moreover, even though oxygenation resulted equally improved by LTOT in polyglobulic and anaemic patients, the latter subset of subjects obtained a smaller and delayed benefit from LTOT in terms of PaCO₂ amelioration, likely due to their original lower Hb content in blood. In other words, the present data suggest the presence of an Hb-dependent gradient in the LTOT effect on Hb, which appears to be independent of the extent of the original impairment of blood gases.

These data tend to confirm those from a previous study carried out on 13 non selected subjects in whom no benefits were obtained in terms of changes in Hb and hematocrit in COPD patients admitted to LTOT for two years, even though their QoL and both anxiety and depression scores improved significantly.³²

The present data are not in agreement with the evidence of poorer outcomes and survival at three years in COPD patients with anemia (hematocrit <35%) when compared to those with polyglobulia (24% vs. 70%, respectively).²⁶ In particular, in our cohort of 132 severe COPD patients on LTOT, mortality and the prevalence of comorbidities resulted equally distributed in polyglobulic and anemic subjects at the end of the 3-year survey (26.7% vs. 23.5%, and 2.2/patient vs. 2.1/patient, respectively).

Conclusions

Differently from earlier studies,³² the data of our survey emphasize the good results of a strict domiciliary telemonitored protocol for LTOT: Hb values tended to improve substantially in parallel to blood gases already from the first year of LTOT in the great majority of severe COPD subjects. Actually, better results were mostly achieved in polyglobulic subjects who, on

the other hand, represented the most frequent picture of severe COPD in our cohort. As suggested in previous studies,^{26,29} these patients proved more sensitive to the effects of long-term oxygen than anemic patients who required a longer period of LTOT to obtain smaller results. While it is plausible that in severe COPD the anemic condition may represent an independent factor that can affect the extent and time course of long-term metabolic outcomes during LTOT, it is however confirmed that LTOT plays a crucial role in optimizing blood gases independently of Hb.

References

- 1 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2009. [<http://www.goldcopd.com>].
- 2 Stradling JR, Lane DJ: Development of secondary polycythaemia in chronic airways obstruction. *Thorax* 1981, 36:321–325.
- 3 Similowski T, Agustí A, MacNee W, Schönhofer B: The potential impact of anaemia of chronic disease in COPD. *Eur Respir J* 2006, 27:390–396.
- 4 Bateman AP, McArdle F, Walsh TS: Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Crit Care Med* 2009, 37:1906–1912.
- 5 Mansen TJ, McCance KL, Parker-Cohen PD: Alterations of erythrocyte function. In *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. 2nd edition. Edited by McCance KL, Huether SE. St. Louis: Mosby- Year Book; 1994:860–877.
- 6 John M, Lange A, Hoernig S, Witt C, Anker SD: Prevalence of anemia in chronic obstructive pulmonary disease: comparison to other chronic diseases. *Int J Cardiol* 2006, 111:365–370.
- 7 O'Reilly P, Bailey W: Long-term continuous oxygen treatment in chronic obstructive pulmonary disease: proper use, benefits and unresolved issues. *Curr Opin Pulm Med* 2007, 13:120–124.
- 8 Dal Negro RW: Long term oxygen tele-home monitoring, the Italian perspective. *Chest Companion Book*. 2000:247–249.
- 9 Dal Negro RW, Turco P: Telemedicine and LTOT in Italy: a 20 year experience. In *Home Long-Term Oxygen treatment in Italy. The additional value of telemedicine*. Edited by Dal Negro RW, Goldberg AI. Heidelberg: Springer Verlag; 2005:69–83.
- 10 Dal Negro RW, Aquilani R, Bertacco S, Boschi F, Micheletto C, Tognella S: Comprehensive effects of supplemented essential amino acids in patients with severe COPD and sarcopenia. *Monaldi Arch Chest Dis* 2010, 73:25–33.
- 11 Gex G, Janssens JP: Long-term oxygen therapy. *Rev Med Suisse* 2007, 3 (2646):2648–2650. 2652–2654.
- 12 Anthonisen NR: Long-term oxygen therapy. *Ann Intern Med* 1983, 99:519–527.
- 13 Penninx BW, Pahor M, Cesari M, Corsi AM, Woodman RC, Bandinelli S, Guralnik JM, Ferrucci L: Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc* 2004, 52:719–724.
- 14 Weiss G, Goodnough LT: Anemia of chronic disease. *N Engl J Med* 2005, 352:1011–1023.
- 15 Agustí AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X: Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003, 21:347–360.
- 16 National Kidney Foundation: NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update

2000. *Am J Kidney Dis* 2001, 37(Suppl. 1):S182–S238.
- 17 Silberberg JS, Rahal DP, Patton DR, Sniderman AD: Role of anemia in the pathogenesis of left ventricular hypertrophy in end-stage renal disease. *Am J Cardiol* 1989, 64:222–224.
 - 18 Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J: Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002, 39:1780–1786.
 - 19 McMurray JJ: What are the clinical consequences of anemia in patients with chronic heart failure? *J Card Fail* 2004, 10(1 Suppl):S10–S12.
 - 20 Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD: Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J* 2004, 25:1021–1028.
 - 21 Belperio PS, Rhew DC: Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: a systematic review of the literature. *Am J Med* 2004, 116(Suppl 7A):27S–43S.
 - 22 Volberding P: The impact of anemia on quality of life in human immunodeficiency virus-infected patients. *J Infect Dis* 2002, 185(Suppl. 2):S110–S114.
 - 23 Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, Wright TL, Mody SH, Tang KL, Goon BL, Bowers PJ, Leitz G, Afdhal NH, PROACTIVE Study Group: Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology* 2004, 40:1450–1458.
 - 24 Kroecker EJ, Leon AS: The association of diffuse obstructive pulmonary emphysema and chronic gastroduodenal ulceration. *Dis Chest* 1962, 42:413–421.
 - 25 Caro JJ, Salas M, Ward A, Goss G: Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer* 2001, 91:2214–2221.
 - 26 Chambellan A, Chailleux E, Similowski T, ANTADIR Observatory Group: Prognostic value of hematocrit in patients with severe COPD receiving long-term oxygen therapy. *Chest* 2005, 128:1201–1208.
 - 27 DeFilippis AP, Law K, Curtin S, Eckman JR: Blood is thicker than water: the management of hyperviscosity in adults with cyanotic heart disease. *Cardiol Rev* 2007, 15:31–34.
 - 28 Graudal N, Galløe AM, Nielsen OJ: Erythropoietin in chronic obstructive pulmonary disease. Relationship between serum erythropoietin, blood haemoglobin and lung function-effect of the calcium antagonist isradipine on serum erythropoietin. *Respiration* 1991, 58:141–144.
 - 29 Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B: Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Eur Respir J* 2007, 29:923–929.
 - 30 Tassiopoulos S, Kontos A, Konstantopoulos K, Hadzistavrou C, Vaiopoulos G, Aessopos A, Tassiopoulos T: Erythropoietic response to hypoxaemia in diffuse idiopathic pulmonary fibrosis, as opposed to chronic obstructive pulmonary disease. *Respir Med* 2001, 95:471–475.
 - 31 Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP: Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999, 160:1856–1861.
 - 32 Deng X, Cai Y, Fang Z: The effects of long-term domiciliary oxygen therapy on patients of chronic obstructive pulmonary disease with hypoxaemia. *Zhonghua Jie He He Hu Xi Za Zhi* 2001, 24:655–659.

Auto-titrating vs Fixed CPAP...continued from page 34

reported in 2009, which reviewed 30 randomized trials enrolling 1,136 patients in total (the Cochrane review had a larger number of RCTs because it included results from posters and conference proceedings). The Cochrane review segregated its analysis by study design into cross-over and parallel design studies but did not provide an aggregate analysis combining both types of study design. In that meta-analysis, a statistically significant difference in compliance of 12.6 minutes per night (95% CI, 4.8 to 21 minutes increase) was found in favor of APAP in cross-over studies, but no significant difference in parallel design studies. It also reported a statistically significant decrease in ESS of 0.64 points (95% CI, 0.12 to 1.16 point decrease) in favor of APAP in cross-over studies, but no significant difference in parallel design studies. We reported similar findings for the two study designs in our full technical review.

Follow-up durations in the studies reviewed tended to be short, in the order of weeks to a few months, and are clearly insufficient for the appraisal of the treatment of a life-long disease whose clinical sequelae may take decades to develop. Study dropout rates were also frequently very high, particularly given the short duration of follow-up. In some studies, up to 40% of participants were lost to follow-up within weeks. The ability to meaningfully interpret the findings from these studies is clearly diminished. Other frequent methodological problems included incomplete reporting and/or inadequate analyses. In particular, relatively few studies provided the net differences between interventions (in parallel design studies) or the difference between final values with appropriate adjustments for correlation (in cross-over studies) with their confidence intervals and P values. Thus for the large majority of studies, we had to estimate the confidence intervals of the differences between interventions. We also did not search for unpublished and non-English language studies.

Conclusions

APAP and CPAP were similar in affecting relatively short-term changes in AHL, quality of life, and most other sleep study measures in the treatment of patients with moderate to severe OSA but without significant comorbidities. APAP, however, did reduce sleepiness by approximately 0.5 ESS points more than fixed CPAP. Patients who received APAP also had objectively measured compliance of 11 minutes per night more than those who received fixed CPAP. We surmise that the clinical significance of these reported improvements in ESS and compliance is marginal at best. It is doubtful that additional short-term trials comparing APAP and CPAP to examine these measures will substantially alter these results. However, longer-term and larger trials that evaluate clinical outcomes, such as cardiovascular events, and directly estimate differential effects in different sub-populations may be of value. Furthermore, the current trial evidence is limited to patients newly diagnosed with sleep apnea or who are otherwise naïve to CPAP; thus, future trials of patients who had previously used CPAP may be of value. For now, based on the available data from experimental studies on short-term effects only, the decision to use APAP versus CPAP may well depend on individual patient preferences, specific reasons for non-compliance, costs and other practical considerations that clinicians and patients will need to assess on an individual basis.

Increased Blood Glycohemoglobin A1c Levels Lead to Overestimation of Arterial Oxygen Saturation by Pulse Oximetry in Patients with Type 2 Diabetes

Li Jin Pu, Ying Shen, Lin Lu, Rui Yan Zhang, Wei Feng Shen

Abstract

Background: Non-enzymatic glycation increases hemoglobin-oxygen affinity and reduces oxygen delivery to tissues by altering the structure and function of hemoglobin.

Objectives: We investigated whether an elevated blood concentration of glycosylated hemoglobin (HbA1c) could induce falsely high pulse oximeter oxygen saturation (SpO₂) in type 2 diabetic patients during mechanical ventilation or oxygen therapy.

Methods: Arterial oxygen saturation (SaO₂) and partial pressure of oxygen (PO₂) were determined with simultaneous monitoring of SpO₂ in 261 type 2 diabetic patients during ventilation or oxygen inhalation.

Results: Blood concentration of HbA1c was >7% in 114 patients and ≤ 7% in 147 patients. Both SaO₂ (96.2 ± 2.9%, 95% confidence interval [CI] 95.7-96.7% vs. 95.1 ± 2.8%, 95% CI 94.7-95.6%) and SpO₂ (98.0 ± 2.6%, 95% CI 97.6-98.5% vs. 95.3 ± 2.8%, 95% CI 94.9-95.8%) were significantly higher in patients with HbA1c >7% than in those with HbA1c ≤ 7% (Data are mean ± SD, all p < 0.01), but PO₂ did not significantly differ between the two groups. Bland-Altman analysis demonstrated a significant bias between SpO₂ and SaO₂ (1.83 ± 0.55%, 95% CI 1.73% -1.94%) and limits of agreement (0.76% and 2.92%) in patients with HbA1c >7%. The differences between SpO₂ and SaO₂ correlated closely with blood HbA1c levels (Pearson's r = 0.307, p < 0.01).

Conclusions: Elevated blood HbA1c levels lead to an overestimation of SaO₂ by SpO₂, suggesting that arterial blood gas analysis may be needed for type 2 diabetic patients with poor glycemic control during the treatment of hypoxemia.

Background

Glycohemoglobin is produced via a non-enzymatic reaction between the free aldehyde group of glucose or other sugars and the unprotonated form of free amino groups of hemoglobin.¹ Glycosylated hemoglobin A1c (HbA1c) is a stable minor hemoglobin variant separated by charge that is composed primarily but variably of glycohemoglobin. A clinical relationship between blood concentration of HbA1c and status of glycemic control has been elucidated,² and elevated HbA1c levels represent increased risk of coronary artery disease and poor outcome in diabetic patients.³⁻⁵ Previous studies have shown that glycosylation alters the structure and function of hemoglobin^{6,7}

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and tends to shift the oxygen dissociation curve to the left, leading to an increase in hemoglobin-oxygen affinity and a reduction in oxygen delivery to tissues.^{6,8,9} Pulse oximetry is widely used as a noninvasive tool for continuous monitoring of artery oxygen saturation (SaO₂),^{10,11} but pulse oximeter oxygen saturation (SpO₂) may overestimate arterial blood gases-determined SaO₂ in acute sickle chest syndrome and severe sepsis.^{12,13} So far, its accuracy for titrating fractional inspired oxygen in type 2 diabetic patients with mechanical ventilation or oxygen therapy remains unclear. Given that chronic hyperglycemia accelerates the accumulation of advanced glycation end products (AGE) in the skin collagen,¹⁴ which poses specific autofluorescence feature, may emit light by absorbing specific wavelengths light,¹⁵ and interfere with the accuracy of pulse oximetry, it is pertinent to examine if elevated blood HbA1c concentrations could result in an overestimation of SaO₂ by SpO₂ with finger probes particularly for type 2 diabetic patients with poor glycemic control.

Methods

Study population: A total of 261 consecutive type 2 diabetic patients undergoing oxygen therapy and/or mechanical ventilation from October 2010 to May 2012 in Rui Jin Hospital, Shanghai Jiaotong University School of Medicine were included. None had any recorded history of carbon monoxide exposure. The diagnosis of type 2 diabetes was made according to the criteria of American Diabetes Association, including symptoms of diabetes plus casual plasma glucose concentration beyond 200 mg/dl (11.1 mmol/l), or an increased fasting (126 mg/dl [7.0 mmol/l]) or 2-hour postprandial glucose (2-h PG) level (200 mg/dl [11.1 mmol/l]) during an oral glucose tolerance test).¹⁶ Patients with type 1 diabetes were excluded by measurement of C-peptide. For the purpose of this study, we also excluded patients who were current cigarette smokers within 3 months or alcohol-dependent, had renal insufficiency, anemia and fever, or were treated with vaso-constrictive agents. Poor glycemic control was defined as blood HbA1c level >7%.¹⁷ The study was approved by the hospital Institutional Review Board (IRB), and written informed consent was obtained from all participants.

Biochemical assessments: Peripheral venous blood was collected after an overnight fasting in all patients, and serum levels of glucose, blood urea nitrogen, creatinine, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured with standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany). Hemoglobin concentrations were determined with a model T-890 Coulter (Beckman Coulter International, Nyon, Switzerland). In order to exclude individuals with abnormal hemoglobin, electrophoresis was carried out according to the method of Marengo-Rowe.¹⁸ Blood HbA1c concentration was assayed using ion-exchange high performance liquid chromatography with a Bio-Rad Variant Hemoglobin

Table 1. Baseline characteristics and biochemical assessments

Variables	HbA1c<7% (n=147)	HbA1c>7% (n=114)	P Value
Male gender(%)	104(70.7)	78(68.4)	0.685
Age (yrs)	67±6	69±7	0.01
Chronic obstructive pulmonary disease (%)	98(66.7)	81(71.1)	0.449
Cardiogenic pulmonary edema (%)	13(8.8)	17(14.9)	0.127
Pneumonia (%)	40(27.2)	46(40.4)	0.025
Hypertension (%)	49(33.3)	40(35.1)	0.243
Systolic blood pressure(mmHg)	131±9	132±9	0.374
Diastolic blood pressure (mmHg)	75±8	76±8	0.317
Red blood cell($\times 10^{12}$ /L)	4.75±0.73	4.91±0.77	0.088
Hemoglobin(g/L)	132±12	134±13	0.199
Body temperature (°C)	37.3±0.1	37.4±0.1	<0.001
Total cholesterol (mmol/L)	4.06±0.91	4.17±0.95	0.343
HDL-cholesterol (mmol/L)	1.19±0.26	1.17±0.27	0.545
LDL-cholesterol (mmol/L)	2.43±0.62	2.41±0.68	0.805
Triglycerides (mmol/L)	1.72±0.75	1.91±0.78	0.047
Fasting Glucose (mmol/L)	5.9±1.8	9.4±2.1	<0.001
2-h postprandial glucose (mmol/L)	9.2±4.1	13.9±4.5	<0.001
HbA1c (%)	5.6±1.2	9.2±2.1	<0.001
Blood urea nitrogen (mmol/L)	5.42±2.35	6.03±2.51	0.045
Creatinine (μ mol/L)	87±16	91±18	0.59
Medical treatments			
ACEI or ARB (%)	46(31.3)	37(32.5)	0.841
Calcium channel blocker (%)	14(9.5)	12(10.5)	0.789
Statins* (%)	121(82.3)	97(85.1)	0.549
Metformin (%)	52(35.4)	45(39.5)	0.497
Sulphonylureas (%)	56(38.1)	37(32.5)	0.345
Alpha-glucosidase (%)	54(36.7)	46(40.3)	0.551
PPAR-gamma agonist (%)	23(15.6)	15(13.2)	0.572

Data are mean ± SD or number (%)

Abbreviation: HbA1c, Glycosylated hemoglobin A1c; HDL, High-density lipoprotein;

LDL, low-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor;

ARB, angiotensin II receptor blocker;

*Statins: mainly simvastatin, pravastatin and atorvastatin

Testing System (Bio-Rad Laboratories, Hercules, CA, USA). Levels of 2, 3-diphosphoglycerate (2,3-DPG) in the red blood cells were assayed within 15 min using enzymatic determination at 340 nm with an ultraviolet test kit from Roche Diagnostics (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

Arterial blood gas analysis: Arterial blood gases were determined during simultaneous SpO₂ monitoring with pulse oximetry. Blood was drawn anaerobically into a preheparinized 1-mL syringe, and mixed well before measurement. After removal of all air bubbles from the syringe, in vivo pH, partial pressure of carbon dioxide (PCO₂), SaO₂, partial pressure of oxygen (PO₂) and carboxyhemoglobin were directly measured using a Cobas b 221 blood gas analyzer (Roche Diagnostics, Germany). All measurements were completed within 5 min of blood sampling. Arterial blood gas analysis and SpO₂ values were one measurement per patient.

Monitoring of pulse oxygen saturation: SpO₂ was monitored continuously with a pulse oximetry (Nellcor NPB 40 MAX,

Table 2. Arterial blood gas analysis, 2,3-DPG level and SpO₂ between two groups

Variables	HbA1c<7% (n=147)	HbA1c>7% (n=114)	P Value
2, 3-DPG(μ mol/gHb)	13.9±1.7	14.2±1.7	0.09
pH	7.37±0.05	7.39±0.05	0.01
PCO ₂ (Kpa)	5.48±0.73	5.53±0.65	0.565
Carboxyhemoglobin (%)	1.08±0.81	1.09±0.78	0.92
PO ₂ (Kpa)	10.0±1.9	10.0±2.2	0.843
SaO ₂ (%)	95.1±2.8	96.2±2.9	0.002
SpO ₂ (%)	95.3±2.8	98.0±2.6	0.001

Data are mean ± SD

Abbreviation: 2,3-DPG, 2, 3-diphosphoglycerate

PCO₂, partial pressure of carbon dioxide

PO₂, partial pressure of oxygen; SaO₂, arterial oxygen saturation

SpO₂, pulse oximeter oxygen saturation

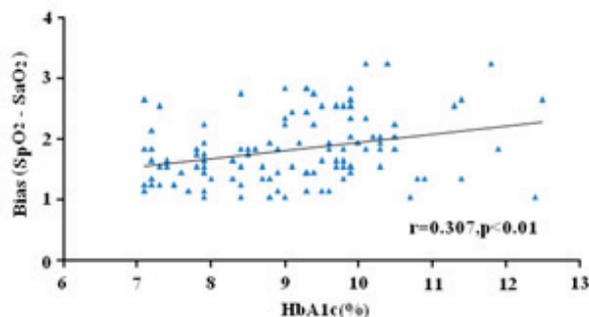


Figure 1. Correlation of the difference between SpO₂ and SaO₂ with blood HbA1c levels in patients with poor glycemic control.

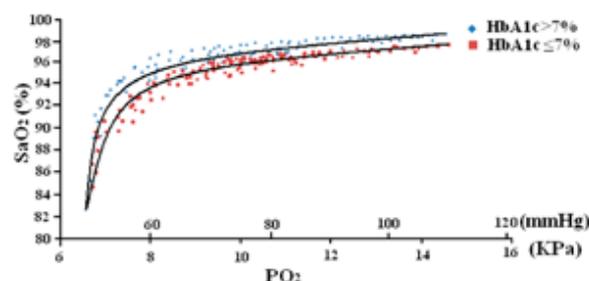


Figure 2. Arterial oxyhemoglobin sigmoid curves (PO₂, partial pressure of oxygen; SaO₂, arterial oxygen saturation).

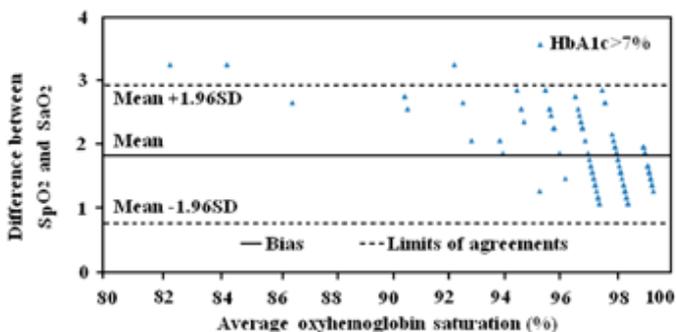


Figure 3. Bland-Altman plots for bias and limits of agreement in patients with poor glycemic control.

Hayward, CA), which detects oxygen saturation by measuring transdermal light absorption in the blood flow through a fingertip (DS 100A finger probe). SpO₂ values were recorded only after a consistent reading, with a strong arterial waveform signal and a pulse reading identical to the patient's heart rate.

Statistical analysis: Baseline characteristics are expressed as mean and standard deviation (SD) for continuous variables, and percentages for categorical ones. Chi-square test was used to analyze dichotomous variables. Comparisons of continuous variables between groups were made by the appropriate Student's t tests. Correlation between difference (SpO₂ - SaO₂) and HbA1c was analyzed using Pearson correlation coefficients. Accuracy (SpO₂ - SaO₂) of SpO₂ was examined by the method of Bland and Altman analysis.¹⁰ Bias was determined by the mean difference and 95% confidence intervals (CI) between SpO₂ and SaO₂, precision was determined by the standard deviation of the mean difference, and limits of agreement (mean difference ± 1.96SD) was defined as a proportional function of distribution for differences between the 2 measurements. Data were analyzed using the Statistical Packages for Social Sciences (SPSS Version 13.0, Chicago, Ill). A 2-tailed p value < 0.05 was considered statistically significant. Only one measurement per patient for arterial blood gas and SpO₂ was made.

Results

Clinical characteristics: Among overall 261 type 2 diabetic patients, 114 patients had a HbA1c >7%, and 147 had a HbA1c ≤ 7%. Patients with HbA1c >7% were older and had higher serum levels of fasting glucose, 2-h postprandial glucose, and triglycerides than those with HbA1c ≤ 7%. The two groups did not differ with respect to occurrence rates of hypertension, chronic obstructive pulmonary disease, and pulmonary edema (Table 1).

Arterial blood gas profiles, pulse oximetry, and 2, 3-DPG: Both SaO₂ (96.2 ± 2.9%, 95% confidence interval [CI] 95.7-96.7% vs. 95.1 ± 2.8%, 95% CI 94.7-95.6%) and SpO₂ (98.0 ± 2.6%, 95% CI 97.6-98.5% vs. 95.3 ± 2.8%, 95% CI 94.9- 95.8%) were significantly higher in patients with HbA1c >7% than in those with HbA1c ≤ 7% (Data are mean ± SD, all p < 0.01), but PO₂ did not significantly differ between the two groups.

Levels of 2, 3-DPG in the red blood cells and PCO₂ were slightly elevated in patients with HbA1c >7%, but did not reach statistical significance levels (p >0.05). Body temperature, pH, and carboxyhemoglobin were similar in the two groups (Table 2). The difference between SpO₂ and SaO₂ correlated closely with blood HbA1c levels (Pearson's r = 0.307, p < 0.01) (Figure 1).

Arterial oxyhemoglobin sigmoid curves: The sigmoid fitted curve for patients with HbA1c >7% shifted to the left compared with that with HbA1c ≤ 7%. The mean difference of SaO₂ between diabetic patients with HbA1c >7% and those with HbA1c ≤ 7% was 1.1% (Figure 2).

Bland-Altman analysis: The simultaneous readings of SaO₂ and SpO₂ were analyzed to determine the bias and limits of agreement. Bland-Altman analysis indicated that the bias (mean difference of SpO₂ minus SaO₂) between the two methods was 1.83 ± 0.55% (95% CI 1.73% -1.94%) and limits of agreement were 0.76% and 2.92% in patients with HbA1c >7% (Figure 3). Overall, there was a significant bias between pulse oximetry and arterial blood gases in patients with HbA1c >7%.

Discussion

The present study is the first to demonstrate that despite similar levels of red blood cell 2, 3-DPG, PO₂, PCO₂, pH and body temperature, type 2 diabetic patients with HbA1c > 7% had higher SaO₂ (the mean difference was 1.1%) and bias (1.83 ± 0.55%) compared with those with HbA1c ≤ 7%, suggesting that elevated blood HbA1c levels led to an overestimation of SaO₂ by pulse oximetry.

Hypoxemia denotes a condition that is characterized by low oxygen content or percent saturation of hemoglobin with oxygen.¹³ Arterial blood gases have been traditionally used to assess the status of oxygenation and to adjust fractional inspired oxygen in patients receiving mechanical ventilation or oxygen therapy.²⁰ Currently, noninvasive continuous monitoring of SaO₂ with SpO₂ has become the standard care for patients with critical conditions,^{13,21} to decrease the likelihood of hypoxemia²²⁻²⁵ and to wean mechanical ventilation.^{10,11,26} In the present study, when comparisons were performed at identical PO₂, SaO₂ was higher in type 2 diabetic patients with HbA1c > 7%, which is likely due to an increased hemoglobin-oxygen affinity. Our results are in line with previous findings that higher blood concentrations of HbA1c significantly reduce oxygen dissociation velocity.²⁷ Although the exact mechanism

remains not fully understood, it may be, at least partly, explained by glycation of multiple β-chain sites of hemoglobin A molecule, accompanied by increasing-chain glycation at high glycohemoglobin concentrations.^{28,29}

The major finding of this study is that in type 2 diabetic patients with poor glycemic control, pulse oximetry overestimated arterial blood gases-determined SaO₂ by a mean of 2.7% when compared with those with HbA1c ≤ 7%. Previous studies showed that older women have higher HbA1c than men, even after controlling for body mass index,³⁰ and accumulation of AGE in human skin collagen is age-dependent.³¹ However, both gender distribution and age did not significantly differ between the two groups in the present study, suggesting that the difference between SpO₂ and SaO₂ may be mainly related to HbA1c levels as higher HbA1c levels were associated with great differences (Pearson's r = 0.307, p < 0.01).

Our findings may be of important clinical relevance. First, falsely high SpO₂ could cause under-diagnosis of hypoxemia in type 2 diabetic patients. Second, because a greater SpO₂ was required to achieve the same arterial blood gases-determined PO₂ for diabetic patients with HbA1c >7% compared with those with HbA1c ≤ 7%, care should be taken in adjusting oxygen supply during mechanical ventilation or oxygen therapy. The reason for a higher SpO₂ than SaO₂ may be partly explained by an extensive accumulation of AGE in the skin collagen in patients with poor glycemic control,¹⁴ interfering with transdermal absorption of the specific wavelength light by hemoglobin with finger probes.^{12,32} These observations support a notion that the causes of high bias does include skin effect,^{33,34} and when SaO₂ needs to be determined with a high degree of accuracy, arterial blood gases are recommended in type 2 diabetic patients with poor glycemic control.

Limitations: Due to relatively small sample size, potential for selection bias may raise some concerns on the statistical precision of the estimates. A large-scale study is warranted to confirm our findings. The other major limitation is that most of the data are at high SaO₂ because of a specially selected study population as all patients were receiving mechanical ventilation and/or oxygen therapy. The oxyhemoglobin dissociation curves could actually be fitted with non-linear regression, and a partial pressure of oxygen in blood associated to a hemoglobin oxygen saturation of 50% (P50) could also be calculated.³⁵ Most oximetry testing intentionally gathers data below 90% by performing desaturation experiments in volunteers. Gather multiple data points on volunteers increase the data set substantially, and allow one to test over a wide range of SaO₂, and control for other effects. By creating a gas pocket with CO₂ and O₂/N₂ mixtures, one can create a much more detailed oxyhemoglobin dissociation curve. The US FDA requires testing balanced by gender and ethnicity. Repeated measures statistics would then be necessary, and P50 is not determined quite as precisely unless the sample is near a SaO₂ of 50%. Certainly, it remains unclear whether the issue with diabetic patients would be safe given the possibility of cardiovascular disease, although younger subjects could be reasonable.

Conclusions

Elevated blood HbA1c concentrations lead to an overestimation of SaO₂ by SpO₂, suggesting that arterial blood gas analysis may be needed for type 2 diabetic patients with poor glycemic control during the treatment of hypoxemia.

References

1. Miedema K: Electrospray mass spectrometry for measurement of glycohemoglobin. *Clin Chem* 1997, 43:705–707.
2. American Diabetes Association: Clinical practice recommendations. *Diabetes Care* 2000, 23:S32–42.
3. Daida H, Takayama T, Hiro T, Yamagishi M, Hirayama A, Saito S, Yamaguchi T, Matsuzaki M: High HbA1c levels correlate with reduced plaque regression during statin treatment in patients with stable coronary artery disease: Results of the coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Cardiovasc Diabetol* 2012, 11:87.
4. Nishimura R, Nakagami T, Sone H, Ohashi Y, Tajima N: Relationship between hemoglobin A1c and cardiovascular disease in mild-to-moderate hypercholesterolemic Japanese individuals: subanalysis of a large-scale randomized controlled trial. *Cardiovasc Diabetol* 2011, 10:58.
5. Ikeda N, Iijima R, Hara H, Moroi M, Nakamura M, Sugi K: Glycated hemoglobin is associated with the complexity of coronary artery disease, even in non-diabetic adults. *J Atheroscler Thromb* 2012, 19 [Epub ahead of print].
6. De Rosa MC, Sanna MT, Messana I, Castagnola M, Galtieri A, Tellone E, Scatena R, Botta B, Botta M, Giardina B: Glycated human hemoglobin (HbA1c): functional characteristics and molecular modeling studies. *Biophys Chem* 1998, 72:323–335.
7. Samaja M, Melotti D, Carenini A, Pozza G: Glycosylated haemoglobins and the oxygen affinity of whole blood. *Diabetologia* 1982, 23:399–402.6.
8. Bunn HF: The glycosylation of hemoglobin: relevance to diabetes mellitus. *Science* 1978, 200:21–27.
9. Ditzel J: Affinity hypoxia as a pathogenic factor of microangiopathy with particular reference to diabetic retinopathy. *Acta Endocrinologica Supplementum* 1980, 238:39–55.
10. Jubran A, Tobin MJ: Reliability of pulse oximetry in titrating supplemental oxygen therapy in ventilator-dependent patients. *Chest* 1990, 97:1420–1425.
11. Moloney ED, Kiely JL, McNicholas WT: Controlled oxygen therapy and carbon dioxide retention during exacerbations of chronic obstructive pulmonary disease. *Lancet* 2001, 357:526–528.
12. Kress JP, Pohlman AS, Hall JB: Determination of hemoglobin saturation in patients with acute sickle chest syndrome: a comparison of arterial blood gases and pulse oximetry. *Chest* 1999, 115:1316–1320.
13. Wilson BJ, Cowan HJ, Lord JA, Zuege DJ, Zygun DA: The accuracy of pulse oximetry in emergency department patients with severe sepsis and septic shock: a retrospective cohort study. *BMC Emerg Med* 2010, 10:9.
14. Dyer DG, Dunn JA, Thorpe SR, Bailie KE, Lyons TJ, McCance DR, Baynes JW: Accumulation of Maillard reaction products in skin collagen in diabetes and aging. *J Clin Invest* 1993, 91:2463–2469.
15. Bos DC, de Ranitz-Greven WL, de Valk HW: Advanced glycation end products, measured as skin autofluorescence and diabetes complications: a systematic review. *Diabetes Technol Ther* 2011, 13:773–779.
16. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003, 26(Suppl 1):S5–20.
17. Kassaian SE, Goodarzynejad H, Boroumand MA, Salarifar M, Masoudkabar F, Mohajeri-Tehrani MR, Pourhoseini H, Sadeghian S, Ramezanzpour N, Alidoosti M, Hakki E, Saadat S, Nematipour E: Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. *Cardiovasc Diabetol* 2012, 11:82.
18. Marengo-Rowe AJ: Rapid electrophoresis and quantitation of hemoglobin on cellulose acetate. *J Clin Pathol* 1965, 18:790–792.
19. Bland JM, Altman DG: Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999, 8:161–179.
20. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, Bosman RJ, de Waal RA, Wesselink R, de Keizer NF: Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008, 12:R156.
21. Birnbaum S: Pulse oximetry: identifying its applications, coding, and reimbursement. *Chest* 2009, 135:838–841.
22. Van de Louw A, Cracco C, Cerf C, Harf A, Duvaldestin P, Lemaire F, Brochard L: Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Med* 2001, 27:1606–1613.
23. Lee WW, Mayberry K, Crapo R, Jensen RL: The accuracy of pulse oximetry in the emergency department. *Am J Emerg Med* 2000, 18:427–431.
24. Seguin P, Le Rouzo A, Tanguy M, Guillou YM, Feuillu A, Malledant Y: Evidence for the need of bedside accuracy of pulse oximetry in an intensive care unit. *Crit Care Med* 2000, 28:703–706.
25. Jubran A: Pulse oximetry. *Intensive Care Med* 2004, 30:2017–2020.
26. Mihm FG, Halperin BD: Noninvasive detection of profound arterial desaturations using a pulse oximetry device. *Anesthesiology* 1985, 62:85–87.
27. Marschner JP, Seidlitz T, Rietbrock N: Effect of 2,3-diphosphoglycerate on O₂-dissociation kinetics of hemoglobin and glycosylated hemoglobin using the stopped flow technique and an improved in vitro method for hemoglobin glycosylation. *Int J Clin Pharmacol Ther* 1994, 32:116–121.
28. Peterson KP, Pavlovich JG, Goldstein D, Little R, England J, Peterson CM: What is hemoglobin A1c? An analysis of glycated hemoglobins by electrospray ionization mass spectrometry. *Clin Chem* 1998, 44:1951–1958.
29. Roberts NB, Amara AB, Morris M, Green BN: Long-term evaluation of electrospray ionization mass spectrometric analysis of glycated hemoglobin. *Clin Chem* 2001, 47:316–321.
30. Martins RA, Jones JG, Cumming SP, Coelho e Silva MJ, Teixeira AM, Verissimo MT: Glycated hemoglobin and associated risk factors in older adults. *Cardiovasc Diabetol* 2012, 11:13.
31. Dunn JA, McCance DR, Thorpe SR, Lyons TJ, Baynes JW: Age-dependent accumulation of N^ε-(carboxymethyl)lysine and N^ε-(carboxymethyl)hydroxylysine in human skin collagen. *Biochemistry* 1991, 30:1205–1210.
32. Gerrits EG, Lutgers HL, Kleefstra N, Graaff R, Groenier KH, Smit AJ, Gans RO, Bilo HJ: Skin autofluorescence: a tool to identify type 2 diabetic patients at risk for developing microvascular complications. *Diabetes Care* 2008, 31:517–521.
33. Bickler PE, Feiner JR, Severinghaus JW: Effects of skin pigmentation on pulse oximeter accuracy at low saturation. *Anesthesiology* 2005, 102:715–719.
34. Feiner JR, Severinghaus JW, Bickler PE: Dark skin decreases the accuracy of pulse oximeters at low oxygen saturation: the effects of oximeter probe type and gender. *Anesth Analg* 2007, 105:S18–23.
35. Severinghaus JW: Simple, accurate equations for human blood O₂ dissociation computations. *J Appl Physiol* 1979, 46:599–602.

Non Drowsy Obstructive Sleep Apnea as a Potential Cause of Resistant Hypertension: a case report

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Abstract

Background: Obstructive sleep apnea (OSA) and arterial hypertension (AH) are common and under-recognized medical disorders. OSA is a potential risk factor for the development of AH and/or may act as a factor complicating AH management. The symptoms of excessive daytime sleepiness (EDS) are considered essential for the initiation of continuous positive airway pressure (CPAP) therapy, which is a first line treatment of OSA. The medical literature and practice is controversial about the treatment of people with asymptomatic OSA. Thus, OSA patients without EDS may be left at increased cardiovascular risk.

Case presentation: The report presents a case of 42 year old Asian woman with symptoms of heart failure and angina-like chest pain upon admission. She didn't experience symptoms of EDS, and the Epworth Sleepiness Scale was seven points. Snoring was reported on direct questioning. The patient had prior medical history of three unsuccessful pregnancies complicated by gestational AH and preeclampsia with C-section during the last pregnancy. The admission blood pressure (BP) was 200/120 mm Hg. The patient's treatment regimen consisted of five hypotensive medications including diuretic. However, a target BP wasn't achieved in about one and a half month. The patient was offered to undergo a polysomnography (PSG) study, which she rejected. One month after discharge the PSG study was done, and this showed an apnea-hypopnea index (AHI) of 46 events per hour. CPAP therapy was initiated with a pressure of 11 H₂O cm. After 2 months of compliant CPAP use, adherence to pharmacologic regimen and lifestyle modifications the patient's BP decreased to 134/82 mm Hg.

Conclusions: OSA and AH are common and often under-diagnosed medical disorders independently imposing excessive cardiovascular risk on a diseased subject. When two conditions coexist the cardiovascular risk is likely much greater. This case highlights a possible clinical phenotype of OSA without EDS and its association with resistant AH. Most importantly a good hypotensive response to medical treatment in tandem with CPAP therapy was achieved in this patient. Thus, it is reasonable to include OSA in the differential list of resistant AH, even if EDS is not clinically obvious.

The author is with Kyrgyz State Medical Academy and the National Centre of Cardiology and Internal Medicine, Kyrgyzstan. Reprinted from BioMed Central, BMC Pulmonary Medicine, © 2012 Mirrakhimov; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Background

Obstructive sleep apnea (OSA) is the disorder characterized by complete or partial breathing disturbances during sleep with a minimum prerequisite frequency of 5 events per hour and lasting for at least 10 seconds.¹ The prevalence of OSA varies in epidemiological surveys, and this can be explained by different populations studied and including excessive daytime sleepiness (EDS) as a criterion for OSA diagnosis.² Thus, it is likely that the real number of the affected population is much higher than reported.

OSA is associated with increased cardiovascular risk and OSA in particular may be an independent risk factor for the development of arterial hypertension (AH).³ AH on the other hand, is a major cardiovascular risk factor and among the most prevalent chronic conditions worldwide.⁴ The association between AH and OSA without symptoms of EDS is conflicting and there are controversies regarding the place of continuous positive airway pressure (CPAP) therapy in such situations. Thus, non-sleepy OSA individuals may be dishonestly left with increased cardiovascular risk.

Case presentation

A 42 year old female of Asian descent was admitted to the ward with complaints of dyspnea and squeezing chest pain without radiation during mild to moderate physical activity, pitting edema of the lower extremities, nocturia and treatment resistant AH. For the last 6 months, the patient experienced shortness of breath and lower extremities pitting edema which had worsened with time. During this period, the patient reported fatigue, which was related to the aforementioned symptoms from the patient's own words. Upon questioning the patient reported loud snoring during sleep, but denied sleepiness during the wake time.

The patient is Gravida 3 Para 0. The first 2 pregnancies were complicated with gestational hypertension (which were resolved after pregnancies) with stillbirths and the last one with preeclampsia and emergent C-section delivery of demised infant at 30 weeks term.

AH was diagnosed at 2006, during regular outpatient visit with measured blood pressure (BP) 186/110 mm Hg at that time. Since then, the patient noticed angina like chest pain during regular physical activity. Family history is remarkable for obesity and AH in both of her parents.

The patient's prehospitalization regimen consisted of 100 mg of

Table 1 Hypotensive regimen at the hospital

Medication	Dose
Bisoprolol	10 mg a day
Candesartan	32 mg a day
Indapamide SR	1.5 mg a day
Amlodipine	10 mg a day
Moxonidine	400 mcg a day

atenolol a day and 20 mg of enalapril a day, which is not believed to be an optimal hypotensive combination therapy.⁵ The patient's BP ranged from 160/100 mm Hg to 240/130 mm Hg (which is the highest retrospectively recorded BP in this patient). The patient denied smoking, alcohol intake or use of any psychostimulating (including caffeine containing products) remedies.

The patient is obese for the last 15 years, but since 2009 she gained approximately 10 kilograms. The patient ate fatty meals with average daily calorie intake of approximately 3000 Kcal/day and followed sedentary life-style. The body weight was 103 kg, height was 156 cm, abdominal circumference was 134 cm and body mass index was 42.3 kg/m² upon admission.

Cardiovascular examination: heart rate (HR) was 85 beats per minute. The loud second heart sound was heard over the right second intercostal space. No murmurs, rubs or gallops upon auscultation were heard. Bilateral pitting edema was present over the shins. Admission BP was 200/120 mm Hg.

On the pulmonary exam, bilateral inspiratory rales were present at the bases with no change on coughing. The respiratory rate was 19 per minute. Digital pulse oximetry revealed oxygen saturation of 95%.

Oral examination revealed redundant pharyngeal soft tissue and Mallampati class 3.⁶ Neck circumference was 43 cm the thyroid gland wasn't palpable. No hair loss, skin changes or alterations in bowel habits were present. Neurological exam was intact. The Epworth sleepiness score (ESS) was seven points.⁷

Complete blood count, Creatinine, electrolytes, glomerular filtration rate, liver function tests (ALT, AST), troponin level, fasting lipid panel, fasting glucose (on 2 separate occasions) and thyroid function tests were all within normal limits.

Electrocardiography (ECG): inverted T waves in leads V3-V6. Holter ECG monitoring: 1 paroxysm of atrial fibrillation with HR

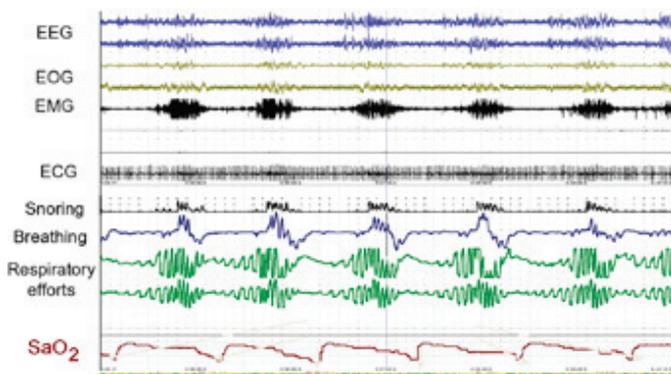


Figure 1. Patient's PSG recording. Abbreviations: ECG-electrocardiography, EEG-electroencephalography, EMG-electromyography, EOG-electrooculography, SaO₂-oxygen saturation.

of 134 beats/minute lasting for 21 seconds. Frequent episodes of T wave inversion without overt ST segment abnormalities.

Echocardiography: left ventricular end diastolic dimension: 6.45 cm, left ventricular end systolic dimension: 5.01 cm, interventricular septum: 1.36 cm, posterior wall of the left ventricle: 1.27 cm and ejection fraction of 43%. Mild diffuse left ventricular hypokinesia was present. Other parameters were within normal limits.

Carotid ultrasound: left common carotid intima media thickness of 0.91 and right common carotid TIM of 0.92 without obvious plaques.

24 hour BP measurement: non dipping pattern, with only 3% of nighttime decline of BP. Important to note that nighttime BP is known to be a stronger predictor of cardiovascular events than daytime BP.⁸

Chest X-Ray: Pulmonary venous congestion and cardiothoracic index of 49%.

The hospital stay was 20 days. The patient's hypotensive regimen is present in Table 1. On this regimen the patient's BP ranged from 150/90 to 170/110 mm Hg. HR was 62–70 beats per minute. Besides the pharmacological intervention, the patient was counseled on proper low fat/calorie diet and other measures to improve her lifestyle.

The patient was considered to have resistant AH. Since this patient was obese and had high diastolic BP some possible alternative etiologies were considered such as obesity related AH, hypothyroidism, OSA etc.

Since OSA was in the differential list, this patient was offered a PSG study, which she rejected at that time.

The patient was discharged with the BP of 160/106 mm Hg and instructed to return for follow up visit in 2 weeks as outpatient.

The patient arrived only 1 month after and assured that she didn't have any compliance related problems. The BP was 158/110 mm Hg. Dyspnea became less severe and the angina episodes less frequent.

The possibility of OSA was again discussed with the patient and PSG study was offered, which was agreed at that time. The recording of the patient's PSG study is present in Figure 1.

The 12 hour PSG revealed the apnea-hypopnea index (AHI) of 46 events per hour, which is consistent with a severe form of the disease.¹ On the next night, the CPAP titration study with the pressure of 11 H₂O cm abolished the sleep disordered breathing events. The patient was instructed on proper and compliant use of CPAP machine. Follow up was scheduled in 2 months.

After 2 months, the patient's CPAP using time was on average 6 hours per night and 7 days a week. The BP on this visit was 140/92 mm Hg on prior pharmacological regimen and CPAP therapy.

One month later, the patient's BP became 134/82 mm Hg. The patient's treatment regimen wasn't modified during this time interval. Home sleep monitoring detected the AHI of six events per hour.

Discussion

Resistant AH is defined as inability to reach target BP using at least 3 different hypotensive medications including diuretic.⁹ The differential list is broad and includes: lack of treatment compliance, inadequate treatment regimen, hypervolemic states, identifiable causes of AH, obesity and OSA.¹⁰

It is well known that OSA is a potential risk factor for AH development and/or a factor complicating its treatment. Currently the symptoms of EDS are considered essential for the initiation of CPAP therapy, while patients with pathologic AHI and without EDS are generally not treated. However, it is noteworthy to mention that OSA with EDS has the strongest association with resistant AH.¹¹

In their landmark study, Barbe and colleagues high-lighted the beneficial effects of CPAP therapy in non-sleepy OSA subjects who were compliant with CPAP therapy. However in their study the effect on BP was only evident after one year of regular CPAP therapy.¹²

In this patient several issues should be considered. First, this is only a case report with all potential limitations. Second, the impact of obesity and insulin resistance weren't measured in the patient, but it is important to mention that the patient didn't lose weight within the 3 months follow up. Third, the patient decreased her sodium intake from eight grams to four grams a day and started mild to moderate aerobic physical exercises. Fourth, the BP decline may be solely explained by hypotensive effect of BP lowering medications. Fifth, ESS is known to have some limitations, since it is a subjective test for EDS.¹³ A recent study highlighted the fact that patients with OSA and concomitant heart failure (HF) can present without symptoms of EDS assessed with ESS.¹⁴ However, others in a smaller number of recruited participants have failed to show that patients with OSA and HF have less EDS.¹⁵ But, on the other hand, ESS may have limited sensitivity for detecting EDS in patients with OSA and concomitant HF.

Nevertheless, this report highlights the possibility of a distinct non sleepy clinical phenotype of OSA and its association with resistant AH. Thus, it is reasonable to include OSA in the differential list of refractory to treatment AH, even when the EDS is not clinically obvious.

Conclusion

OSA and AH are common and often underdiagnosed medical disorders independently imposing excessive cardiovascular risk on diseased subject. When two conditions coexist the burden is likely much greater. This case highlights a possible association between non-sleepy OSA and AH, with good hypotensive response to BP lowering medications in tandem with CPAP therapy. Thus, it is reasonable to include OSA in the differential list of refractory to treatment AH, even when the EDS is not clinically obvious.

References

- 1 Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task force. *Sleep* 1999, 22:667–689
- 2 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurrence of sleep disordered breathing among middle aged adults. *N Engl J Med* 1993, 328:1230–1235.

- 3 Gonçalves SC, Martinez D, Gus M, de Abreu-Silva EO, Bertoluci C, Dutra I, Branchi T, Moreira LB, Fuchs SC, de Oliveira AC, Fuchs FD: Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest* 2007, 132:1858–1862.
- 4 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J: Global burden of hypertension: analysis of worldwide data. *Lancet* 2005, 365:217–223.
- 5 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007, 28:1462–1536.
- 6 Hiremath AS, Hillman DR, James AL, Noffsinger WJ, Platt PR, Singer SL: Relationship between difficult tracheal intubation and obstructive sleep apnoea. *Br J Anaesth* 1998, 80:606–611.
- 7 Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991, 14:540–545.
- 8 Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E: Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005, 46:156–161.
- 9 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003, 289:2560–2572.
- 10 Pisoni R, Ahmed MI, Calhoun DA: Characterization and treatment of resistant hypertension. *Curr Cardiol Rep* 2009, 11:407–413.
- 11 Calhoun DA: Obstructive sleep apnea and hypertension. *Curr Hypertens Rep* 2010, 12:189–195.
- 12 Barbé F, Durán-Cantolla J, Capote F, de la Peña M, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Río F, de Aauri JD, Terán J, Mayos M, Monasterio C, del Campo F, Gomez S, de la Torre MS, Martinez M, Montserrat JM: Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010, 181:718–726.
- 13 Short M, Lack L, Wright H: Does subjective sleepiness predict objective sleep propensity? *Sleep* 2010, 33:123–129.
- 14 Ferreira S, Marinho A, Patacho M, Santa-Clara E, Carrondo C, Winck J, Bettencourt P: Prevalence and characteristics of sleep apnoea in patients with stable heart failure: Results from a heart failure clinic. *BMC Pulm Med* 2010, 10:9.
- 15 Patidar AB, Andrews GR, Seth S: Prevalence of obstructive sleep apnea, associated risk factors, and quality of life among Indian congestive heart failure patients: a cross-sectional survey. *J Cardiovasc Nurs* 2011, 26:452–459.



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1. Coffin, SE, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. Infection Control and Hospital Epidemiology 2008;29 (Supplement 1): 31-40.
2. AARC Evidence-based clinical practice guidelines: care of the ventilator circuit and its relation to ventilator-associated pneumonia. Respiratory Care 2003;48(9):869-879.
3. Restrepo RD, Walsh BK. AARC CPG: Humidification during invasive and noninvasive mechanical ventilation. Respiratory Care 2012;57(5): 782-788.