

Volume 7 Number 3 June-July 2012

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The Journal of Pulmonary Technique

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Respiratory Therapy™

The Journal of Pulmonary Technique

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Editorial

Going Viral

The New York Times recently editorialized about the so-called “doomsday virus,” the bird flu virus modified in a lab to make it transmissible through the air, noting that if it got loose or into the wrong hands, it could kill millions.

The scientist who did the research said such fears were unfounded because the virus didn’t spread easily and wasn’t lethal if transported by coughing or sneezing, only if large doses were injected. But the Times pointed out that this might well be disingenuous in light of what he published in his paper, which said the new virus was in fact transmissible through air and virulent.

According to the Times, the issue needs to be publicly debated and “needs an objective, independent arbiter. The public needs to know whether this virus is a potentially big killer, and if so, how it should be contained. It needs to know what details can be published without giving terrorists a recipe for a biological weapon. And it needs to know that a mechanism will be put in place to assess all the risks and benefits of such research before it is approved — not after a new virus has been created.”

Subsequent to the creation of the virus, the WHO concluded that the research should eventually be published for all to see, and the NIH is thinking of publishing the info as well. The Times said, “We hope it will look beyond the security and terrorism issues and voice its opinion on what safety precautions should be required to prevent the virus from escaping and whether the work should proceed at multiple labs or possibly be halted...”

The World Health Organization should be in the best position to oversee a response to what is a global problem. Its first effort was one-sided and disappointing, but it has pledged to convene further meetings with a much broader range of experts and interested parties...

These are complicated issues, and the stakes are enormous. Governments and scientists have a clear responsibility to get this judgment and future efforts right.”

Les Plesko, Editor

PS: A reminder – June 1 is the deadline for companies to return their forms to receive a listing in Respiratory Therapy’s Buyers Guide, which will be our August/September issue. If you have not returned your form, or have not received a form, please contact us immediately. Completed forms can be e-mailed, faxed, or mailed.



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CERTIFICATION

We received a message from Steven W. Lichtman, EdD, FAACVPR, president of AACVPR (American Association of Cardiovascular and Pulmonary Rehabilitation), sent to his pulmonary rehab colleagues. Here is what he wrote: As you all know, AACVPR offers certification to programs that meet a high level of quality, both in pulmonary and cardiac rehabilitation. AACVPR makes every effort to set a high, but reasonable, level of quality for certification. We have recently been upgrading the process for certification, some evident to the user and some behind the scenes. This includes: 1) the launch of the online application process; 2) increasing the reliability of our review process by increasing the training of reviewers and the addition of multiple reviewers for each application; 3) creating a uniform application used for both certification and recertification; and 4) striving to have each requirement for certification be evidence-based, and where evidence is lacking, seeking consensus from known experts in the field. This process is continually undergoing review and refinement. Recently, it was brought to my attention that one of the requirements for pulmonary certification/recertification (Emergency Preparedness) may conflict with accepted program management and customary medical practice in some parts of the country. In addition, it is not consistent with information listed in the most recent AACVPR Guidelines for Pulmonary Rehabilitation. To address this issue, I called together the leaders of the certification process, as well as pulmonary rehabilitation experts, program directors, and physicians from various parts of the country, and over a series of conference calls, discussed this issue. It was decided to modify the Emergency Preparedness Requirements for Pulmonary Rehabilitation based on available evidence and expert consensus, and to align them with the requirements listed in the published AACVPR Guidelines for Pulmonary Rehabilitation, even though it is late in the certification cycle. In addition to modifying the Emergency Preparedness Requirements for Pulmonary Rehabilitation, I am also proposing to the AACVPR Board of Directors that we create Expert Panel Review Groups, one for pulmonary rehabilitation and one for cardiac rehabilitation, that will review the scientific evidence, expert consensus, and the AACVPR-published Guidelines prior to the release of each year's certification application, and make recommendations back to the certification committee for adjustments to the application. I am also proposing that the final certification instructions be released no later than the end of July in the year prior to the January cycle. We hope to have these changes in place by the next cycle, but certainly no later than the subsequent cycle. Based on all the recommendations

we received and reviewed, it has been decided to clarify the requirements for pulmonary certification and recertification (the requirements are now identical) regarding the Emergency Preparedness equipment and medications. Programs will now be required to have each of the items and medications listed below to achieve pulmonary certification. Clarification on this year's Certification/Recertification Requirement for Pulmonary Rehabilitation Programs as to the Emergency Preparedness page of the Pulmonary Rehabilitation AACVPR Certification Application: Appropriate emergency procedures and supplies must be available. All staff must be familiar with these procedures. The following, at a minimum, must be immediately available in the rehabilitation room or an adjacent area: oxygen source, oxygen delivery apparatus, Automatic External Defibrillator (AED) or standard defibrillator, resuscitation mask, bronchodilator medications, ability to monitor oxygen saturation (pulse oximeter), glucose, and first aid supplies. The supervising physician must be immediately available and accessible to respond to an emergency. Depending on or calling 911/EMS alone to bring these supplies/medications is not acceptable.

BOYCOTT

David Hill writes, on Huffington Post: Academic research is behind bars and an online boycott by 8,209 researchers (and counting) is seeking to set it free...well, more free than it has been. The boycott targets Elsevier, the publisher of popular journals like *Cell* and *The Lancet*, for its aggressive business practices, but opposition was electrified by Elsevier's backing of a Congressional bill titled the Research Works Act (RWA). Though lesser known than the other high-profile, privacy-related bills SOPA and PIPA, the act was slated to reverse the Open Access Policy enacted by the National Institutes of Health (NIH) in 2008 that granted the public free access to any article derived from NIH-funded research. Now, only a month after SOPA and PIPA were defeated thanks to the wave of online protests, the boycotting researchers can chalk up their first win: Elsevier has withdrawn its support of the RWA, although the company downplayed the role of the boycott in its decision, and the oversight committee killed it right away. But the fight for open access is just getting started. Seem dramatic? Well, here's a little test. Go to any of the top academic journals in the world and try to read an article. The full article, mind you... not just the abstract or the first few paragraphs. Hit a paywall? Try an article written 20 or 30 years ago in an obscure journal. Just look up something on PubMed then head to JSTOR where a vast archive of journals have been digitized for reference. Denied? Not interested in paying \$40 to the publisher to rent the article

for a few days or purchase it for hundreds of dollars either? You've just logged one of the over 150 million failed attempts per year to access an article on JSTOR. Now consider the fact that the majority of scientific articles in the US, for example, has been funded by government-funded agencies, such as the National Science Foundation, NIH, Department of Defense, Department of Energy, NASA, and so on. So while taxpayer money has fueled this research, publishers charge anyone who wants to actually see the results for themselves, including the authors of the articles. Paying a high price for academic journals isn't anything new, but the events that unfolded surrounding the RWA was the straw that broke the camel's back. It began last December when the RWA was submitted to Congress. About a month later, Timothy Gowers, a mathematics professor at Cambridge University, posted rather innocently to his primarily mathematics-interested audience his particular problems with Elsevier, citing exorbitant prices and forcing libraries to purchase journal bundles rather than individual titles. But clearly, it was Elsevier's support of the RWA that was his call to action. Two days later, he launched the boycott of Elsevier at thecostofknowledge.com, calling upon his fellow academics to refuse to work with the publisher in any capacity. Seemingly right out of Malcolm Gladwell's book *The Tipping Point*, researchers started taking a stand in droves. And the boycott of Elsevier continues on, though with less gusto now that the RWA is dead. It's important to point out though that the boycott is not aimed at forcing Elsevier to make the journals free, but protesting the way it does its business and the fact that it has profits four times larger than related publishers. The Statement of Purpose for the protest indicates that the specific issues that researchers have with Elsevier varies, but "...what all the signatories do agree on is that Elsevier is an exemplar of everything that is wrong with the current system of commercial publication of mathematics journals."

FRUSTRATING

Douglas Farrago, writing on Authentic Medicine.com, commented on new guidelines for participating in the Electronic Medical Records program. He writes, "The AMA News is listing some of the changes to come upon us in 2014. Here are what EMRs will be expected to do in Stage 2 of the Meaningful Use criteria. Some optional EMR functionality objectives in stage 1 would become

mandatory in stage 2. Overall, physicians would need to use their EMRs to meet 20 functionality objectives at minimum levels to earn bonuses and avoid penalties. Patient portals and secure messaging sound great unless they are not paid for, which they are not. Okay, take a look at the never ending hoops that are being added on and remember, it never ends. Core set (must meet all): Use computerized physician order entry for medication, lab and radiology orders; prescribe electronically, record patient demographics, record and chart vital signs, record smoking status, use clinical decision support, incorporate clinical lab results into EMR, generate lists of patients by specific condition, set patient reminders for preventive and follow-up care, provide patient portal access, provide clinical summaries for patients, identify education resources for patients, use secure messaging with patients, use medication reconciliation, send summary of care records for referrals and care transitions, send electronic data to immunization registries, ensure EMR privacy and security.

BMC NEWS

It just got easier to find open access research for textmining/redistribution. The challenges faced by researchers in obtaining access to published research articles for textmining purposes has been in the news again this month. BioMed Central makes its full open access corpus available online, but in general obtaining permission from publishers can be a major headache. PubMed Central, the NIH's archive of almost 2 million freely-accessible articles is a promising resources for textminers but unfortunately, due to licensing restrictions, only a fraction of those articles are available for redistribution and mining. Nevertheless the PubMed Central Open Access Subset already contains almost 400,000 articles and is growing rapidly. A technical tweak at the NCBI has just made the open access subset even more useful. It has long been possible to restrict a PubMed search to include only articles in PubMed Central, by including `pubmed pmc[sb]` in the search. And PubMed Central's full article search has provided the ability to limit to the open access subset only, by adding `open access[filter]`. Until recently, though, it hasn't been possible to filter a PubMed search to find open access, redistributable articles. The good news is that NCBI just fixed this omission – you can now restrict a PubMed search to just the articles that

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ASTHMA UP OR DOWN?

The Huffington Post recently wrote about asthma as a nationwide concern, stating that the number of asthma cases in the US has doubled since 1980, and now affects one in 10 children. HuffPost reported that, overall, asthma is the number one chronic childhood disease, the leading reason for school absenteeism, and tops the list of causes for child hospitalizations and emergency room visits, according to the Asthma and Allergy Foundation of America. And not only do more children now have asthma, but these children also are typically experiencing more attacks and those attacks are becoming more severe, even deadly. In 2007, 3,447 Americans died from asthma, according to the CDC. However, a reader, Louis Burgher with Clarkson College wrote to remind us: "In regard to the 'scholarly' article from the Huffington Post you might have your staff look at the enclosed article. The asthma mortality has been falling (per capita) since 1999. The age group 1-14 has the lowest per capita mortality, the older than 75 the highest." According to the article she refers to, American Lung Association, Epidemiology & Statistics Unit, Research and Program Services: After a long period of steady increase, evidence suggests that asthma mortality and morbidity rates continue to plateau and/or decrease. Mortality figures due to asthma have been continuing declining for the past 4 years. The number of deaths due to asthma in 2002 was approximately 8.5% lower than the number of deaths seen in 1999. Hospital discharges have been declining since 1995. The number of hospital discharges has decreased 5% between 1995 and 2002 while the hospital discharge rate has declined 13% since it peaked at 19.5 per 10,000 in 1995. Lifetime and attack prevalence rates have fluctuated over the past six years but have remained stable and there is only three years of data on current asthma. More years of data from the revised National Health Interview Survey are needed to accurately assess the prevalence trend. However, asthma remains a major public health concern. In 2003, approximately 20 million Americans had asthma and the condition accounted for an estimated 12.8 million lost school days in children and 24.5 million lost work days in adults. Asthma ranks within the top ten prevalent conditions causing limitation of activity and costs our nation \$16.1 billion in healthcare costs annually.

IT STARTS EARLY

Children who develop asthma by age seven had deficits in lung function and increased bronchial responsiveness as neonates, according to researchers at the University of Copenhagen. Their prospective study enrolled a birth cohort of 411 at-risk children of asthmatic mothers. Spirometry was performed at one month

in 403 children and again at age seven in 317. Significant neonatal airflow deficits, as measured by forced expiratory flow at 50% of vital capacity and forced expiratory volume after 0.5 seconds, were observed among the 14% of children who developed asthma by age seven. Bronchial responsiveness to methacholine was also significantly associated with the development of asthma. Neonatal airway reactivity was a stronger predictor of asthma than neonatal lung function.

DEPRESSING

Obstructive sleep apnea and other symptoms of OSA are associated with probable major depression, regardless of factors like weight, age, sex or race, according to a new study from the CDC. Snorting, gasping or stopping breathing while asleep was associated with nearly all depression symptoms, including feeling hopeless and feeling like a failure. The study surveyed 9,714 American adults. The likelihood of depression increased with the reported frequency of snorting and/or instances when breathing stopped.

BRONCHIOLITIS

A 16-hospital study, led by researchers at Children's Hospital Boston and Massachusetts General Hospital, is challenging common wisdom about bronchiolitis, a respiratory illness and the leading cause of hospitalization in infants. Currently, clinicians treating babies with severe bronchiolitis generally don't test for pathogens, assuming the specific infectious cause to be irrelevant to the child's care. The new study, the largest prospective, multicenter study of US children hospitalized with bronchiolitis, suggests it should be viewed as more than one disease, especially when considering treatments. "Our data show that the infecting pathogen in bronchiolitis affects hospital length-of-stay," says Jonathan Mansbach, MD, a hospitalist physician at Children's Hospital Boston and first author of the study, published recently by the Archives of Pediatrics & Adolescent Medicine. "Most research on treatments currently lumps all children with bronchiolitis together, and may miss findings that are important in a particular subgroup." Mansbach and senior investigator Carlos A. Camargo, MD, DrPH, of Massachusetts General Hospital, tracked more than 2,200 children under age 2 who were hospitalized with bronchiolitis during the 2007 to 2010 winter seasons, as part of the Multicenter Airway Research Collaboration (MARC), a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org). PCR testing was done for multiple viruses and bacteria. While most infants in the study had respiratory syncytial virus (RSV), a quarter were infected with the common cold virus (rhinovirus). These infants were less likely than those with RSV to have hospital stays of three days or longer (odds ratio, 0.36). Compared with infants infected with RSV alone, infants with rhinovirus alone were less likely to have hospital stays of three days or longer (odds ratio, 0.36) after adjustment for other factors affecting disease severity. Infants with both RSV and rhinovirus were more likely to have 3-day or longer stays than infants with RSV alone (odds ratio, 1.33). "There seems to be some interaction between RSV and rhinovirus that needs further study," Mansbach says. The findings also call into question a common hospital practice of rooming babies with RSV bronchiolitis together. Although this practice is frequently necessary, it has the potential to expose children to new infections. In the study, at least one other virus was detected in 32% of the RSV-positive babies and in 23% of RSV-negative babies. And some of the co-infecting pathogens require different kinds of infection-control precautions in the hospital, Mansbach

says. Currently, there is much variability in how babies with bronchiolitis are treated, with nothing consistently proven to be beneficial aside from supportive measures. Under a new five-year grant, Mansbach and colleagues have begun a study to test and track children hospitalized with bronchiolitis prospectively, to see if the type of infecting virus, among many other factors, predicts long-term outcomes such as recurrent wheezing at age 3 or asthma at age 6. The above was provided by Children's Hospital Boston.

A GIRL THING

The negative health effects of early-life exposure to secondhand smoke appear to impact girls more than boys, particularly those with early-life allergic sensitization, according to new research from the University of Cincinnati College of Medicine. Researchers found that children exposed to high levels of secondhand smoke who also had allergic sensitizations during early childhood (age 2) are at greater risk for decreased lung function at age 7 compared to children who had not developed allergic sensitizations by this age. Lung function among girls was six times worse than in boys who were exposed to similar levels of both secondhand smoke and allergen sensitization. This was the first study to explore the differential gender effects of secondhand smoke exposure using an internal biomarker, hair cotinine, for secondhand smoke, while also accounting for the importance of timing and extent of allergic sensitization on lung function. Researchers examined a population of 476 children in the Greater Cincinnati metropolitan area identified from birth to be at increased risk for allergies based on family history and proximity to major roads. Hair samples were collected at age

2 and 4 to measure average cotinine concentrations. At age 7, all children had lung function and asthma diagnosis testing. This information was then correlated with data about allergy sensitization collected through annual skin prick allergy testing, self-report questionnaires about allergy symptoms and the home/school environment.

GOING NUTS

An anecdotal observation of a possible link between sleep apnea and post-surgical delirium has been measured and confirmed by a team of researchers at the Duke University Medical Center. Delirium involves an acute and fluctuating consciousness and ability to understand, and is associated with health problems and higher risk of death right after surgery. It is a strong predictor of mortality even 10 years after surgery. The study investigated patients who were having a total knee replacement. Out of 106 patients, 27 developed delirium after surgery. Eight out of the 15 patients who had been diagnosed with obstructive sleep apnea experienced post-operative delirium, in comparison to 20% of the patients without apnea. The causes of postsurgical delirium are still unknown, but lack of oxygen before or after surgery or possibly immune factors that lead to inflammation may play a role.

TAKE A LOOK

Using a bronchoscope to visually examine the airways and collect fluid and tissue can help guide effective therapy for difficult-to-treat asthma patients, according to researchers at National Jewish Health who identified five distinct phenotypes among the refractory asthma patients, and successfully treated



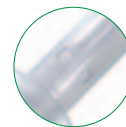
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TRACOE twist plus is available as non-fenestrated and double fenestrated tracheostomy tube with inner cannula and also with or without cuff. Soon available for the percutaneous dilation set in size 10! For more information, visit www.tracoe.com.



Detail of the additional fenestration at the inner bend

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twist

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four of them, often with reduced asthma medications. The research team examined 58 patients with difficult-to-treat asthma, which is generally characterized as needing oral corticosteroids for more than half the previous year or remaining symptomatic in spite of high doses of inhaled corticosteroids. Twenty of the patients received standard guidelines-based treatment for four months, followed by a bronchoscopy and personalized therapy. Thirty-eight received personalized therapy based on the bronchoscopy results. The bronchoscopy included visual inspection of the upper and lower airway, bronchoalveolar lavage, endobronchial biopsy and brush. The researchers identified gastroesophageal reflux, subacute bacterial infection, tissue eosinophilia, a combination of two or three of these phenotypes and non-specific phenotype. Those with GER received therapy or surgery in addition to their standard asthma therapy. Those with subacute bacterial infections received antibiotics, and those with high numbers of eosinophils received omalizumab. After 24 weeks, patients showed marked improvements in both lung function and asthma control. FEV1 rose from 58.9% percent of predicted to 74.3%. ACT test scores rose from 11.6 to 18.5. The 20 patients who received standard, guidelines-based therapy in the control period improved only after beginning targeted therapy.

ANTIBIOTICS AND ASTHMA

Antibiotics can increase the incidence and severity of allergic asthma in kids, according to researchers at the University of British Columbia. They examined how streptomycin and vancomycin affected the bacterial ecosystem in the gut, and found that vancomycin profoundly alters the bacterial communities in the intestine and increases severity of asthma in mouse models. The same antibiotics did not impact adult mice's susceptibility to asthma. The researchers said that modern societal practices, such as improved sanitation methods and widespread antibiotic use, are causing the disappearance of ancestral species of bacteria in our gut that may be critical to a healthy immune system.

GLOBAL WARNING

Global climate change is going to cause a rise in asthma, allergies, and infectious and cardiovascular diseases, according to a position paper by the American Thoracic Society. The biggest issue will be air quality, especially smoke and particulate matter from wildfires which will increase as the climate warms. The authors noted that, by way of example, mold spores that were previously only seen in Central America have been found as far north as Vancouver, BC, promoting increases in allergy and asthma, with climate-change conditions implicated. Infectious diseases common in the Mediterranean region now are being seen as far north as Scandinavia as that area grows warmer. The researchers noted that some of the prospective respiratory health impacts from global climate change will be direct, such as more asthma due to increases in particulate matter in the atmosphere because of desertification, or increases in pollen because of more and extended plant blooms. But some will be indirect, due to populations displaced by extreme weather. It was also pointed out that higher surface temperatures, especially in developed urban areas, will promote the formation of greater amounts of ground-level ozone, exposure to which has been linked to exacerbations of asthma, lung cancer and acute lower-respiratory infections.

INFLAMMATORY

Adding inflammatory biomarkers to clinical variables improves

the prediction of mortality for patients with COPD, according to researchers at Harvard Medical School and Brigham and Women's Hospital. The researchers examined data on 1,843 individuals with COPD from the ECLIPSE study. During the three-year follow-up, the researchers found that 168 (9.1%) of the 1,843 participants died. Mortality predictors included the number of hospitalizations due to COPD, age, and BODE index. The researchers found that the C-statistic considerably improved to 0.708 by adding interleukin-6 (IL-6) to the predictive model. In addition, adding a group of biomarkers, including IL-6, white blood cell counts, fibrinogen, chemokine (C-C-motif) ligand 18 (CCL-18), C-reactive protein (CRP), surfactant protein D (SP-D), and interleukin-8 (IL-8) improved the C-statistic to 0.726. This panel of biomarkers was not only elevated in non-survivors, but was associated with mortality over three years of follow-up after adjusting for clinical variables known to predict mortality in patients with COPD. Information for the above was written by Grace Rattue for Medical News Today, copyright Medical News Today.

WIKI FOR ASTHMA

Dr Samir Gupta, a respirologist at St Michael's Hospital, has found that a wiki website developed collaboratively by a community of users, allowing any user to add and edit content, can be an innovative new tool for developing individual asthma action plans. Dr Gupta said a lot of asthma action plans are developed by experts without input from patients or the clinics that distribute them. When they are difficult to read or understand, patients don't follow them, especially these days when health care providers face competition from the Internet and apps. He assembled a group of respirologists, patients, family doctors and asthma educators, set up a wiki and allowed his group to choose their own content, fonts, color and design for an asthma action plan. There were also voting mechanisms to select choices and a blog to explain them. Participants could log on as often as they wanted. He said the results were collaborative and without the frequent hierarchical issues that can define the patient-doctor relationship. For more see his article in the publication *Journal of Medical Internet Research*.

HEART SHAPE

Researchers with the University of Birmingham discovered that moderate to severe obstructive sleep apnea can cause changes in the heart's shape and function, similar to the effects of hypertension, including increased mass, thickening of the heart wall and reduced pumping ability. However, six months after CPAP treatment, the abnormalities returned to near-normal measurements in sleep apnea patients. The researchers said their findings implied that OSA could be crucial in the development of left ventricular diastolic dysfunction, which can lead to heart failure and increased mortality if left untreated. They evaluated 40 patients with moderate to severe OSA and compared the results with those obtained from 40 people with high blood pressure and 40 healthy people. The OSA patients had abnormal cardiac structure and performance changes typically associated with chronic high blood pressure, even though their blood pressure was only moderately elevated. The scientists concluded that physicians should question patients with hypertension or abnormal echocardiograms about snoring and other signs of sleep apnea.

STOP IT

Many premature infants throughout the US continue to receive inhaled nitric oxide (iNO) during their NICU stay, despite the

lack of evidence to support its use. According to a study at Nationwide Children's Hospital, whether or not a preemie will receive iNO treatment, when and for how long, varies greatly throughout the country, as its use in premature infants appears to be unstandardized. The National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ) have concluded that there is no evidence to support the routine use of iNO in preterm infants who require respiratory support. Nationwide Children's faculty and members of the Ohio Perinatal Research Network (OPRN) performed a retrospective study using the Child Health Corporation of America's Pediatric Health Information Database. The study cohort included 22,699 premature infants born less than 34 weeks gestation admitted to NICUs in 37 US children's hospitals during a three-and-a-half-year period. Findings revealed that the use of inhaled nitric oxide in premature infants was variable, even when controlling for demographic characteristics and disease. There was substantial variation in the age of initiation of iNO treatment and the average number of days of use. Hospitals that used iNO in more patients also used iNO for a longer duration. Higher volume NICUs used less iNO and had lower mortality rates. Northeastern hospitals reported less use of iNO. Infants who received iNO were less likely to survive, suggesting that iNO is used in infants already at high risk of death.

COPD FOUNDATION

Led since inception by Boehringer Ingelheim Pharmaceuticals Inc, the DRIVE4COPD campaign will now be led by the COPD Foundation, a not-for-profit organization dedicated to the education, early diagnosis, research and enhanced therapy for

people with lives impacted by COPD. This change will enable the Campaign to engage broader support and collaboration with more stakeholders. Boehringer Ingelheim will continue as a founding sponsor and financial contributor to the DRIVE4COPD as the campaign shifts its focus to include not only screenings but also continued sharing of health-related information with those at risk. Through continuing relationships with US businesses, the campaign hopes to increase awareness among employees, families and health care providers about COPD and its potential for prevention, early identification and treatment. contact copdfoundation.org or drive4copd.org.

DRINK UP

Red wine = higher lung volumes and white wine = lower risk of airway obstruction, according to a study from the Netherlands. Based on a number of scientific studies, moderate wine intake appears to have a favorable effect on lung function. The doses of resveratrol seen in these epidemiologic studies are at levels that could be expected from moderate wine consumption, unlike the huge doses of resveratrol, which researchers doubt are capable of being metabolized, being evaluated as a potential life-extending drug in pharmaceutical studies.

SLEEP OR ACT UP

A study of more than 11,000 children over six years found that young children with sleep-disordered breathing are prone to developing behavioral difficulties such as hyperactivity and aggressiveness, as well as emotional symptoms and difficulty with friendships, according to researchers at Albert Einstein College of Medicine of Yeshiva University. SDB peaks from two



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TRACOE **phon assist I** is a speaking valve for fenestrated TRACOE *twist* and *twist plus* tracheostomy tubes.

This valve has a silicone membrane with a fast occlusion time and side openings to adjust the supply or the expiration of air individually. That means it allows to set any desired resistance to exhalation which improves the respiratory situation. This innovative and unique feature helps to avoid air trapping especially during the weaning process. Due to the adjustable side openings the patient will find his voice much easier and the valve can be opened completely without detaching it in case of shortness of breath.

It comes with or without an oxygen supply port to allow intermittent oxygen supply for hypoxic or weak patients.

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to six years of age, but also occurs in younger children. About 1 in 10 children snore regularly and 2 to 4% percent have sleep apnea. This study analyzed the combined effects of snoring, apnea and mouth-breathing patterns on the behavior of children enrolled in a longitudinal study of parents and children. Parents were asked to fill out questionnaires about their children's SDB symptoms and a behavior questionnaire at various intervals, from 6 to 69 months of age. Children with sleep-disordered breathing were from 40 to 100% more likely to develop neurobehavioral problems by age 7, compared with children without breathing problems with hyperactivity as the biggest increase. Children whose symptoms peaked at 6 or 18 months were 40% and 50% more likely to experience behavioral problems at age 7 compared with normally-breathing children. Children with the most serious behavioral problems were those with SDB symptoms that persisted throughout the evaluation period and became most severe at 30 months. Researchers surmise that SDB decreases the brain's oxygen levels and increases carbon dioxide levels in the prefrontal cortex, interrupting the restorative processes of sleep and disrupting the balance of various cellular and chemical systems. Behavioral problems resulting from these adverse effects on the brain include impairments in executive functioning (ie, being able to pay attention, plan ahead, and organize), the ability to suppress behavior, and the ability to self-regulate emotion and arousal.

INHALE FOR TREATMENT

Inhaled interferon-gamma may be an effective treatment for idiopathic pulmonary fibrosis, according to researchers at the State University of New York, and NYU School of Medicine. Delivery of aerosolized interferon-gamma directly into the lungs was shown to be safe and was associated with significantly reduced levels of profibrotic regulatory proteins. Inhalation of interferon-gamma in aerosol form three times a week for at least 80 weeks was well-tolerated by patients, with no systemic side effects. The researchers verified the presence of the drug in the material collected on lung washes and documented no change in the level of interferon-gamma in the blood during the treatment period.

NATURAL KILLERS

Researchers at Oxford University found that immune cells called natural killer T cells may reduce the overwhelming numbers of another type of immune cell, inflammatory monocytes, which lead to lung injury at the end stage of severe flu infection. Scientists infected three groups of mice with H1N1 flu virus. The first group included normal mice; the second group was devoid of natural killer T cells, and the third was given a treatment that specifically activated natural killer T cells. Researchers found that the mice without natural killer T cells did worst, and those with activated killer T cells did best. Mice that lacked natural killer T cells had increased amounts of monocytes in the lungs, and severe lung injury similar to those seen in Spanish flu and lethal swine flu. Using fluorescent antibody technology, this study was one of the first to document the sequential changes in innate immune response in the lungs during severe flu infection. These findings essentially provide a road map of the chronological changes in the lungs during severe flu infection.

PRODUCTS

BOOMERANG

AG Industries is now offering The Boomerang Gel Pad, a patent pending CPAP accessory that helps to increase patient

compliance by creating a more secure seal around both nasal and full-face masks. This enhanced seal helps to decrease irritating air leaks and episodes of apnea and will help patients sleep more soundly. In addition, Boomerang also improves overall comfort of nasal and full face masks by reducing skin irritation and soreness across the bridge of the nose and cheeks. The Gel Pad is manufactured out of a non-toxic, proprietary USP grade mineral combined with other skin-soothing essential oils. Safe for all types and even sensitive skin, The Boomerang Gel Pad is hypoallergenic, both latex & silicone free. Contact agindustries.com.

IN THE CLOUD

ResMed Inc announced the release of its new patient compliance management solution, EasyCare Online. The innovative new tool aggregates usage and efficacy data from obstructive sleep apnea patients who use continuous positive airway pressure (CPAP) treatment. The data can be used by sleep labs, home medical equipment and other health care providers involved in managing obstructive sleep apnea. The new tool employs a secure, cloud-based system. EasyCare Online enables users to access all their CPAP patients' therapy data online, anywhere with an internet connection, whether the data is gathered wirelessly or by secure digital (SD) data card. With EasyCare Online, health care providers can quickly identify patients struggling with compliance and address therapy issues. At-a-glance reports are easily accessed with just a few clicks, saving both staff training and execution time. Contact resmed.com.

TAKE A WALK

Futuremed introduces Spiropalm 6MWT, a new concept for the assessment of pulmonary disease. Spiropalm 6MWT combines a complete diagnostic spirometer with a comprehensive tool for real-time recording during the 6 Minute Walk Test. This compact device is worn by the patient at the waist, either on a belt or using its soft harness. Throughout the test, a lightweight oximeter sensor measures the patient's SpO2 and heart rate and stores the information onto the control unit. In addition, Spiropalm 6MWT comes with a mask, through which it continuously records the patient's ventilation and breathing pattern. The finished result is a comprehensive report that incorporates standard 6-Minute Walk records (such as distance and Borg score) with Ventilatory Parameters (VE, RF, Breathing Reserve and Inspiratory Capacity), enabling the clinician to evaluate Dynamic Hyperinflation and air trapping in COPD patients. Spiropalm 6MWT also performs screening spirometry, including Forced Vital Capacity (FVC), Pre- and Post Medication Comparisons, Slow Vital Capacity (SVC), Maximal Voluntary Ventilation (MVV), and Bronchial Challenge Testing. For more information, and for a catalog of Futuremed's cardio-pulmonary equipment, visit futuremed.com or call (800) 222-6780.

REPEATABLE

Custom engineered aerosol nozzle plates, spray nozzles, and related fluid dispensing and control components requiring highly precise sub-micron holes for medical, pharmaceutical, biotech, and instrumentation applications are available from Stork Veco International, Inc of Burlington, MA. Stork Veco Fluid Dispensing and Control Components are custom engineered and can be produced with 2 micron holes and tolerances $> \pm 0.5$ micron. Mostly fabricated from nickel, these high precision parts are electroformed which permits sharp edge definition with a venturi profile and virtually any hole shape and pattern design, including complex apertures and slits. Permitting precise

drop size control, Stork Veco Fluid Dispensing and Control Components can be produced in prototype to production quantities. Since electroforming involves growing the parts ion-by-ion, they are burr-free and ultra-precise. Typical parts include nebulizers, orifice plates for flow control, filters, and field stops for endoscopes. Contact spgveco.com.

GRANTED

Covidien announced that the FDA has granted 510(k) clearance to market the Covidien Nellcor Respiration Rate Version 1.0 software and the Adult Respiratory Sensor. In late 2011, Covidien labeled the respiratory monitoring platform with the CE Mark and began to market it throughout the European Economic Area. The company planned a limited market release in the US, starting in April, which allows select hospitals to be the first to use the new technology. The addition of Respiration Rate to the Covidien Nellcor Respiratory Function portfolio provides a more holistic monitoring solution using a single, integrated sensor. Instead of merely knowing a patient's blood oxygen levels, users can now look at aspects of ventilation, or the passing of air into and out of the body. This gives healthcare professionals a more complete picture of a patient's respiratory status, so they can provide effective treatment and maintain patient safety. Contact covidien.com.

APPROVED

Discovery Laboratories, Inc announced that the United States Food and Drug Administration (FDA) has approved SURFAXIN (lucinactant) for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS. SURFAXIN is the first synthetic, peptide-containing surfactant approved for use in neonatal medicine. Discovery Labs anticipates that SURFAXIN will be commercially available in the United States in late 2012. The safety and efficacy of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a large, multinational phase 3 clinical program that included 1294 patients. For more visit www.surfaxin.com.

TWO FROM FOREST

Forest Laboratories, Inc announced that it has been granted European Medicines Agency (EMA) approval to market **Colobreathe** dry powder colistimethate sodium for inhalation for treating cystic fibrosis patients aged 6 years and older with chronic lung infection caused by *P. aeruginosa*. The study of Colobreathe demonstrated the benefits and its ability to prevent deterioration of respiratory function in Cystic Fibrosis patients. The pivotal study which was submitted to EMA for authorization was an open-label active comparator study comparing the efficacy of Colobreathe to TOBI (tobramycin nebulizer solution for inhalation). This study also demonstrated better patient acceptability of Colobreathe. Importantly, data from the study of Colobreathe showed that overall the product was well tolerated and there was no emergence of antibacterial resistance. Colobreathe is a capsule containing 1,662,500 IU of colistimethate sodium which is approximately equal to 125 mg. It is used with a Turbospin inhaler device which is a relatively small (10 cm long), portable medical inhalation device, and uses the patients inspiratory flow to activate delivery of the dry powder into the lung. Each pack of Colobreathe will contain 56 capsules which is enough for 28 days treatment, and one Turbospin inhaler device, which is discarded at the end of the period... Forest also announced that the FDA Pulmonary-Allergy Drugs Advisory Committee (PADAC) voted 12 to 2 in favor of approving the New Drug Application for **aclidinium bromide**, a new long-acting

antimuscarinic for the maintenance treatment of COPD. The Committee was also asked to separately evaluate if the efficacy and safety of the 400 ug twice daily dose had been adequately demonstrated. The members voted unanimously in favor of efficacy and 10 to 3 (1 member abstained) in favor of safety. Acclidinium bromide is a novel, long-acting inhaled antimuscarinic agent, which is often referred to as an anticholinergic that has a long residence time at M3 receptors and a shorter residence time at M2 receptors. When given by inhalation, acclidinium leads to bronchodilation by inhibiting airway smooth muscle contraction. Acclidinium is rapidly hydrolyzed in human plasma to two major inactive metabolites. Acclidinium bromide was administered to patients in the trials using a novel, investigational state-of-the-art multidose dry powder inhaler (MDPI). This inhaler was designed with a feedback system which, through a "colored control window" and an audible click, helps confirm that the patient has inhaled correctly. It contains multiple doses of acclidinium, includes a visible dose-level indicator, and also incorporates safety features such as an anti-double dosing mechanism and an end-of-dose lock-out system to prevent use of an empty inhaler. Contact frx.com.

COMPLEMENTARY

Covidien announced a definitive agreement to acquire Oridion Systems Ltd, based in Jerusalem. Oridion develops Microstream capnography monitors and modules, in conjunction with specialized algorithms, as well as etCO₂ breath sampling lines. Oridion's products will complement Covidien's portfolio of solutions to monitor respiratory function. Once the transaction has been completed, Covidien will report the Oridion Systems business as part of its Oximetry & Monitoring product line in the Medical Devices segment. Contact covidien.com.

OSA OKAY

ImThera Medical Inc announced European CE Mark (Conformité Européenne) approval of its aura6000 system for the treatment of obstructive sleep apnea (OSA). The aura6000 system delivers mild electrical pulses to stimulate targeted muscles of the tongue during sleep, operating as a pacemaker for the tongue. The system uses ImThera Medical's patented Targeted Hypoglossal Neurostimulation (THN Sleep Therapy) method to focus neurostimulation on certain muscles of the tongue during sleep. The aura6000 system consists of an 11 cm³ rechargeable neurostimulator—among the world's smallest—that generates electrical pulses and a lead (wire) with multiple electrodes that delivers the pulses to the hypoglossal nerve, which controls all muscles of the tongue. Patients use a remote control and charger (RCC) to turn the system on/off and to recharge the neurostimulator. (The aura6000 is not available in the US.) Contact intheramedical.com.

IT'S ACADEMIC

As part of the company's ongoing commitment to training and education, Dräger has released an innovative online educational program entitled "Dräger Academy – Basics of Respiration and Ventilation." Having launched an entire new portfolio of latest generation products to serve critical care, neonatal care and acute/chronic care, Dräger worked with industry leaders in respiratory care management and education to develop a complementary educational program that covers the fundamentals of respiratory physiology and mechanical ventilation. "Our customers demand not only high quality products, but also comprehensive and flexible training," says Ed Coombs, Regional Marketing Director, for Draeger Medical,

Inc. “This new Dräger Academy program is interactive and Web-based, so it can be completed at the convenience of the clinician’s schedule. At Dräger, we are committed to providing best-in-class service and programs to support and promote improvements in patient care.” The Dräger Academy program, which qualifies for continuing education credit, is available to all clinicians who practice respiratory care. For more information, please go to draeger.com/academy.

ANTIBODIES

AstraZeneca and Amgen announced an agreement to jointly develop and commercialize five monoclonal antibodies from Amgen’s clinical inflammation portfolio: AMG 139, AMG 157, AMG 181, AMG 557 and brodalumab (AMG 827). The companies believe all the molecules have novel profiles and offer the potential to deliver important treatments across multiple indications in inflammatory diseases. The collaboration will provide Amgen with additional resources to optimally progress its portfolio, and Amgen will benefit from the strong respiratory, inflammation and asthma development expertise of MedImmune, AstraZeneca’s biologics arm. The collaboration will also capitalize on AstraZeneca’s global commercial reach in respiratory and gastrointestinal diseases. Contact astrazeneca.com or amgen.com.

R&D

Springer Science+Business Media has launched a new corporate platform, Springer for R&D (rd.springer.com), which provides access to over 5.6 million research documents, all optimized for specific corporate markets. Springer for R&D aims to become the primary resource destination for all new corporate and medical customers. All articles in Springer for R&D are taken from Springer’s online platform SpringerLink, which will remain in its existing form serving the academic community. Featuring new content navigation by industry sectors, Springer for R&D provides instant access to pertinent materials to groups of customers in industry sectors from Automotive to Oil, Gas & Geosciences and from IT to Biotechnology. The platform utilizes agile software development methodologies, enabling Springer to quickly develop and deploy new features. This same methodology allows Springer to optimally offer content to both the niche research organization and the large multinational company alike.

MOBILE

Medical technology company iSonea Ltd announced that it will design and market a home and mobile asthma monitoring platform with global telecommunications corporation Qualcomm Life Inc. The new technology will combine iSonea’s proprietary Acoustic Respiratory Monitoring (ARM) devices and mobile health asthma management systems with Qualcomm’s 2net platform. The integration will automatically and securely link patient asthma symptom and trend monitoring data to a cloud-based portal for physicians and caregivers, to improve asthma management and outcomes. The effort leverages Qualcomm Life’s 2net Hub, a plug-and-play connectivity gateway to the cloud-based 2net platform data server, to collect and transmit patient health data from iSonea’s monitoring devices. The technology will ultimately allow physicians to securely access patient monitoring data, review treatment progress and medication adherence and adjust patient action plans accordingly. Family and caregivers will be able to view trends for reassurance about patient care. Contact isoneamed.com.

QUICK

Kimberly-Clark announced the launch of the QR (Quick Response) Code Patient Safety Education Program in collaboration with Safe Care Campaign to provide hospitals and healthcare facilities with free patient and caregiver education available instantly at the bedside. Kimberly-Clark and Safe Care Campaign teamed up with the Centers for Disease Control and Prevention, The Joint Commission’s Speak Up Educational Campaign and the Patient Channel to issue the “Learn How to Be Safe While Receiving Medical Care” QR-code enabled poster to healthcare facilities nationwide. The free poster delivers critical patient education information directly into the hands of patients and their families when they need it most and requires no staff time or training. The Patient Safety Education Program poster offers instant access via a QR reader app or text message to nine educational vignettes related to healthcare facilities’ safety issues: insisting on proper hand hygiene from your caregiver; preventing an infection when you’re having surgery, preventing a blood stream infection, preventing medication errors, preventing an infection when you have a urinary catheter, preventing errors during medical care, preventing patient falls, safety when your loved one is on a ventilator, and a Patient’s Guide to a Clean Healthcare Environment. Contact safecarecampaign.org or kchealthcare.com.

VP NAMED

Restech (Respiratory Technology Corporation), innovator of the first airway reflux detection device, the Dx-pH Measurement System, announced the addition of James Pittman to its staff as Senior Vice President, Global Sales, Marketing and Business Development. Pittman will lead commercialization and marketing activities as well as business development initiatives to increase growth potential for Restech worldwide. He has twenty-six years of sales and marketing experience in ambulatory pH monitoring. He has worked for Synectics Medical, Medtronic, and Sierra Scientific. Contact restech-corp.com.

WIPEOUT

Mada Medical Products, Inc, CPAP Mask Wipes are designed to clean CPAP masks safely and effectively. Their unique features include the wipes construction of 100% pure cotton, and the ingredients consisting of 100% natural cleaners derived from coconut and other plant extracts. Mada has been manufacturing respiratory therapy and infection control products for 42 years. Contact madamedical.com.

RAGWEED

Merck announced the results from a Phase III clinical study of its investigational allergy immunotherapy tablet (AIT) for ragweed pollen. The study results showed that the use of ragweed AIT significantly reduced the total combined score that measured nasal and eye symptoms and use of rescue allergy medicines, compared to placebo, in ragweed-allergic adults with or without asthma. The study was conducted during peak ragweed pollen season. These data were presented at the American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting in Orlando. Merck’s AIT is an investigational, dissolvable oral tablet designed to treat the underlying cause of allergies, and is being studied to determine whether AIT may help to prevent allergy symptoms by generating an immune response to protect against targeted allergens. The company is investigating disease-modifying AITs for the treatment of allergies caused by ragweed pollen, grass pollen and house dust mites. Merck has partnered with ALK-Abello to develop AITs to treat these allergens in North

America and plans to file New Drug Applications (NDAs) for its ragweed and grass AITs with the FDA. The multicenter, double-blind, randomized, placebo-controlled, parallel group Phase III trial was designed to assess the efficacy and safety of two doses of ragweed AIT. The study involved 565 adults who were 18 to 50 years old with ragweed-induced allergic rhinoconjunctivitis, with or without asthma. The majority of these patients (85%) were sensitive to multiple allergens. Patients were randomized to receive a once-daily tablet of Ambrosia artemisiifolia (ragweed) allergen extract at a dose of 6 Amb a 1-U or 12 Amb a 1-U or placebo for approximately 16 weeks prior to and throughout the ragweed pollen season, for a total treatment period of 52 weeks. During ragweed pollen season, patients recorded their symptoms and rescue medication use daily in electronic diaries. During peak ragweed season, patients treated with ragweed AIT 12 Amb a 1-U or AIT 6 Amb a 1-U showed 27% and 21% reductions in total combined score, respectively, relative to placebo. Specifically, both doses of ragweed AIT resulted in significant reductions in daily symptom score relative to placebo during peak ragweed season. Contact merck.com.

INHALE

Novartis Pharmaceuticals Corporation today announced that once-daily Arcapta Neohaler (indacaterol inhalation powder) 75 mcg is now available in the US and in pharmacies nationwide. Arcapta Neohaler is indicated for the long-term maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD, including chronic bronchitis and/or emphysema. Arcapta Neohaler is not indicated to treat asthma. It is also not indicated to treat acute deteriorations of COPD and should not be used as a rescue medication for acute symptoms. Arcapta Neohaler is the only once-daily, 24-hour long-acting beta2-agonist (LABA) approved in the US for maintenance treatment of airflow obstruction in patients with COPD. Arcapta Neohaler is an inhaled, steroid-free COPD treatment. Arcapta Neohaler 75 mcg was studied in a total of 641 COPD patients in two key Phase III trials lasting 12 weeks. The primary endpoint results at week 12 showed that Arcapta Neohaler significantly improved lung function (FEV1) at 24 hours compared to placebo. As a secondary endpoint, lung function (FEV1) improvements were seen at five minutes after the first dose compared to placebo, and improvements observed at week 4 were consistently maintained over the course of 12 weeks in both trials. Once-daily Arcapta Neohaler also reduced the need for patients to use short-acting beta2-agonists (albuterol) as rescue therapy, measured as a secondary endpoint. Additionally, Arcapta Neohaler is the only COPD treatment approved with demonstrated improvements in health-related quality of life, as measured by the St George's Respiratory Questionnaire (SGRQ). The safety and tolerability of Arcapta Neohaler was assessed in a clinical program of more than 5,400 COPD patients, with more than 2,500 who received Arcapta Neohaler for at least 12 weeks at doses of 75 mcg or higher. Adverse reactions were reported by 48% of patients treated with any dose of Arcapta Neohaler compared with 43% of patients treated with placebo. The most common serious adverse reactions were COPD exacerbation, pneumonia, angina pectoris, and atrial fibrillation, which occurred at similar rates across treatment groups. Contact novartis.com.

SLEEP THE DAY AWAY

Royal Philips Electronics joined with the World Association of Sleep Medicine (WASM) as an official sponsor of World Sleep Day 2012, held on Friday, March 16. This year's theme, "Breathe Easily, Sleep Well, centered on raising awareness of sleep disorders

that affect a person's breathing, such as obstructive sleep apnea. Through Philips Respironics, a global leader in the sleep and respiratory markets, Philips provides medical sleep products, especially for people suffering from OSA and those who seek to improve their quality of sleep. To educate people on the risks, diagnosis and treatment options for OSA, Philips Respironics launched an OSA educational program on featuring an interactive OSA risk assessment "sleep quiz." Contact philips.com.

ENHANCED

Philips Respironics recently launched an enhanced version of the Actical physical activity monitoring system. The device is intended for researchers who need real-time ambulatory monitoring in real-world applications. The Actical system allows users to collect and examine high-resolution data easily on a subject's physical activity, steps, and energy expenditure levels for longer periods of time than was possible with the previous Actical system. With enhancements that include fast and more epoch length options, including the ability to collect epoch lengths as short as one second, and collect raw data at 32Hz, users can better meet the specific needs of their studies. The flexible and powerful software enables data to be viewed and analyzed in multiple ways for research endpoints such as physical activity, energy expenditure, and step count. These values can be calculated quickly over minutes, hours, days, and weeks. Enhancements to the Actical system were made without altering its size. The compact, lightweight, and noninvasive design of the device allows subjects to continue to go about their activities of daily living without noticing they are wearing it. Actical also has a waterproof enclosure which is especially useful for certain activities such as swimming. Contact philips.com.

IT'S BACK!

The Salter Labs #7900 High Flow Humidifier is now available for order. The #7900 High Flow Humidifier is the first and only dry bubble humidifier cleared for oxygen flows of 6-15 LPM. It is the ideal complement to the 1600HF Series of High Flow Cannulas. This system provides unmatched performance for patients requiring oxygen flow rates of 6-15 LPM. The product line is available in multiple configurations including convenient prepackaged kits that contain a high flow cannula to enable efficient and effective patient setups for clinicians and caregivers. Contact (800) 421-0024, salterlabs.com.

PARTNERS

Philips Respironics has launched its Partners in Training website. The website is designed to help increase the awareness and identification of obstructive sleep apnea among physicians and other healthcare professionals. The website is philips.com/partnersintraining. Philips Respironics' Partners in Training (PIT) program offers marketing and educational materials and provides the tools needed to design, build and manage a successful sleep apnea treatment program.

GIVEAWAY

TheraBiogen, Inc creator of the homeopathic remedy TheraMax Cold and Flu has generously offered their product to India's Minister of Health and Family Welfare to help in their H1N1 Flu outbreak. TheraMax Cold and Flu has been tested in vitro on various strains of influenza and in vitro specifically on H1N1 strain. It is delivered through a nasal spray. It is a non-addictive all natural decongestant formula that aids in speedy relief of sneezing, runny nose, itch-watery eyes, nasal congestion and sinus pressure from the flu and colds. It has the potential to

be a preventative if used at the first signs of a cold or flu. This product is completely homeopathic and doesn't contain zinc, reducing the risk of side effects caused from zinc remedies. Contact theramaxrelief.com.

BLOOD GAS ROUNDTABLE

Alere, Inc

Please describe your blood gas products and their applications.

The epoc Blood Analysis System, marketed by Alere, Inc, provides blood gases, electrolytes and metabolic panel results at the bedside in about 30 seconds on a PDA, with wireless transmission to the patient record. It's the cost effective POC testing solution, easily integrating into any critical care setting, and delivering accurate, actionable results to enable timely clinical decisions. It features: • Room Temperature Test Card Storage; • 9 measured analytes on a single Test Card: pH, pCO₂, pO₂, Na⁺, K⁺, Ca⁺⁺, Glu, Hct, Lac; • 6 calculated Values: cHCO₃⁻, cTCO₂, BE(ecf), BE(b), cSO₂, cHgb; • Critical Result Reporting; • 92uL sample size; • No maintenance.

What type of training and customer assistance/support programs do you offer?

Alere provides full on-site operator training prior to go-live, as well as on-site support at the time of the go-live. Alere provides 24x7 customer technical support.

Tell us about your company's latest R&D efforts.

Epocal, Inc submitted to the FDA for 510k clearance for Creatinine and Chloride, all on the same test card. Future enhancements will include BUN as well as coagulation.

Discuss point of care testing and your product.

What distinguishes epoc when compared to other blood gas devices, whether at the bedside or benchtop, is that it is designed to easily integrate into your clinical care process. epoc gives you the right result at the right time, on a PDA in about 30 seconds. With its small size and wireless capability, epoc allows the caregiver to stay at the bedside where they are needed most, not running back and forth between a distant workstation or laboratory. It seamlessly integrates into the hospital's existing wireless network and easily interfaces into their LIS/HIS system. The epoc system is designed to allow for seamless integration of a growing test menu, and will have additional panels available in the near future. It's completely modular – which allows customized implementation solutions to fit the specific needs of any clinical workflow throughout the organization.

How does your product provide for accuracy in measurement?

The epoc system leverages potentiometric, amperometric and conductometric signals from a Sensor Interface Circuit, similar technology found on legacy blood gas devices. There are also three phases of QC tests performed by the epoc System: 1) Initialization: An initial battery of tests covering two different levels over the dynamic range is performed by the epoc Reader (epoc Reader electronic QC test) every time the Reader connects with an epoc Host. In addition, QC tests are performed by the epoc Reader on the card and on the operator process after card insertion during initialization. 2) In-calibration: QC tests performed to assess the card and sensors' conformance during

the calibration interval before sample is introduced. 3) During sample measurement: QC tests performed to monitor the operator procedure and sample integrity during and after sample introduction.

Nova Biomedical

Please describe your blood gas products and their application.

Nova Stat Profile pHox blood gas/critical care analyzers offer the broadest test menu of any blood gas/critical care analyzers, at low cost. With up to 20 tests on board, fast, economical critical care results, and the industry's best overall user satisfaction, Nova's products are the best value in critical care testing. Our Stat Profile pHox Ultra is the only blood gas/critical care analyzer to provide a comprehensive stat menu including blood gases, essential chemistry and hematology, and co-oximetry tests. No other blood gas/critical care analyzer can match the clinical value of pHox Ultra to effectively manage high acuity, critically ill patients.

What type of training and customer assistance/support programs do you offer?

Immediately following analyzer installation, training of operators on all shifts is provided by Nova training and applications staff. Correlation and transition studies are included as part of the training process. We maintain a highly skilled and experienced technical support "hotline" staff to answer calls 24/7/365, as well as one-day on-site service by a trained Nova representative. Our Peak Performance Plus program includes: • Onsite Validation Assistance by a Nova Clinical Application Specialist including Linearity, Precision, Correlation, and Data Processing; • Onsite Linearity Testing Assistance every 6 months by a Nova Clinical Applications Specialist; • Onsite Assistance every 6 months by a Nova Clinical Applications Specialist to perform patient cross checks to the Clinical Laboratory Reference Analyzer; • Proactive Weekly Onsite Visits by the Nova Field Support Specialist for the first 90 days after implementation. These onsite visits include: ongoing operator training for all levels of users; ongoing review of QC program and QC range establishment; • Routine PMs performed on all systems by the Nova Field Support Specialist every 6 months. Nova administers a periodic Customer Satisfaction Survey to allow customers to grade our performance and offer suggestions, thereby helping us improve in ways that are meaningful to them.

Tell us about your company's latest R&D efforts.

Nova has introduced, this year, the pHox Ultra analyzer featuring the broadest test menu in one analyzer, with 20 user selectable tests including pH, PCO₂, PO₂, sO₂%, Hct, Hb, Na⁺, K⁺, iCa, iMg, Cl⁻, Glucose, BUN, Creatinine, Lactate, CO-Oximetry and tBil. pHox Ultra's large, high resolution, color touch screen offers fast and easy operation. Bright color and graphic highlighting provide exceptional readability. Nova's onboard, automated Internal Quality Assurance (IQA) performs over 40 automatic checks during sample and calibration cycles to verify correct performance—saving time and labor versus manual QC, and assuring optimum analyzer performance. pHox Ultra's complete, onboard Data Management System, networking and interface capabilities save thousands of dollars compared to the purchase of a separate data manager. The Data Manager can consolidate multiple, networked pHox Ultras into a comprehensive database for capture, archiving, and extensive data reporting. It also

provides a single HIS/LIS interface for multiple pHox Ultras throughout a network, saving thousands of dollars in separate interface costs. Remote review and remote control of multiple, network connected analyzers can also be performed from the onboard Data Manager.

Discuss point of care testing and your product.

As the acuity of patients seen in the hospital increases, point of care testing for blood gases and other critical care tests continues to expand. As a result, more and more blood gas/critical care analyzers are being placed at the point of care. For example, blood gas/critical care analyzers are playing a role in addressing the overcrowding crisis in the emergency department by providing improved turnaround time of urgent tests such as blood gases and Chem 8. In many institutions, RTs are leading the way to improving patient care by providing more tests from a single sample using fewer resources and generating faster results. Increased use of point-of-care testing also demands that devices be more automated. Nova analyzers feature fully automated operation with analysis of selected test menus with just a push of a button. They perform an automated two-point calibration at pre-set intervals to assure that the instrument is ready for analysis at all times. Automated, on-board, true liquid quality control eliminates the steps involved in manually performing QC thereby dramatically reducing labor costs.

How does your product provide for accuracy in measurement?

Nova analyzers feature state-of-the-art biosensors that have been well characterized and proven to provide excellent accuracy throughout their analytical measurement range. Sophisticated, computerized self-monitoring of the entire analysis and calibration cycles assures error-free and accurate analyzer performance. Extensive automation of Nova analyzers eliminates variability due to operator technique.

RNA Medical

Please describe your blood gas products and their applications.

RNA Medical has a wide variety of quality control materials for the laboratory. Our daily QC materials offer aqueous, dye-based and bovine based products for use with blood gas, critical blood analyte, CO-Oximetry, and diabetes care instrumentation. Our blood gas controls are assayed for most blood gas analysis systems measuring pH, pCO₂, pO₂, Na⁺, K⁺, Cl⁻, Ca⁺⁺, Mg⁺⁺, BUN, glucose, and lactate. RNA Medical quality control materials for use with CO-Oximetry offer the choice of using an aqueous dye-based material or bovine hemoglobin solution compatible across multiple platforms. RNA Medical does not sell or distribute analyzers; therefore we provide an unbiased source of QC products for most blood gas analysis systems.

What type of training and customer assistance/support programs do you offer?

RNA Medical offers an on-line Statistical Services Program (PeerQC), which is available at no cost to users of RNA Medical quality control materials. PeerQC is a simple to use web-based application with error prevention technology that provides instantaneous peer reports while preventing data transcription errors. This program enables our quality control customers to enter their data to this on-line program, and review their results in comparison with a peer group in real-time. RNA Medical has a

well established, experienced Customer and Technical Support Group that is available for questions about the products and services offered.

Tell us about your company's latest R&D efforts.

RNA Medical is currently working on extending the ranges of our CVC 123, Calibration Verification Controls for pH, pCO₂, pO₂, Na⁺, K⁺, Cl⁻, Ca⁺⁺, Mg⁺⁺, glucose, and lactate. We keep a close ear to the needs of our end users, and are continually adding instruments and analytes to our product inserts.

Discuss point of care testing and your product.

With the need for hospitals to provide faster patient results, more testing is provided at the point of care. RNA Medical's quality control materials are essential for keeping point of care instruments in compliance, and help to assure the equipment is working properly so that accurate critical medical decisions can be made.

How does your product provide for accuracy in measurement?

RNA Medical is known for the lot to lot consistency of our quality control products which our customers have depended upon for years. Our most popular products are the Calibration Verification kits (CVC 123 for Blood Gas and Electrolytes, and CVC 223 for CO-Oximetry) which enables linearity reporting. RNA also provides free online linearity graphing and peer group comparison through our PeerQC website.

Roche

Please describe your current blood gas products.

As a world leader in diagnostic testing, the Roche **cobas b 221** blood gas system was uniquely designed to help provide virtually uninterrupted performance. One way of doing this is by resolving blockages often caused by blood clots. Blood clots are commonplace for most blood gas analyzers and it can be time consuming to return the analyzer to reliable performance. If a clot enters the **cobas b 221** blood gas system, a powerful fluidic system that includes both peristaltic pump and vacuum pump mechanics can remove the source of trouble and help minimize downtime. The **cobas b 221** configurable menu has options for blood gas (pO₂, pCO₂, and pH), electrolytes (Na⁺, K⁺, Cl⁻, Ca⁺, Hematocrit), metabolites (glucose, lactate, BUN), and Co-oximetry (O₂Hb, HHb, COHb, MetHb, tHb, Bilirubin). The **cobas b 221** blood gas system was the first FDA 510(k) cleared for testing pleural fluid pH. With the ability to trend patient data and automated acid-base mapping trending, the **cobas b 221** system provides actionable information and simplifies regulatory compliance. The **cobas b 221** blood gas system coupled with **cobas bge link** Instrument Manager software enables monitoring and control of decentralized system from one location. **Cobas bge link** enhances operational efficiency of all connected systems through screen sharing to provide immediate real-time performance status, maintenance updates, and remote access for administrative management.

What type of training and customer assistance/support programs do you have in place?

Roche Diagnostics provides a variety of educational materials to help healthcare professionals operate the **cobas b 221** system properly and help maintain operator certification. These educational materials include: • Onboard video tutorials and a

customer-based training CD-ROM along with Instruction manuals that provide detailed descriptions to help operators avoid errors using the equipment. • Roche offers a two-day training programs at its Indianapolis headquarters for two operators as well as on-site training at the customer facility. • Roche offers extensive on-line support through MyLabOnline, which gives users web-based access to all current documentation such as MSDS sheets, package inserts, customer bulletins and manuals. • Online CEU courses are available for staff members to help maintain their lab and/or Respiratory Therapy accreditation. • Roche's Indianapolis-based Tech Support team provides telephone support for immediate, real-time troubleshooting which may help reduce downtime and the need for a service visit.

Tell us about your company's latest R&D efforts.

As a global leader in diagnostics and pharmaceuticals, Roche is focused on helping patients live longer, healthier lives. Roche Group is one of the top three R&D investors in the human healthcare field, investing \$9 billion annually into solutions for personalized healthcare. Roche Diagnostics is committed to continuous research and development in blood gas systems. The **cobas b 123 POC System*** is the next generation portable POC blood gas instrument in the Roche portfolio that is currently in 510(k) submission with the FDA. The **cobas b 123 POC** system is a fully automated POC system to measure pH, blood gases (BG), electrolytes (ISE), hematocrit (Hct), metabolites (Glu, Lac), total hemoglobin (tHb), hemoglobin derivatives (O₂Hb), HHb, COHb, MetHb), oxygen saturation (SO₂). In addition, the **cobas b 123 POC** system calculates derived parameters. It is dedicated for use in a point-of-care environment and laboratory. The integrated AutoQC module and the oximeter module are available as options. * This product isn't cleared or available for use in the US. A 510(k) submission is pending.

Discuss point of care testing and your product.

The **cobas b 221** blood gas system can help improve point of care testing by delivering results in 60 seconds for fast turnaround time and enhanced workflow efficiency. The speed to results combined with the low blood sample volume (88 µl), required by the **cobas b 221**, helps healthcare professionals get blood gas test results faster and reduces the time for physicians to make critical medical decisions that impact patient outcomes. In addition, the **cobas b 221** offers direct interfacing options to the hospital HIS/LIS which allows the respiratory therapist to run the sample and enable the physician to interpret the results in another part of the hospital or remotely. The automated acid-base mapping on the **cobas b 221** system can help clinicians rapidly identify metabolic and respiratory acid-base disturbances without the need for a calculator and help differentiate between acute and chronic patient conditions in complex environments such as the ED or ICU. The **cobas b 123 POC** system is a near patient blood gas analyzer that is currently in FDA 510(k) submission. The **cobas b 123 POC** system is designed for hospital point of care testing in the ED, ICU, OR, and RT.

How does your product provide for accuracy in measurement?

The **cobas b 221** system maintains accuracy through calibrations with NIST calibration solutions and an AutoQC module. The **cobas b 221** can be programmed to run a 1-point calibrations every 30 minutes or 1 hour, 2-point calibration every 4, 8, or 12 hours, and a 2-point system calibration every 8, 12, or 24 hours. The AutoQC module utilizes a 120 ampoule based system that can be programmed to perform individual QC

sampling at the times and frequency programmed by the user. A sample can only be run after a valid calibration has been completed. If a calibration error is detected, the **cobas b 221** system automatically reruns the calibration. The AutoQC system can also be set to rerun and lock out future samples should they fail in order to assist with regulatory compliance. In the critical care setting, spectrophotometer analysis of hemoglobin and its derivatives (co-oximetry), in combination with blood gas analysis, provides immediate actionable information about oxygen transport in human blood. The accuracy of the hemoglobin and bilirubin results depends on the performance of the co-oximetry technology. The co-oximetry module of the **cobas b 221** blood gas system measures both hemoglobin derivatives and bilirubin spectrophotometrically in the visible spectrum (460nm to 660nm). Absorbance of the sample is measured at a total of 512 discrete wavelengths. The concentration of hemoglobin, hemoglobin derivatives and bilirubin are determined by applying an accepted mathematical algorithm. This enables the **cobas b 221** systems' co-oximetry technology to detect the presence of light-absorbing substances necessary to prevent the reporting of incorrect values due to interfering substances. This advanced co-oximetry design helps improve the accuracy of patient test results, while demonstrating a high correlation with results from accepted clinical chemistry methods.

Siemens Healthcare Diagnostics

Please describe your blood gas products and their applications.

Siemens Healthcare Diagnostics offers a comprehensive portfolio of blood gas solutions with our RAPIDSystems family of analyzers, which are designed to meet the full range of customer testing needs, from low-volume critical care settings to high-throughput laboratory environments. The most recent addition to our RAPIDSystems portfolio is the RAPIDPoint 500 System, a compact, cartridge-based analyzer intended for ease of use in point-of-care (POC) settings. The RAPIDPoint 500 system leverages proven Siemens technology to deliver laboratory-quality results for a complete critical care test menu in approximately 60 seconds from a single, whole blood sample. Further, the RAPIDPoint 500 system is engineered to maximize uptime, with automated calibration and quality-control functions that help POC and laboratory professionals satisfy organizational and regulatory compliance requirements, and 28-day measurement and Automatic Quality Control (AQC) cartridges that operate without manual intervention. Our analyzer for cost effective testing in high-volume, centralized settings is the RAPIDLab 1200 system. It offers an extensive critical care menu, including pH and blood gas, electrolytes, glucose, lactate and full CO-oximetry. With this analyzer, patient results are also available in approximately 60 seconds, allowing clinicians to initiate appropriate therapies as quickly as possible. Also, integrating Siemens blood gas systems with the RAPIDComm Data Management System gives POC coordinators the ability to manage and control the quality of their testing over multiple blood gas, urinalysis, and HbA1c analyzers on their network. In addition to device management, the RAPIDComm system also enables the ability to manage operator access and set operator certification requirements, manage QC results, and remotely troubleshoot devices on the network.

What type of training and customer assistance/support programs do you offer?

With clinical laboratory managers facing staffing shortages, cost constraints and greater workloads, the value of education becomes increasingly important. Siemens offers both live and virtual training for its customers. In addition to providing onsite training from application specialists, Siemens recently launched Personalized Education Plan (PEP) to help address many of these challenges via an innovative approach to professional healthcare education. PEP is the industry's first competency-based clinical laboratory educational model focused exclusively on the individual. Healthcare professionals, guided by their own instructional avatar, are easily able to plan a wide variety of product-specific, professional development and job-relevant courses. Specific to blood gas education, PEP currently offers both instrument-specific training as well as courses on the clinical significance and measurement principles of blood gas testing.

Tell us about your company's latest R&D efforts.

Siemens Healthcare Diagnostics is committed to driving innovation in the critical care POC market and continues to make significant investments in R&D to enhance our existing systems and launch new products. We are always looking to further adapt our test menus to meet the evolving needs of our customers, as well as expand our instrument product line, as is evidenced by the introduction of the RAPIDPoint 500 analyzer last year. Additionally, we will continue to update the RAPIDComm informatics platform by increasing connectivity to Siemens devices and growing overall functionality.

Discuss point of care testing and your product.

With demand for POC testing increasing, it's important that clinicians have access to diagnostic solutions that deliver fast, laboratory-quality results. Siemens' blood gas solutions for the point of care are designed to help meet these needs so that clinicians feel confident in testing that is conducted closer to the patient. For example, the RAPIDPoint 500 analyzer helps preserve sample integrity and improve safety with features such as automated sample aspiration, self-cleaning probe and clot-detection features. Further, automatic QC and calibration systems help ensure accuracy and simplify compliance.

How does your product provide for accuracy in measurement?

For more than 40 years, Siemens Healthcare Diagnostics has been developing critical care systems, including blood gas analyzers that incorporate innovative AQC systems. Our Quality Control products and services are designed to help laboratories monitor the reliability and performance of their instrumentation, measure the variability of tests performed and evaluate the integrity of all results reported. Our commitment to consistency and stringent quality control helps laboratories meet ever-increasing regulatory demands and higher performance goals.

SLEEP ROUNDTABLE

Fisher & Paykel Healthcare

Tell us about your company's sleep products.

At Fisher & Paykel Healthcare we believe everyone should enjoy a good night's sleep. Our comprehensive range of CPAP devices, masks and humidifiers deliver the best in sleep performance for an energized lifestyle. **Mask Solutions:**

Only Fisher & Paykel Healthcare offers a mask in all delivery categories. There are four different delivery categories which should be considered when choosing a mask. Our range of masks and their inherent performance features delivers greater flexibility, because they are designed to meet the needs of every sleeper. Our range offers a unique combination of features and technologies that allow for simple fitting and maintenance such as FlexiFit technology for auto contouring, the Glider Strap, which compensates for movement during the night, and the FlexiFoam Cushion that conforms naturally to a patient's face.

CPAP & Humidifier Solutions: The F&P ICON has been designed from the outside-in to answer the CPAP user's strong call for a compact, stylish CPAP that blends seamlessly into any bedroom environment. The F&P ICON is stylish on the outside and smart on the inside so CPAP users can feel at ease knowing they are being taken care of by a range of the world's leading clinical technologies for treating sleep apnea. The F&P ICON has a range of useful features such as integrated heated humidifier, clinically proven ThermoSmart Technology for optimal delivery of humidification without condensation, and SensAwake technology which senses irregular breathing indicative of wakefulness and reduces the pressure to aid the transition back to sleep.

Where can your sleep product be used (ie sleep lab, home, etc).

F&P sleep products can be used in sleep centers, as well as in-home.

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

Increasing patient compliance is a constant need in the PAP market and is an area of strength for Fisher & Paykel Healthcare. Patient compliance requires a total solution. This solution must be focused on the three primary areas that create challenges for the patient such as interface, humidification, and pressure relief. Our Interfaces offer 3 primary market differentiators: 1. Patient ease of use: no dials and no need for complicated adjustments to adjust the T-piece to relieve bridge of the nose pressure and prevent leaks. Instead, by utilizing the FlexiFit auto-contouring technology available in all of our nasal and full face masks, we provide one-step ease of fitting and optimized seal for the patient. 2. Patient freedom of movement: By offering the unique Glider Strap, patients can rotate their heads side to side while maintaining the mask seal and minimizing the occurrence of leaks. 3. Simple: Less parts to deal with, which simplifies the cleaning and maintenance for patients. Additionally, to further enhance compliance, the F&P ICON has been developed to be equipped with an "InfoUSB" which is a custom USB memory stick. This allows patients to transfer compliance data directly from their home to an interested party, by simply inserting it into their computer. The data is received by InfoSmart web, a cloud-based compliance management service which allows providers and physicians to collaborate and optimize patient therapy.

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

F&P continues to provide training to assist non-credentialed staff to assist with patient follow up to address the common questions or concerns about CPAP or F&P equipment which is easily-overcome. This process allows for an immediate response to be offered to a patient by the call-center personnel, allowing the therapist to focus on revenue-generating activities. Additionally, our customers have access to multiple CEU courses provided

at no cost, as well as new and existing product in-services on demand. We also offer customers and patients a training, education, and support website (www.vigor8.com) which includes instructional streaming videos on our product line, literature reviews, and clinical pathways.

Discuss any issues relevant to reimbursement.

Given recent industry changes, it remains our goal to work with our customers to provide them with effective and cost efficient solutions and technology that creates market differentiation. Solutions include reducing costs associated with inventory management and augmenting existing revenues while improving staff efficiencies. We have taken steps to help provide solutions for our customers such as offering masks with greater fit across the normal population (Zest Q Nasal Mask) and masks with multiple sizes in one package (Forma Full Face Mask & OPUS Direct Nasal Mask). These types of solutions will allow our customers to manage their inventory more efficiently while ensuring a great fit for their patients.

Ventus Medical, Inc

Tell us about the sleep products your company offers.

Provent Sleep Apnea Therapy is a prescription device indicated for the treatment of obstructive sleep apnea. It is an easy-to-use, disposable treatment that works across mild, moderate and severe OSA. 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.

Discuss any issues relevant to cost-control/reimbursement.

As Provent Therapy is relatively new, it may not be covered by insurance plans or prescription programs. In many cases, tax-free, flexible spending accounts may be used to cover the cost of Provent Therapy.

Guest Commentary – Dr Carlos Nunez

My post-graduate fellowship training in critical care medicine was heavily influenced by an intensivist who was quite renowned for his controversial use of high levels of positive end expiratory pressure (PEEP) for the management of patients receiving mechanical ventilation. In the ICUs at my alma mater, dialing up the PEEP by multiples of five or 10 cmH₂O was as routine as ordering an arterial blood gas. The fear of hemodynamic compromise that was supposed to follow was usually replaced by the reality of the situation: In most cases you could arrive at an optimal level of PEEP that would support the goals of oxygenation without adversely affecting circulation and perfusion. Outside of our institution, it was not uncommon for colleagues to call us the disciples of “super PEEP” and assume that we were routinely using levels that were well above 50 cmH₂O. In fact, in most cases where we had to go above 10 cmH₂O, it was usually in the 10 to 25 cmH₂O range – a range that would seem quite acceptable today.

Our belief in higher levels of PEEP was based on years of observation and some basic physiologic principles. We knew that it worked because we saw that it worked, and we were pretty sure why it worked. The years since then have been kind to our way of thinking, as more and more evidence seems to show that lung protective strategies for mechanical ventilation, including levels of PEEP that once were considered “high,” have become quite routine. In fact, if you follow the ARDSnet Mechanical Ventilation Protocol, you may apply PEEP as high as 24 cmH₂O. So, what has changed in the years since my training? In short, we have a better understanding of the pathophysiology

Dr Carlos Nunez is the chief medical officer and senior vice president of Medical Affairs for CareFusion. Before joining CareFusion, Dr Nunez served as the chief physician executive for a division of UnitedHealth Group, and prior to that he was a practicing anesthesiologist, intensivist and hospitalist. He has published and presented extensively on the topics of healthcare informatics, clinical workflow automation, analytics and decision support, cerebral blood flow auto-regulation, ischemia-reperfusion injury and medical history. Dr Nunez holds a Doctor of Medicine degree from the University of Miami School of Medicine, where he also completed postgraduate training in anesthesiology and fellowships in both critical care medicine and clinical research. He has an active appointment as adjunct professor of Biomedical Informatics at San Diego State University, where he also serves as associate director of the Biomedical Informatics Research Center. This commentary is from Dr Nunez's blog and was provided by CareFusion. Dr Nunez's blog can be viewed here: http://www.carefusion.com/safety-clinical-excellence/perspectives/trends_in_healthcare.aspx

of ARDS and ventilator-induced lung injury (VILI). We also have better methods for measuring the intrathoracic pressure gradients that contribute to the successful application of PEEP, without causing the undesired cardiovascular effects.

I recently had the privilege of moderating a panel presentation and discussion at the ISICEM 2012 conference in Brussels. The topic was: “The Management of Lung Injury and ARDS Using Transpulmonary Pressure.” One of the three presentations, prepared by Dr Edgar Jimenez, showed beautiful video microscopy clips that clearly demonstrated differential recruitment of alveoli as the level of PEEP was increased. All three panel presentations described how the levels of PEEP applied in the treatment of ARDS or for the prevention of lung injury could be driven by the measurement of transpulmonary pressure. Having the ability to measure transpulmonary pressure built right in to the ventilator at the bedside, makes it much easier to feel comfortable with levels of PEEP that were once considered high, because the relative pressure gradients now make sense.

Despite how far we've come in understanding lung injury and protective strategies for mechanical ventilation, old notions, like old habits, die hard. At the end of the session, when we opened the floor for questions, someone stood up and asked why the presenters didn't observe the hemodynamic consequences that must accompany such high levels of PEEP. Each presenter in turn made the point that the absolute level of PEEP in isolation is less meaningful without measuring the transpulmonary pressure. A “high” level of PEEP is not high, if the intrathoracic forces you are working against are also high. That is true for the lungs and for the heart, and there is no practical way of knowing this without knowing the transpulmonary pressure. Back in the day, we made assumptions as to why it worked, now you can see it right on the screen of your ventilator.

Ambulatory Augmented Ventilation – An Unmet Need: Breathe Technologies - Non-Invasive Open Ventilation (NIOV) Evaluation

Nishith Patel, BSRC, RRT-NPS, CPFT; Robert McCoy, BS, RRT, FAARC

Overview

The progression of chronic respiratory disease eventually produces respiratory insufficiency and limits a patient's mobility. Portable oxygen systems are essential for patients who exhibit hypoxemia with activity, and these systems have evolved to provide light-weight, long lasting devices that can increase FiO₂.¹ Yet, these oxygen systems cannot compensate for reduced ventilatory capacity.

In order to maintain cardiovascular status, respiratory status, secretion clearance, and most importantly, a positive mental attitude, patients with chronic lung disease need to remain active and mobile for as long as possible. The lack of an effective portable method of ventilation and oxygenation for patients with chronic lung disease encourages a pattern of reduced activity, decreased clearance of secretions, infections, exacerbations, and hospitalizations. Unfortunately, these “frequent flyer” patients are well known to hospitals and caregivers, and attempts to prevent re-hospitalization are often unsuccessful. Patients return to their homes and the vicious downward pattern begins again.²

Oxygen therapy, even when effectively prescribed and applied, does not address the need for augmented ventilation. Yet, the combination of augmented ventilation and oxygen therapy during ambulation has not been available. The recent development of a novel Non-invasive OPEN Ventilation (NIOV) System that provides both oxygenation and ventilation in a lightweight system (1lb), portable enough to be worn by a patient, may change the playing field. The ventilator is light enough to be carried by a patient and uses a proprietary “open” nasal pillow interface. Because of its portability and comfortable nasal pillows interface, the NIOV System is uniquely positioned to provide patients with a means of receiving truly ambulatory supplemental oxygen plus augmented ventilation.

Patient Case Study

An evaluation of the NIOV System was conducted in an outpatient setting on oxygen dependent patients with a primary diagnosis of chronic obstruction pulmonary disease (COPD). After acclimating the patient to the NIOV System, the patients were walked on the NIOV System at various distances in an attempt to titrate the patients augmented volume settings to all 3 levels of activity (mild, moderate, high). When exerting these patients continuous SpO₂, HR, and RR were recorded in addition to a Borg Scale reading as a measurement tool for assessing

dyspnea. The low activity setting was titrated for comfort and stable SpO₂ readings at rest, the medium activity titration was approached in a similar fashion but during an exertional walk, and the high activity titration during a brisk walk (if tolerated).

Summary of Data

Patient #1: 66 y/o female diagnosed with emphysema with a history of multiple hospitalizations for acute COPD exacerbation. She is a former smoker with a pack-year history of 9 and is on continuous oxygen at 3 lpm. She has dyspnea with heavy exertion when climbing flights of stairs, walking up hills or inclines. Her symptoms are moderate. While continuing her current medication regimen her degree of exercise limitation is moderate.

Pulmonary function testing reveals:

Spirometry at BTPS	Actual	Predicted	% Pred.
FVC	0.88	2.59	33
FEV1	0.30	1.84	16
FEV1/FVC	34	73	46
PEFR	1.82	5.21	34

Spirometry impression: very severe obstructive lung disease. DLCO is severely reduced.

	3 lpm O ₂ via N/C	NIOV Low Activity Setting at 120 mL during rest	NIOV Medium Activity Setting at 190 mL during walk	NIOV High Activity Setting at 230 mL during brisk walk
SpO ₂	94	95	95	92
HR	90	89	110	120
RR	14	17	19	20
Borg	1	0.5	3	3

Patient's final augmentation volumes on low, medium, high activity levels were titrated to 120mL / 190mL / 230mL. Trigger sensitivity set at 6 with a 30% delivery percent time. This patient walked a total of 3 rounds at distances of 176ft the first round, 176ft the second round and 230ft the third round. Initial volume settings of 100mL/130mL/170mL were inadequate as suggested by Borg scale reading, SpO₂, HR, and RR during activity. Low activity augmentation volume (120mL) was titrated at rest. The medium augmentation volume (190mL) was titrated during a

This article was provided by Breathe Technologies, Inc.

mild exertional walk. This particular patient had the capacity to perform a brisk walk for a distance of 230ft which the high augmentation volume (230mL) was titrated too. Overall, when using the NIOV System the patient observed an improvement in her exercise tolerance, oxygen saturation, and walking distance, with a reduction in dyspnea respectively during mild to moderate exertional activity compared to her traditional oxygen therapy. The patient also noted that her recovery time after exerting herself was noticeably short.

Patient #2: 67 y/o female patient diagnosed with COPD. As a former smoker she has a documented 22 pack-year history. She has dyspnea with heavy exertion with moderate exercise limitations. She is currently using oxygen at 2lpm at rest, and adjusts her liter flow consumption with activity to high as 4lpm.

Pulmonary function testing reveals:

Spirometry at BTPS	Actual	Predicted	% Pred.
FVC	1.35	2.34	57
FEV1	0.43	1.64	26
FEV1/FVC	32	72	44
PEFR	1.16	4.94	23

Spirometry impression: moderate-to-severe obstructive lung disease.

	2 lpm O ₂ via N/C	NIOV Low Activity Setting at 110 mL during rest	NIOV Medium Activity Setting at 150 mL during walk	NIOV High Activity Setting at 190 mL during brisk walk
SpO ₂	90	94	94	92
HR	87	83	88	96
RR	20	18	24	26
Borg	0.5	0.5	4	5

Patient's final augmentation volumes on low, medium, high activity levels were titrated to 110mL / 150mL / 190mL. This patient walked a total of two rounds at distances of 176ft the first round, and 176ft the second round. Initial volume settings of 80mL/110mL/150mL were inadequate as suggested by Borg scale reading, SpO₂, HR, and RR during activity. The patient's low activity augmentation volume (110mL) setting was titrated to at rest. The medium augmentation volume (150mL) setting was titrated during a mild exertional walk. With this patient's limited exercise capacity we encouraged her to increase her walking pace on the last walk which the high augmentation volume (190mL) was titrated too. She walked a total distance of 88ft at a brisk pace. The patient's trigger sensitivity was set at 5 with the delivery percent time set at 25%. Overall, the patient observed a significant gain in her exercise tolerance, and improved oxygen saturation, with a reduction in dyspnea respectively during rest and at mild to moderate activity compared to her traditional oxygen therapy. While using the NIOV System we also found the patient to be "full of color." She ended the evaluation with a good understanding of when appropriate levels of activity were to be selected and was quite fascinated with ease of use.

Patient #3: 53 y/o female diagnosed with COPD and moderate pulmonary hypertension. She currently uses a portable liquid oxygen system with 6lpm continuous flow. She is a current

smoker and has a documented 40 pack-year history. With mild exertion she has moderate dyspnea with acrocyanosis. While continuing her current medication regimen her degree of exercise limitation is severe.

Pulmonary function testing reveals:

Spirometry at BTPS	Actual	Predicted	% Pred.
FVC	2.61	3.35	77
FEV1	1.59	2.52	63
FEV1/FVC	61	75	81
PEFR	5.88	6.03	97

Spirometry impression: mild obstructive lung disease. Reduced DLCO with actual reading of 9.11 mL/min/mmHg which is 39% of predicted.

	6 lpm O ₂ via N/C	NIOV Low Activity Setting at 220 mL during rest	NIOV Medium and High Activity Setting at 250 mL during walk
SpO ₂	90	92	95
HR	88	92	99
RR	18	16	15
Borg	2	2	3

Patient's final augmentation volumes on low, medium, high activity levels were titrated to 220mL / 250mL / 250mL. Trigger sensitivity was set to 8 with a 35% delivery time. With her particular disease process she required aggressive settings to maintain acceptable SpO₂ readings. That being said, her low activity augmentation volume (220mL) was titrated at rest and then proceeded to walk this patient at the 250mL augmentation volume. During this first attempt to walk the patient, the patient found such a dramatic improvement in her exercise tolerance and oxygenation she walked a total of 1,232 feet. During the walk the patient maintained SpO₂ >88%, and commented that she didn't experience the "blackout feeling" she normally experiences when she performs in any mild to moderate activity. Overall, the patient observed a dramatic increase in her exercise tolerance capacity, with improved oxygen saturation, and a reduction in dyspnea respectively during any level of activity compared to her traditional oxygen therapy. While using the NIOV System we also found the patient to be "full of color," and quite enthusiastic with the level of improvement she gained.

Conclusion

Augmented ventilation for patients with respiratory insufficiency may provide the necessary ventilatory assistance to allow patients to participate more fully in life and to perform the ADLs in and outside their homes in an attempt to improve conditioning and prevent complications associated with a sedentary life-style. The Breathe NIOV System has proven to address an unmet need for many patients with chronic respiratory insufficiency. This case study, along with prior clinical trials^{3,4} using the NIOV System, support the premise that a truly portable ventilator can provide utility in improving mobility and exercise tolerance. As with LTOT, further research and education will create a solid foundation and scientific bases for using NIOV to improve the outcomes of patients requiring continued treatment of their chronic respiratory disease.

Continued on page 28...

Continuous Control of Tracheal Cuff Pressure

Jeff Borrink, BS, RRT

A critical function of the artificial airway cuff is to seal the airway. Tracheal cuff pressure (Pcuff) should be maintained within a narrow range, generally between 20-30cm H₂O. Insufficient Pcuff occurs frequently in critically ill patients, and represents a risk factor for microaspiration of oropharyngeal secretions that play a major role in the pathogenesis of ventilator associated pneumonia (VAP). Insufficient Pcuff can also lead to leaks past the cuff during positive pressure ventilation causing a loss of tidal volume and can also increase the risk of accidental extubation. Excessive Pcuff may cause tracheal damage, tracheal ischemic lesions, tracheal stenosis, or tracheoesophageal fistula.

In the clinical setting, it is difficult to adequately and consistently maintain proper Pcuff with a manual manometer or other available cuff inflation devices on the market. In the process of routine checking of Pcuff, the existing devices can lower cuff volume and pressure. Techniques such as the minimal leak technique or palpation of the pilot balloon have proven to be inadequate in protecting against risk factors related to insufficient or excessive cuff pressure. Recently, devices that allow for the efficient and continuous monitoring and controlling of Pcuff have been developed. These devices have proven to be more efficient at controlling Pcuff than routine checks using a manual manometer or other cuff inflation devices. In order to ensure that Pcuff is maintained within the recommended range of 20-30cm H₂O, it should be continuously monitored and controlled.

The authors of a recent study published in the American Journal of Respiratory and Critical Care Medicine, sought to determine what impact the continuous control of (Pcuff) would have on microaspiration of gastric contents. Saad Nseir et al developed a prospective randomized controlled trial that was performed in a single medical ICU. 122 patients that were expected to receive mechanical ventilation for at least 48 hours through a tracheal tube were enrolled in the study. Half were randomized to receive continuous control of Pcuff using a pneumatic device (intervention group, n=61) and half were randomized to receive routine care of Pcuff which included checks three times a day (control group, n=61). Tracheal aspirates were collected during the 48 hours following randomization to measure the level of gastric contents, incidence of VAP, and bacterial concentration in tracheal aspirates. Fiberoptic bronchoscopy was utilized within 24 hours following extubation to determine tracheal ischemic lesions.

The pneumatic device proved to be efficient in controlling Pcuff as only 18% of patients in the intervention group had abundant microaspiration, compared to 46% of patients in the control



Automatic cuff pressure regulation over a 12 hour trend. (Pcuff in upper right trend panel). Brief period of increased cuff pressure is due to coughing episode (Peak Pressures in upper left hand panel).

group. Bacterial concentration in tracheal aspirates was lower in the intervention group compared with the control group (mean±SD 1.6±2.4 vs 3.1±3.7 log₁₀ cfu/mL). The VAP rate was significantly lower in the intervention group compared with the control group (9.8% vs 26.2%). No significant difference was found in tracheal ischemia score between the two groups.

The continuous control of Pcuff was associated with significantly decreased microaspiration of gastric contents and a significantly decreased VAP rate in these critically ill patients requiring mechanical ventilation.

Although further studies are warranted, continuous control of Pcuff, along with continuous measurement and display of Pcuff by cuff-inflation devices may provide increased clinician awareness and adherence to maintaining cuff pressure within an acceptable range. Furthermore, continuous control of Pcuff could help improve patient outcomes through a reduction in microaspiration of secretions, and a reduction in VAP rates compared to current manual devices and techniques used for cuff pressure management.

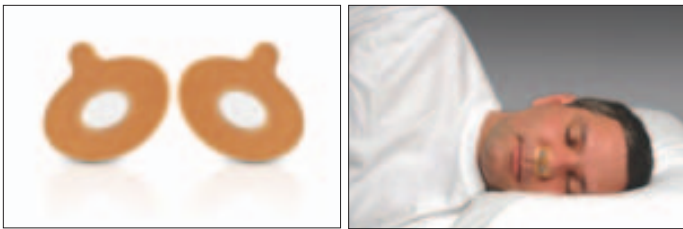
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Treating Obstructive Sleep Apnea (OSA) using Home Sleep Testing and Provent Sleep Apnea Therapy

Jay Berland, MD, FCCP, FAASM



Introduction

Patient MT is a high-functioning 75 year-old, 216 lb woman who presented with chronic fatigue and loud snoring which was bothersome to family and friends. She was subsequently diagnosed with moderate-to-severe OSA, and also has a history of hyperlipidemia, hyperthyroidism and non-insulin dependent diabetes.

History: Diagnosis and Prior Treatment

MT presented with loud snoring and excessive daytime sleepiness in August 2004 and underwent nocturnal polysomnography that confirmed moderate-to-severe OSA with an AHI of 30 and 61 while supine. Over the next several years, she tried various treatment options including:

- CPAP therapy
- Two different mandibular advancement devices and
- Lifestyle changes such as diet modification, exercise and weight loss

She discontinued usage of CPAP therapy, which she found intolerable, and was only partially responsive to oral appliances with which she also struggled. She had some benefit from her lifestyle changes; however she ultimately regained weight.

In October 2008, home sleep testing with the Watch-PAT Portable Sleep Apnea Diagnostic System was performed and confirmed moderate OSA with an AHI of 26.6. (See Figure 1.)

About Provent Therapy

Provent Therapy is a disposable, nightly-use, prescription device that incorporates a novel Micro-Valve design that is placed over the nostrils and secured with hypoallergenic adhesive. It is

Jay Berland is Medical Director, North Shore Pulmonary Associates Sleep Apnea Program and Medical Director, Ultimate Health Sleep Disorders Center. This article was provided by Ventus Medical, Inc. © 2012 Ventus Medical, Inc. Provent, Ventus Medical and the V logo are registered trademarks or trademarks of Ventus Medical, Inc in the US and other countries. Watch-PAT is a trademark of Itamar Medical, Ltd.

indicated for the treatment of obstructive sleep apnea (OSA) and works across mild, moderate, and severe OSA.

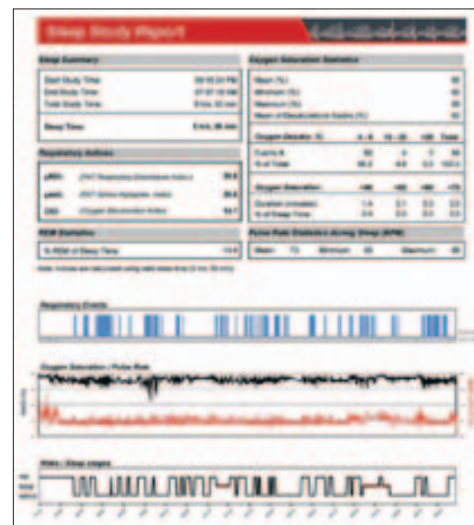


Figure 1. Diagnostic Sleep Study Report October 2008. Diffuse respiratory events and sawtooth oximetry pattern are consistent with OSA in addition to significant sleep fragmentation. No positional or snoring data is available for this study.



Figure 2. Sleep Study Report July 2009 using Provent Device. Fewer respiratory events, improved oximetry and improved sleep continuity are observed while on Provent Therapy. Almost complete elimination of sleep-disordered breathing is observed in non supine sleeping position.

New Treatment Approach

In July 2009, MT, weighing 225 lbs, continued to present with loud snoring, daytime sleepiness and inability to tolerate earlier treatment alternatives. She inquired about new options. She was prescribed Provent Sleep Apnea Therapy and underwent home sleep testing with a Watch-PAT 100 Polysomnography System to immediately confirm treatment efficacy. (See Figure 2.)

MT experienced a nearly complete resolution of respiratory events and snoring while non-supine and a marked improvement in sleep continuity. She also reported feeling more energized.

She continues to use Provent Therapy on a nightly basis. She believes that it fits her home life as well as her active lifestyle which includes travel, dog-sledding, zip-lining and other adventures.

Summary

This study highlights an example of Provent Therapy becoming the mainstay treatment for a patient who has failed traditional OSA treatment options. Efficacy with the Provent Device was demonstrated immediately after trial of the device using home monitoring with the Watch-PAT 100 System and patient's subjective response. Her initial AHI of 26.6 was reduced to 6.9 and the fatigue and snoring were resolved. Adjunctive diet and exercise programs continue to be recommended as well as non-supine positioning.

Augmented Ventilation...continued from page 25

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NIPPV Improves Severe Chronic Lung Disease

A success story of the HAMILTON-C2 nCPAP-PS mode applied on a 6 months old boy with bronchopulmonary dysplasia (BPD)

Christian Mann, MD; Axel Zolkos, Intensive Care Specialist

A former preterm of 29 weeks gestation with chronic lung disease was at risk of urgency intubation while in need of an oxygen concentration of 100% via nasal cannula to achieve a pulse oxymetry saturation of 90%. Born with lung hypoplasia due to premature rupture of the membranes, the boy had been on mechanical ventilation for 25 days and on nasal CPAP for 71 days. Actually, at the age of 6 months, he was in permanent tachypnea and dyspnea.

It was impossible to reinstall nasal CPAP because of the boy's natural movements. The use of sedative drugs was contraindicated due to the side effect of reducing respiratory drive and thus putting the boy at risk of respiratory insufficiency. The challenge was to improve respiratory mechanics in his lungs with highly overinflated basal lung areas and irregularly inflated upper lung areas. Additionally, episodes of airway obstruction had been evident from auscultation. Reintubation would have carried the risk of prolonged mechanical ventilation, failure to wean and need for tracheostomy and home ventilator therapy.

We decided to install NIPPV for its positive effects on recruitment and airway stabilization. A trial with a conventional system of NIPPV was unsuccessful due to patient-ventilator dyssynchrony. Then we introduced the HAMILTON-C2 ventilator. The HAMILTON-C2 is characterized by a high responsiveness and accuracy of the expiration and inspiration valves and a blower driven flow generation of up to 240 l/min. The biphasic pneumatic concept of the ventilator allowed the child to freely breathe regardless of ventilator induced inspiration or expiration phases.

With the mode nCPAP-PS, the flow sensor is not positioned at the Y-piece, but rather directly at the exhalation valve. This allows to connect a nasal interface without losing the possibility to synchronize inhalation and exhalation efforts of the patient with the ventilator. Leak is compensated over an ingenious algorithm called IntelliTrig. IntelliTrig detects the present leak and adapt flowtrigger threshold and expiratory trigger sensitivity for a perfect synchronization even in the presence of leaks. Ventilator settings were PEEP 6 cmH₂O, P_{insp} 4 cmH₂O, Flow trigger 1.4 l/s, Pramp 25 ms, ETS 10%, Timax 0.7 s.

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	day-time FIO ₂ (nasal cannula)	night-time FIO ₂ (nCPAP-PS)	respiratory rate (nCPAP-PS)	PaCO ₂ (nCPAP-PS)
start of NIPPV	100 – 80 %	55 – 65 %	64 /min	58 mmHg
after 7 weeks of NIPPV	80 – 60 %	40 – 45 %	50 /min	44 mmHg

Tab.1: Significant reduction of required oxygen, decrease of respiratory rate and normalization of PaCO₂ over 7 weeks of NIPPV therapy with the HAMILTON-C2.



Fig.1: NIPPV therapy via nasal mask with the HAMILTON-C2

In the course of 7 weeks there was a significant clinical improvement with a reduction in oxygen need, decrease in respiratory rate and a decrease in the level of CO₂ (Table 1). According to the literature on mechanisms of action we think that NIPPV was highly efficient as it improves respiratory drive,¹ enhances ventilation uniformity,² increases functional residual capacity,³ and thus effects lung recruitment.

After this treatment, the boy could be discharged from hospital for the first time in his life on home oxygen therapy via nasal cannula. Since then half a year has passed, no hospital readmission was necessary for this boy.

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Chronic Cough and Obstructive Sleep Apnea in a Community-Based Pulmonary Practice

Krishna M. Sundar, Sarah E Daly, Michael J. Pearce, William T. Alward

Abstract

Background: Recent reports suggest an association between unexplained chronic cough and obstructive sleep apnea (OSA). Current guidelines provide an empiric integrative approach to the management of chronic cough, particularly for etiologies of gastroesophageal reflux (GERD), upper airway cough syndrome (UACS) and cough variant asthma (CVA) but do not provide any recommendations regarding testing for OSA. This study was done to evaluate the prevalence of OSA in patients referred for chronic cough and examine the impact of treating OSA in resolution of chronic cough.

Methods: A retrospective review of chronic cough patients seen over a four-year period in a community-based pulmonary practice was done. Patients with abnormal chest radiographs, abnormal pulmonary function tests, history of known parenchymal lung disease, and inadequate followup were excluded. Clinical data, treatments provided and degree of resolution of cough was evaluated based on chart review. Specifically, diagnostic testing for OSA and impact of management of OSA on chronic cough was assessed.

Results: 75 patients with isolated chronic cough were identified. 44/75 had single etiologies for cough (GERD 37%, UACS 12%, CVA 8%). 31/75 had multiple etiologies for their chronic cough (GERD-UACS 31%, GERD-CVA 5%, UACS-CVA 3%, GERD-UACS-CVA 3%). 31% patients underwent further diagnostic testing to evaluate for UACS, GERD and CVA. Specific testing for OSA was carried out in 38/75 (51%) patients and 33/75 (44%) were found to have obstructive sleep apnea. 93% of the patients that had interventions to optimize their sleep-disordered breathing had improvement in their cough.

Conclusions: OSA is a common finding in patients with chronic

cough, even when another cause of cough has been identified. CPAP therapy in combination with other specific therapy for cough leads to a reduction in cough severity. Sleep apnea evaluation and therapy needs to be considered early during the management of chronic cough and as a part of the diagnostic workup for chronic cough.

Background

The revised ACCP guidelines provide a step-wise approach for managing patients with chronic cough.¹ These guidelines recommend basing the etiology of chronic cough upon clinical opinions derived from historical information and therapeutic interventions.¹ Considerable variations therefore result in the management of chronic cough. Variations in management also stem from the diagnostic workup used to ascertain the cause of cough² and also from the occurrences of multiple etiologies of chronic cough.³ Recent reports have suggested an association between chronic cough and obstructive sleep apnea (OSA).⁴ There is also evidence that treatment of sleep apnea can improve chronic cough.⁵ Despite the lack of any specific guidelines on testing for OSA in patients with chronic cough,^{6,7} the impact of treatment of OSA is being noted in community-based pulmonary practices where chronic cough is most frequently encountered.

This study was undertaken to evaluate current strategies in approaches to chronic cough in non-smokers without known parenchymal lung disease in a large community-based pulmonary clinic. Besides evaluating treatment regimens and diagnostic testing, the impact of diagnosis and treatment of sleep apnea on the course of chronic cough was also assessed.

Methods

A retrospective review of medical records of patients seen in the Utah Valley Pulmonary Clinics in Provo and American Fork between 2005 and 2009 was done. Charts with diagnoses of “cough” and “bronchitis” were reviewed for cough lasting longer than 8 weeks. Since this study was confined to the evaluation of chronic cough in non-smokers without parenchymal lung disease, patients with abnormal chest X-rays, any prior smoking history, history of asthma requiring maintenance therapy, history of chronic parenchymal lung disease were excluded. Also patients that were not compliant with follow-up visits were excluded. Patients with only “normal” spirometry were included. Pulmonary function tests were conducted and interpreted based on the Intermountain Thoracic Society standards.⁸

Following above exclusions, 75 patient records were identified

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Table 1: Patient demographics, comorbidities and etiology of chronic cough.

Patient characteristics	N = 75
Age in years (mean ± SD)	57 (± 14)
Female:Male ratio	1.5
BMI kg/m ² (mean ± SD)	
Overall	32 (± 8)
Male	31 (± 5)
Female	33 (± 9)
Duration of cough in weeks (mean ± SD)	
Overall	127 (± 274)
Male	55 (± 101)
Female	175 (± 337)
Comorbidities	
Hypertension	25 (33%)
Diabetes mellitus	9 (12%)
Rheumatoid arthritis	1 (1%)
Known sleep apnea	13 (17%)
Coronary artery disease	1 (1%)
ACE-I therapy	10 (13%)
Single diagnoses for cough	43/75 (57%)
GERD	28 (37%)
UACS	9 (12%)
CVA	6 (8%)
Multiple diagnoses for cough	31/75 (41%)
GERD & UACS	23 (31%)
UACS & CVA	2 (3%)
GERD & CVA	4 (5%)
UACS, GERD & CVA	2 (2%)

Abbreviations: BMI - Body mass index, ACE-I - Angiotensin converting enzyme inhibitors.

and reviewed for clinical data, diagnostic workup and therapeutic interventions. Clinical data obtained included demographic information, cough duration, comorbidities, etiologies for chronic cough, treatments provided and ancillary laboratory, radiological, and physiological workup. Patient records were specifically reviewed for mention of details regarding concomitant or pre-existing evaluation for OSA. Details regarding sleep history, physical exam pertinent to sleep apnea (pharyngeal crowding, neck circumference more than 17" in males and 16" in females, moderate to morbid obesity) were looked for.

Polysomnography was done based upon pulmonologist's decision to pursue testing for OSA based upon findings of sleep

history, physical exam consistent with a possibility of sleep disordered breathing and results of overnight oximetry. For patients undergoing polysomnography, the severity of sleep apnea was estimated based on the calculated apnea-hypopnea index.⁹ Treatments and effects of therapy for chronic cough at the initial and following visits were reviewed. Improvements in cough were ascertained based on self-reported assessments of cough during followup visits.

Waiver of consent for the study was obtained from the Intermountain Office of Research. Part of the study findings were presented in an abstract form during CHEST 2009, San Diego, USA.¹⁰

Results

Patient records were reviewed from 8 different American Board certified pulmonologists. The number of included patients varied from 1 to 23 patients per provider, with a mean of 9. Patient characteristics, duration of cough, body mass index and co-morbidities are as shown in Table 1. Out of 75 patients, 44 patients had a single diagnosis for chronic cough at the time of the first visit with gastro-esophageal reflux disease (GERD) being the most common etiology (37%) followed by upper airway cough syndrome (UACS) (12%) and cough variant asthma (CVA) (8%) (Table 1). One patient was diagnosed and treated only for OSA. 31/75 (41%) patients had multiple diagnoses for chronic cough with the combination of GERD-UACS being the commonest followed by GERD-CVA and UACS-CVA (Table 1). Two patients received therapy for all three causes - UACS, GERD and CVA at first visit.

GERD was the commonest etiology for chronic cough (irrespective of whether diagnosis was made as part of single or multiple etiologies) followed by UACS and then CVA. Proportion of patients with diagnoses of GERD, UACS and CVA (single or multiple diagnoses of cough) were 76%, 48% and 19% respectively. In 39% of patients, there was a history of an upper or lower respiratory tract infection at the onset of cough although this occurred more than 8 weeks before the patient presented to the pulmonary clinic. 5/75 patients had stoppage of angiotensin-converting enzyme inhibitors as a part of their management of chronic cough.

The investigative workup for these patients is detailed in Table 2. Two patients underwent methacholine challenge testing with one test demonstrating bronchial hyperreactivity. All chest CT scans performed were normal. Sinus radiographs or CT scans were ordered in 10 patients with 3 showing evidence of sinusitis (Table 2). ENT referrals were made in 4 patients. Two patients underwent upper gastrointestinal endoscopy with one undergoing 24 hour pH monitoring (Table 2).

67 patients in this study came as referrals from primary care providers (5 patients were self-referred to clinic). Two patients were referred from an ENT specialist and 1 from a gastroenterologist. Most if not all had been tried on multiple previous therapies including those for GERD, CVA and UACS. Despite this all patients were tried on therapeutic interventions based on the clinical impression of the treating pulmonologist. No patient underwent additional workup beyond chest X-rays and PFTs at the time of the initial visit. Initial and subsequent therapies were guided entirely by pulmonologist's empiric diagnosis of etiology of cough and therapeutic responses to rendered therapies. Although this approach broadly followed

Table 2: Investigative workup for etiology of chronic cough and sleep-apnea specific workup in patients with chronic cough

INVESTIGATIONS PERFORMED	N (%)
Pulmonary Function Tests	
Spirometry	70/75 (93%)
Diffusion capacity	60/75 (80%)
Lung volumes	44/75 (59%)
Methacholine challenge testing	2/75 (3%)
Six-minute walk test	1/75 (1%)
Radiologic studies	
Chest X-ray	54/75 (72%)
Chest CT scan	10/75 (13%)
Sinus imaging	10/75 (13%)
Endoscopic studies	
Bronchoscopy	0/75
Upper GI endoscopy	2/75 (3%)
24 hour pH monitoring (Bravo* pH probe)	1/75 (1%)
Laboratory studies	5/75 (7%)
SLEEP APNEA RELATED WORKUP	
Sleep history obtained	
Abnormal	36/75 (48%)
Screening overnight oximetry	
Abnormal	6/75 (8%)
Polysomnography	
Sleep disordered breathing	33/75 (44%)
No OSA (AHI < 5)	4/75 (5%)
Mild OSA (AHI 6-15)	6/75 (8%)
Moderate OSA (AHI 16-30)	6/75 (8%)
Severe OSA (AHI >31)	14/75 (19%)
Periodic limb movement disorder	1/75 (1%)
Sleep efficiency (mean)	89%
Arousal index (mean)	17
Oxygen saturation (mean)	91%
Lowest oxygen saturation (mean)	78%

Abbreviations: OSA - Obstructive sleep apnea; AHI - Apnea hypopnea index.
* Bravo pH capsule with delivery system (Medtronic, Inc. Minneapolis, MN, USA)

the outlines of the pathway for the management of chronic cough in the ACCP guidelines, there were variations from this pathway based on intention to pursue therapy based upon the

perceived etiology. Percentage of improvement with different initial therapies for GERD, UACS and CVA was 82%, 56%, 83% respectively. In the groups with multiple diagnoses, initial therapies were successful in 78% of the UACS-GERD group, 50% of the GERD-CVA group and 100% of the UACS-GERD-CVA and UACS-CVA groups. Inhaled steroid therapy was done in 19% of patients and oral steroids were given in 4% of patients. 12 patients received empiric macrolide therapy in conjunction with other therapies that improved cough in 7 patients. Significant variations were noted in the proportion of patients treated for GERD, UACS and CVA between different providers.

A sleep history was elicited in 55% of the patients (Table 2). This included history of duration of sleep, sleep quality, daytime somnolence, history of snoring and apneic spells. The decision to elicit history pertinent to the diagnosis of OSA varied amongst providers. A sleep history was consistently elicited in pulmonologists who were American Board certified in Sleep Medicine as well. Similarly details regarding historical aspects pertaining to OSA were variable. All six patients that underwent screening oximetry had abnormal studies. 12 patients had previously known OSA that was inadequately treated out of which 3 patients were not on any CPAP due to non-compliance with previously tried CPAP therapy. 34/38 patients had abnormal polysomnographies with 33 being diagnostic for OSA. Out of these 33 patients, 16 patients had initiation of CPAP therapy and 11 patients had re-titration of their CPAP therapy. Improvement in cough was noted in 25/27 (93%) patients that had initiation of new CPAP therapy or re-titration to optimal CPAP pressures. CPAP therapy was initiated or re-titrated in 18/27 of patients following the first visit, 6/27 following the second visit and 3/27 of patients thereafter. Patient characteristics, duration of cough, concomitant diagnoses, and comorbidities of patients who were diagnosed with OSA during evaluation for chronic cough is shown in Table 3.

Discussion

The development of guidelines for evaluation and management of chronic cough represents a major milestone in the history of treatment of this common health problem.¹ Chronic cough accounts for 3.6% of outpatient physician visits in the US and is the commonest complaint for which medical attention is sought in the US.¹¹

Current guidelines emphasize empirical management of GERD, UACS and CVA depending on historical information gathered in favor of these diagnoses. This is based on the fact that a number of studies have consistently shown that UACS, GERD and CVA account for the majority of cases of chronic cough in the nonsmoker.^{12,13} However, there is no understanding of the pathobiologic mechanisms by which these conditions lead to cough. Neither is there a defined pathological substrate that triggers cough from these conditions. This has led to difficulty in associating the results of investigative testing for UACS, GERD and CVA with the occurrence of cough. In addition, the common occurrence of these predisposing conditions in chronic cough patients and the lack of reliable tests to link GERD and UACS to cough results in therapeutic interventions being the mainstay for the diagnosis and resolution of the cough.

This study explores current approaches towards chronic cough in community-based pulmonologists from a single center in the United States. There has been a paucity of studies from North America on chronic cough evaluating current diagnostic and

Table 3: Characteristics of patients diagnosed with OSA.

Patient characteristic	N = 33
Age (mean ± SD)	57 (± 13)
Female:Male ratio	1.3
BMI kg/m ² (mean ± SD)	
Overall	35 (± 7)
Male	33(± 4)
Female	36 (± 8)
Duration of cough in weeks (mean ± SD)	
Overall	88 (± 262)
Male	23 (± 26)
Female	136 (± 341)
Comorbidities	
Hypertension	12 (37%)
Diabetes mellitus	7 (21%)
Known sleep apnea	12 (37%)
Coronary artery disease	1 (3%)
ACE-I therapy	6 (18%)
Single diagnoses for cough	
GERD	17/33 (52%)
UACS	2/33 (9%)
CVA	0
Multiple diagnoses for cough	
GERD & UACS	10/33 (30%)
UACS & CVA	0
GERD & CVA	1/33 (3%)
UACS, GERD & CVA	2/33 (6%)

Abbreviations: OSA - Obstructive sleep apnea; BMI - Body mass index; ACE-I - Angiotensin converting enzyme inhibitors.

therapeutic trends over the last decade. This retrospective study evaluates management patterns of chronic cough over a time period overlapping and following the revised ACCP guidelines. Not surprisingly, it continues to show the same preponderance of etiologic diagnoses, namely GERD, UACS and CVA in patients with chronic cough and a tendency towards treating multiple etiological diagnoses during the initial visit. As reflected in the guidelines, the etiological diagnoses for chronic cough were based on therapeutic interventions despite the fact that a number of these referred patients underwent similar therapeutic interventions prior to evaluation by the pulmonologist.

The extent of therapeutic testing for chronic cough has been debated upon.¹⁴ In this study, invasive testing for GERD, non-acid reflux disease, abnormal esophageal motility and testing for sputum eosinophilia was limited or lacking. The lack of

a standardized protocol for evaluating sputum eosinophilia resulted in empiric therapy for CVA in a number of patients. Testing for OSA in patients with chronic cough has been recently recommended.⁵ OSA is a common condition increasing in prevalence with age and body mass index¹⁵ and therefore, likely to occur in a significant proportion of patients with chronic cough. Even though chronic cough has been reported to be a presenting symptom of OSA, no large prospective studies evaluating for OSA in chronic cough patients exist.

A major finding of this retrospective study was the impact of concomitant evaluation and treatment for OSA. OSA has been reported in prior case reports of chronic cough and one case series of four patients that resolved their cough with treatment for OSA.^{16,17} In our current study, 44% patients with chronic cough were found to have OSA and following optimization of nocturnal positive pressure therapy, improvement or resolution of cough was noted in 93% of the patients. Since therapy for OSA was done in conjunction with other therapies for chronic cough in all but one patient, it is not clear to what degree the treatment for OSA had impact on the resolution of chronic cough. Despite this, the evaluation for OSA in the management of chronic cough requires important consideration given the increasing number of reports reporting improvement in cough with treatment of OSA. OSA can lead to or has been associated with GERD, asthma symptoms and upper respiratory complaints, all of which underlie the “pathogenic triad” leading to more than 95% of chronic cough.¹⁸ OSA has been shown to be associated with airway inflammation that can contribute to chronic cough. In a study performed in Sweden, the number of patients with chronic bronchitic symptoms that were found to have sleep-disordered breathing was up to 14-29%.¹⁹ Other studies on patients with OSA have shown an increase in exhaled nitric oxide values and other markers of inflammation on sputum analyses.^{20,21} A number of OSA patients can present with bronchitic symptoms and demonstrate bronchial hyperreactivity.^{22,23} Treatment of OSA has been shown to improve other known disorders of airway inflammation, especially asthma and COPD. Whether this is as a result of lessening gastroesophageal reflux that is common with OSA²⁴ or due to improvement in airway inflammation is unknown.

As compared to other series, the diagnosis of unexplained cough was not given to any of our patients. A significant incidence of unexplained cough has been noted in different series.²⁵ Interestingly the profile of patients reported for unexplained cough patients fits in with those patients in our series that improved with specific therapy for OSA.²⁵ A number of these patients start out with a post-infectious cough that fails to resolve despite multiple therapies directed at GERD, UACS or CVA. Whether OSA can perpetuate cough by impairing resolution in patients with acute bronchitis needs to be evaluated in future studies. OSA can potentially contribute to abnormal esophageal motility²⁶ and an enhanced cough reflex,¹⁶ both of which have been shown to contribute to or perpetuate cough.

This study is limited by a retrospective design, non-standardized protocol and data collection with only 55% of subjects being screened for OSA. Despite this a significant number of patients were found to have OSA. Whether this high prevalence of OSA in our chronic cough population is due to some kind of referral bias or due to a higher body mass index of patients is not clear. The majority of cough patients came from primary providers who considered possible etiologies for chronic cough as outlined

in the ACCP guidelines but failed to ascribe any relationship between the possibility of sleep-disordered breathing and the cough. Henceforth a number of these patients were not evaluated for possibility of sleep-disordered breathing or if they had known OSA, the possibility of inadequately treated OSA contributing to cough was not entertained. Although only half the patients underwent workup for OSA and this was expected to reduce the estimate of OSA-cough in this population, the prevalence of OSA encountered in this study is nevertheless very high (44%). The majority of patients undergoing sleep apnea-related workup had an elevated BMI that makes obesity a confounding factor in this study purporting a link between OSA and chronic cough. Ascribing a relationship between chronic cough and OSA in obese subjects may also carry an overlap bias given the common occurrence of these problems and the linear relationship between obesity and OSA. However, the majority of obese patients in this study improved their cough following CPAP therapy and since resolution of cough remains the sine qua non for the diagnosis of the etiology of cough,⁶ further prospective studies researching the link between chronic cough and OSA will have to be designed factoring in the contribution of obesity. In addition, treatment for OSA can improve the contribution from multiple etiologies especially GERD that improves with the treatment of OSA. This study was also confined to the evaluation of cough in non-smokers without parenchymal lung disease. A number of recent studies have shown a high prevalence of OSA in patients with interstitial or airway lung disease.^{27,28} Treating OSA early on in patients with parenchymal lung disease may not only offer the potential of impacting the course of the underlying lung disease but also the potential for amelioration of the cough seen in these disorders.²⁹

A small number of patients in this study received macrolides that were effective in 70% of those treated. Azithromycin used for up to 12 days improved cough in subsets of patients that also received PPIs. Macrolides have been shown to have beneficial effects on lower respiratory tract inflammation in a number of diseases ranging from asthma to post-transplant bronchiolitis.³⁰ Whether resolution in cough following macrolide therapy is due to its salutary effects on lower-respiratory tract inflammation or due to effects on sinus inflammation needs to be proven.

Conclusions

This retrospective evaluation of management of patients with chronic cough in nonsmokers found that GERD, UACS and CVA continued to be the commonest etiologies for chronic cough. A significant proportion of patients had multiple etiologies for their chronic cough and specific diagnostic workup was limited. Clinicians primarily relied on the results of therapeutic interventions in cases with single or multiple etiologies for chronic cough. A number of patients improved with therapy of OSA that was given in conjunction with other therapies for chronic cough. The impact of OSA in occurrence and perpetuation of chronic cough needs to be evaluated prospectively in future studies of chronic cough.

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Inhaled Vasodilators in ARDS

Melissa Turner, BA, RRT, RCP

The use of inhaled vasodilators as a therapy in patients with ARDS is a non-FDA approved, off-label use. Not only is it off-label, it is also costly. Weighing the decision to use an inhaled vasodilator or not is a clinical decision that surely cannot be taken lightly. Let's explore some of the pros and cons for using inhaled vasodilators in ARDS patients through a review of Siobal and Hess' article.^{1,2}

Inhaled vasodilators work to reduce pulmonary artery pressure and redistribute the blood flow in the lungs to ventilated regions which helps with oxygenation and gas exchange. The pulmonary arteries are dilated, decreasing pulmonary vascular resistance (PVR) and improving ventilation-perfusion matching. The two most commonly used inhaled vasodilators are inhaled nitric oxide (INO) and aerosolized prostacyclins to include Iloprost and Epoprostenal. They are termed selective pulmonary vasodilators when inhaled because of the local effects they have on the lungs with minimal or no systemic effects.

In the lungs of an ARDS patient, one expects there to be atelectasis and decreased lung compliance which leads to hypoxemia and pulmonary hypertension. The increased pulmonary artery pressures in turn cause a decrease or even failure in the right ventricle of the heart. It has been shown that pulmonary vascular resistance and pulmonary hypertension remained elevated in ARDS non-survivors. Knowing the local effect that inhaled vasodilators have on the lungs, it would seem a good choice in ARDS patients, so let's look first at the pros.

The inhaled vasodilators may prevent cardiopulmonary failure in an ARDS patient by decreasing pulmonary artery pressures (PAP) and thereby preventing right heart failure. It may also significantly improve oxygenation which gives clinicians time to put other therapies into practice. INO was shown to improve oxygenation for at least 24 hours after its initiation and perhaps longer as other studies may suggest. Using this therapy could also be lung protective when considering the other measures taken to improve oxygenation in the same patients could be injurious. The correction of severe hypoxemia will allow a high FiO₂ to be reduced thus preventing further inflammation in the lung. As I mentioned INO earlier, it is important to note that physiologic responses to prostacyclins are identical to INO. Also, prostacyclins have anti-thrombotic and thrombolytic properties which may help to further diminish the inflammation in the lungs.

Let's now consider the cons of using inhaled vasodilators. One of the benefits of prostacyclin was its thrombotic properties which could also be a negative, especially for patients with bleeding disorders. Also, even though decreasing pulmonary artery pressure was positive, it also could be a negative in patients with left heart failure in that it could worsen pulmonary edema. Toxicity is always a concern. Methemoglobinemia can occur especially with high doses. Pulmonary surfactant can be damaged when the nitric oxide reacts with free radical oxygen in the lungs. If there was an abrupt discontinuation in therapy, the patient could have rebound hypoxemia and pulmonary hypertension. The safety of prostacyclins is not yet known. Lastly, the outcomes show no benefit of using inhaled vasodilators for ARDS patients. In studies so far, there is no benefit shown in either mortality or vent free days. I must note here that all studies are done with INO administration and not prostacyclin.

Also worth mentioning, Iloprost, a prostacyclin, is approved by the FDA for inhalation, but not for mechanically ventilated ARDS patients. The dose of the prostacyclin being nebulized can also be affected by the ventilators bias flow. INO is very expensive and requires its own delivery system to be used in order to administer the drug. INO costs are around \$137.50 per hour which caps at \$13,200 per month. For off-label use, some hospitals are dumping upward of a million dollars for inhaled vasodilators. Prostacyclins cost around \$275 per day.

With all the aforementioned considered, the bottom line is that there is no benefit in mortality for ARDS patients with use of inhaled vasodilators. These drugs should not be recommended for routine use with ARDS patients. Perhaps their use as rescue therapy may have a benefit for ARDS with severe life threatening hypoxemia. Prostacyclin should be considered an alternative to INO although at present there is no evidence of outcomes benefit as studies are needed. Clinicians should consider the evidence carefully before using inhaled vasodilators with ARDS patients.

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Development of a Proxy-reported Pulmonary Outcome Scale for Preterm Infants with Bronchopulmonary Dysplasia

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Abstract

Background: To develop an accurate, proxy-reported bedside measurement tool for assessment of the severity of bronchopulmonary dysplasia (also called chronic lung disease) in preterm infants to supplement providers' current biometric measurements of the disease.

Methods: We adapted Patient-Reported Outcomes Measurement Information System (PROMIS) methodology to develop the Proxy-Reported Pulmonary Outcomes Scale (PRPOS). A multidisciplinary group of registered nurses, nurse practitioners, neonatologists, developmental specialists, and feeding specialists at five academic medical centers participated in the PRPOS development, which included five phases: (1) identification of domains, items, and responses; (2) item classification and selection using a modified Delphi process; (3) focus group exploration of items and response options; (4) cognitive interviews on a preliminary scale; and (5) final revision before field testing.

Results: Each phase of the process helped us to identify, classify, review, and revise possible domains, questions, and response

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options. The final items for field testing include 26 questions or observations that a nurse assesses before, during, and after routine care time and feeding.

Conclusions: We successfully created a prototype scale using modified PROMIS methodology. This process can serve as a model for the development of proxy-reported outcomes scales in other pediatric populations.

Background

Bronchopulmonary dysplasia (BPD), or chronic lung disease (CLD), is one of the most common sequelae of preterm birth,¹ and its severity is an important predictor of long-term outcomes in premature infants.² The infants most vulnerable to BPD are those born before the 28th week of gestation (extremely low gestational age newborns, ELGANs). Compared to their peers without lung disease, ELGANs with BPD have increased mortality.^{2,3} Those who survive with BPD have prolonged initial hospitalizations⁴ and an increased risk of neurodevelopmental impairment such as mental retardation and cerebral palsy.⁵⁻⁷ These BPD associated morbidities lead to increased family stress, economic hardship, and increased health care costs throughout childhood.^{4,8,9}

The most common definitions of BPD include the receipt of oxygen at 36 weeks post-menstrual age, with or without a physiologic test of oxygen dependency,^{10,11} and the National Institutes of Health (NIH) consensus categorization of "none," "mild," "moderate," and "severe," which is based on the duration of oxygen therapy and the amount of oxygen received at 36 weeks.¹² These NIH categories help determine the effect of therapies designed to reduce the incidence of BPD in a clinical trial, but they are not useful to providers who are attempting to examine the day-to-day pulmonary function of an infant, and this

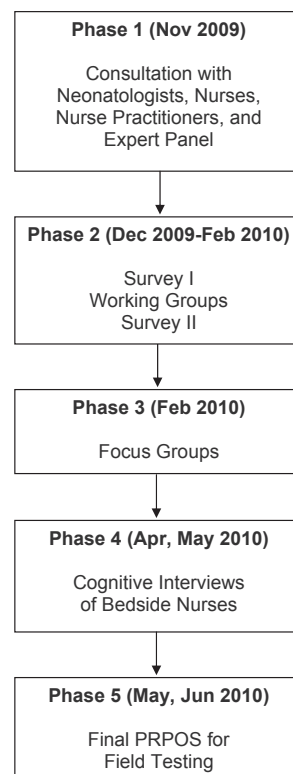


Figure 1. PRPOS development phases. Phases of development of the Proxy-Reported Pulmonary Outcomes Scale, from November 2009 to June 2010.

Table 1 Demographic information on participants in the modified Delphi process

	Survey 1	Working Groups	Survey 2
Total No. Participants	38	14	43
Missing data	3		1
Institution, n (%)			
UNC	13 (34%)	7 (50%)	9 (21%)
Duke	6 (16%)	7 (50%)	7 (16%)
Stanford	7 (18%)	0	9 (21%)
UAB	1 (3%)	0	3 (7%)
Iowa	8 (21%)	0	8 (19%)
Expert Panel	0	0	7 (16%)
Role, n (%)			
MD	10 (26%)	2 (14.3%)	14 (33%)
NP	9 (24%)	1 (7.1%)	10 (23%)
RN	10 (26%)	6 (42.9%)	13 (30%)
Specialist	6 (16%)	5 (35.7%)	6 (14%)
Years in Practice, mean*			
MD	14.7	12.3	11.4
NP	21.1	30	23.5
RN	18.8	15	20.1
Specialist	18.7	17.5	15.3

*Note: Years in practice have missing data for four cases in survey 1 and 16 cases in survey 2.

Table 2 Scenarios to describe level of CLD severity

Severity Level	Scenarios
No CLD	Baby Doe was extubated to CPAP and off supplemental oxygen by DOL ^a 22. He is now DOL 84 (36 weeks corrected age). Baby Doe has NO CLD.
Mild CLD	Baby Doe came off all oxygen on DOL 65. He is now DOL 84 (36 weeks corrected age). Baby Doe has MILD CLD.
Moderate CLD	Baby Doe is now DOL 84 (36 weeks corrected age) and on 0.1 lpm oxygen. Baby Doe has MODERATE CLD.
Severe CLD	Baby Doe is now DOL 84 (36 weeks corrected age) and on high-flow oxygen blended to an FIO ₂ of 0.65. Baby Doe has SEVERE CLD.

^aDOL - day of life.

oxygen-based categorization does not capture the nuances of disease-related functional limitations.

A valid bedside assessment tool of pulmonary function will give clinicians and researchers a more effective way to test therapies by reliably identifying subtle effects on infant pulmonary function or by identifying subgroups of infants who respond to therapies such as diuretics or bronchodilators. Our goal was to develop a scale to assess the effects of lung disease on functional outcomes using proxy-reported measures. We adapted Patient-Reported Outcomes Measurement Information System (PROMIS) methodology, a widely recognized system of instrument item selection and refinement for patient-reported outcomes,¹³⁻¹⁸ to develop a parsimonious Proxy-Reported Pulmonary Outcomes Scale (PRPOS).

Our most significant adaptation of current PROMIS methods is our entire reliance on proxy-reported measures for this neonatal population because of their inability to report on their own.

The ultimate goal of PRPOS is to provide clinicians with a set of items and responses in various functional domains that can discriminate between infants with differing degrees of BPD severity. Our secondary goal is to present a model instrument development process that might be replicated for use in diseases of infancy. This paper describes the first five of six steps in the scale development process: (1) identification of domains, items, and responses; (2) item classification and selection using a modified Delphi process; (3) focus group exploration of items and response options; (4) cognitive interviews of proxy reporters on a preliminary scale; (5) final revision before field testing; and (6) reliability testing (for which analysis is ongoing).

Methods

We developed PRPOS in the five phases illustrated in Figure 1.

Phase 1: Identification of domains, items, and responses: We identified an appropriate set of activity domains and assessments for inclusion in the scale using face-to-face interviews with experienced neonatologists, nurses, and neonatal nurse practitioners at two academic medical centers (The University of North Carolina at Chapel Hill [UNC] and Duke University) and input from a panel of national experts in neonatology, pediatric pulmonology, feeding, and development.

We conducted interviews individually or in small groups using a “brainstorming” format. We asked respondents to use their clinical experience to identify characteristics of an infant diagnosed with BPD [CLD] at 36 weeks and any activities that precipitated these characteristics. During this phase of the process, items were included if at least two participants agreed on their discriminative utility, with the goal of identifying a complete set of potential items. The resulting set of activity domains and assessments, which grew in the course of the discussions from nine original “assessments and domains” to what began to be called 15 “qualities and conditions,” was used in the next phase of the development process.

Phase 2: Item classification and selection: We used a modified Delphi process, a method of obtaining consensus on a subject matter from experts in the field through anonymous solicitation or polling of their opinions,¹⁹ to identify, classify, review, and revise possible items and domains. Modified Delphi process participants included experienced neonatologists, nurses, and neonatal nurse practitioners, developmental specialists, and feeding specialists at five academic medical centers (UNC, Duke University, Stanford University, University of Alabama at Birmingham [UAB], and University of Iowa [Iowa]).

Our modified Delphi process included three steps: (1) a survey, (2) working group meetings, and (3) a second survey reflecting areas where consensus had not yet been achieved. The surveys were designed and administered using the web-based survey software Qualtrics (Provo, UT), and each respondent received a unique URL to the surveys. The entire process took place from December 2009 to February 2010.

We invited 59 clinicians from five academic medical centers to participate in the two surveys (Table 1); in addition, we asked our eight expert panel members to take the second survey.

The first survey (step one) had three parts. In part one, respondents described how certain qualities or conditions (alertness, tone of back/trunk, lower body, and upper body, eye

Table 3 Domains and behaviors used in survey 2

Domain	Behavior
Sleep	Interrupted sleep/restlessness Excessive sleepiness Sustained active or quiet sleep
Arousal/transition	Transitions well between states Arouses easily, but to agitation Arouses with difficulty
Awake state: General state during care time	Mainly quiet alert or active alert Wiped out, persistent drowsiness Restless, agitated
Awake state: Calming during care time	Calms, but with some difficulty Irritable, not easily calmed Calms with containment, voice soothing
Awake state: Eye appearance during care time	Eyes intermittently opened and closed Eyes tightly closed Engaged/alert Panicked/wide-eyed Glazed/blank
Awake state: Eyebrow appearance during care time	Raised Relaxed/neutral Furrowed
Awake state: Color change during care time	Mottled Pale Dusky None
Awake state: Tone during care time	Arched/shoulders elevated or retracted Floppy Mainly flexed/hands loosely flexed or opened and closed Some increased extensor tone, fingers splayed
Feeding mechanics: Rooting/feeding cues	Roots and initiates feeding cues independently Minimal cues/rooting
Feeding mechanics: Mouth/tongue position during first 5 minutes of feeding	Opened and rounded/seals on nipple spontaneously or with prompting Turns head away/hesitant to open mouth Refuses to eat Open mouth posture/tongue and chin positioned to open airway
Feeding mechanics: Tone during first 5 minutes of feeding	Floppy Mainly flexed/hands loosely flexed or opened and closed Arched/shoulders elevated or retracted Some increased extensor tone, fingers splayed
Feeding mechanics: Desaturation during first 5 minutes of feeding	Not able to accept nipple without desats Frequent breaks required for pacing Desats with sustained sucking; recovers with intervention
Feeding mechanics: Respiratory rate (RR) with feeding	RR above baseline during sucking pause periods/recovers slowly Tachypnea at onset of feeding only RR above baseline during sucking pause periods/recovers quickly
Respiratory: desaturation during care time	Severe or frequent Mild or intermittent or occasional Moderate or somewhat common
Respiratory: tachypnea during care time	Constant No tachypnea Occasional or intermittent

Table 4 Sample focus group questions from nine domains

Topic area	Sample questions
Arousal from sleep	How would you describe babies who 'arouse with difficulty'? What would that look like?
Calming	What would "may have trouble calming" look like if you were describing a baby with moderate CLD? What would someone observe? How about with severe CLD?
Agitation	How would you describe a CLD baby who is 'very agitated'? What are all the observations you might make about a baby at the far end of that spectrum (severe disease)?
Energy level/activity	Describe a CLD baby in "a high energy" state. How, if at all, would an agitated baby look different from a baby in a state of high energy level/activity level?
Eye appearance	Is it helpful to include a 'glazed/blank' assessment of eye appearance? If so, is 'glazed/blank' on the spectrum from 'engaged' to 'panicked/wide-eyed' or is 'glazed/blank' indicating something different?
Color change	What color change do you observe in babies with CLD? What words best describe that color change?
Tone	What is a specific word or a modifier that describes a baby that has such bad lung disease and is so tired and wiped out that they become low-tone?
Desaturations	Do babies with no lung disease sometimes desat? Would 'normal' include an occasional desat?
Respiratory rate	How would you describe respiratory rate with feeding in a baby with no CLD?

appearance, eyebrow appearance, desaturations, presence of tachypnea, recovery time from tachypnea, retractions, and heart rate) appear in infants with four levels of BPD [CLD] severity—none, mild, moderate, severe—in three situations (e.g., at baseline before care, during care time, and during the first five minutes of feeding). Table 2 presents the scenarios used to describe level of CLD severity. Respondents also described the appearance of three feeding cues: opening the mouth, dropping the tongue, and the position of the chin. The survey provided three "other" categories where respondents could fill in additional characteristics they thought were important and describe the appearance of those characteristics in infants at each of the disease states.

In part two of the survey, respondents rated how well each of the observation domains and feeding cues would discriminate levels of CLD severity using a scale of 1 to 9, where 1=not at all well and 9=extremely well.

In part three, respondents provided open-ended feedback on the types of things that should be recorded before the assessment (e.g., whether a retinopathy of prematurity exam had taken place that day, or the timing of a furosemide dose) and made comments on other things we should consider in developing the scale.

Following the survey, we conducted three multidisciplinary workgroups (step two of the modified Delphi process) at UNC and Duke. At the start of the workgroups, we asked participants

to score how well a set of items—quality of sleep; alertness, arousability, facial expression; disorganization; difficulty in calming; color change; tone; and feeding mechanics—reflects the severity of CLD in an infant during five states (sleep, transition, awake state, care time, and feeding) using a five point scale (0=no; 1=some; 2=moderately, 3=pretty closely; and 4=yes, very much). We then had guided discussions in which we asked participants to help refine our set of domains, narrow similar terms to a single, best descriptor, and clarify and simplify complex items. At the end of the workgroup, participants completed the score card again, and we determined whether discussion had changed preferences.

The feedback we received from the working groups contributed to development of our second survey (step 3), in which respondents estimated at what severity of lung disease they might observe a particular behavior or action and how well those items discriminate levels of CLD severity. Table 3 lists the five behavior domains. We also asked whether the following terms were familiar and useful in describing breathing: intercostal, subcostal, and substernal retractions; head bobbing; and nasal flaring. The survey included space for respondents to provide additional comments. At the conclusion of the modified Delphi process, we developed a preliminary scale.

Phase 3: Focus groups: In February 2010, we conducted two focus groups of bedside nurses, a physical therapist, and a developmental specialist to clarify domains, confirm item definitions, and refine the wording of potential scale items

Table 5 Initial set of activity domains and assessments

Activity Domains	Assessments
At rest	Position: Tone (arched, relaxed)
Feeding by mouth	Pulse oximetry: Desaturation (length, depth)
Oro-gastric feeding	Retraction (subcostal, intercostal, head bob)
Handling/transitions/care time	Tachypnea (change in respiratory rate, time to baseline)
Family holding	Apnea (number, severity)
Noise	Heart rate (bradycardia)
Transition to awake	Alertness (engages, averts gaze, frantic)
Stooling	Circumoral cyanosis (presence of)
Sleep time (quiet alert/engaged periods versus prolonged sleep time)	Oro-motor dysfunction

Table 6 Survey 1 results of average ratings of appropriateness of CLD observation

Observation domain	MDs (n = 10)	RNs/NPs (n = 19)	Specialists (n = 6)
Alertness, mean (SD)	4 (2.03)	5 (2.29)	5 (2.48)
Tone:			
back/trunk	4 (2.12)	5 (2.03)	6 (2.77)
upper body	3 (1.77)	6 (2.02)*	6 (2.34)*
lower body	3 (1.81)	5 (1.76)*	4 (2.07)
Eyes	4 (2.20)	6 (1.97)	6 (2.51)
Eyebrows	4 (2.10)	6 (2.06)	6 (2.25)
Feeding cues:			
opens mouth	4 (1.98)	7 (1.46)*	6 (2.86)*
drops tongue	4 (1.81)	7 (1.73)*	6 (2.83)
position	5 (2.20)	7 (1.83)	6 (2.93)
Desaturation	8 (1.90)	8 (1.00)	8 (0.84)
Tachypnea:			
over baseline	8 (1.57)	8 (0.94)	9 (0.55)
time to recover	8 (1.51)	8 (0.61)	9 (0.55)
Retractions	8 (1.81)	8 (0.97)	9 (0.55)
Heart rate	6 (1.72)	7 (1.09)	7 (1.50)

*p < 0.05 vs MD responses (ANOVA with post-hoc analysis using the Student-Newman-Keuls all pairwise multiple comparison procedure)

and corresponding response options.^{13,20} An experienced focus group moderator conducted both focus groups, and members of the research team observed the discussions and provided background and clarification when necessary. The moderator used a semi-structured interview guide to elicit group participation and discussion on specific topic areas. We audio-recorded the focus group sessions and compared and collated notes taken by investigators in the group with the moderator's notes from the transcripts.

Each focus group was presented with the same scenario describing the clinical course of a premature infant at 36 weeks, and then asked to think about the infant in four disease states, no CLD, mild, moderate and severe CLD (see Additional File 1, Box S1). The focus group moderator instructed the participants to refer to the scenario throughout the discussion. Questions during the discussion centered on nine areas (Table 4).

Phase 4: Cognitive interviews: Following the focus groups, we conducted semi-structured cognitive interviews to obtain information about what items actually meant to potential respondents in terms of their comprehension of individual questions (ie, the question intent and meaning of terms), the sense of the questions overall, retrieval from memory of relevant information (ie, recallability of information and recall strategy), decision processes, response processes, and instructions for using the tool.^{13,18,21,22}

The cognitive interviews were approved by the Institutional Review Board at UNC, and all interviewees gave their informed consent prior to the interview. The interviews took place in April and May 2010 and included bedside nurses from three academic medical centers (UNC, Stanford, and Iowa), chosen to elucidate possible regional differences in response to terms. In our cognitive interview process, a bedside nurse used the scale on an infant and then participated in a cognitive interview. The

experienced cognitive interviewer followed a semistructured interview guide with questions about each item, the overall scale, and the directions.

Examples of the cognitive interview questions include:

- On a scale of 1 to 5, with 1 being easiest and 5 being hardest, how easy or hard was it to choose an answer?
- How sure are you of your answer? -or- How sure are you that it is [X]?
- Would it be easier for you if you could choose from fewer options? (If yes, probe: what response options would you eliminate?)
- Would it be easier for you if you could choose from more options? (If yes, probe: what other response options would you like to see here?)
- Is there another response that should be added that would more fully describe what you observe?
- Why do you say [X]? -or- Tell me why you chose [answer] instead of some other answer on the list.

After the first three interviews, we assessed each nurse's feedback and revised items and response options in the scale that respondents had thought were unclear. We then conducted three more interviews and made minor changes to the scale after each one.

Phase 5: Final scale revision: We used the results of the focus groups and cognitive interviews to develop a prototype PRPOS and prepare it for field testing in five geographically dispersed academic centers with varying rates of BPD.

Results

Phase 1: Identification of domains, items, and responses: During the brainstorming phase, 15 experienced clinicians identified an initial item pool of nine activity domains and nine assessments (Table 5). The national expert panel included two neonatologists, two pediatric pulmonologists, two infant feeding experts, and two neurodevelopmental specialists (seven from the United States and one from Canada). They confirmed that these domains and assessments were comprehensive, observable, and related to CLD at age 36 weeks adjusted gestational age. However, the expert panel raised a potential concern about assessing feeding behaviors because of the interaction of immaturity, respiratory disease, and feeder skill. Based on this input, we modified the feeding assessment to include only the initial period of feeding. Using input from the face-to-face interviews and expert panel, we arrived at a set of 15 activity domains and assessments, or "qualities and conditions," to be included in the next phase of the development process.

Phase 2: Item classification and selection (modified Delphi and workgroups): We received 38 responses to the first survey (response rate=64%) and 43 responses to the second survey (response rate=64%). Seventeen people took part in the working groups: ten from UNC, including nurses and a feeding specialist, and seven from Duke, including developmental/family specialists, researchers, and a nurse.

First Survey: The open-ended responses to the first survey provided us with user-generated, specific terms and phrases with which respondents could describe an infant's appearance at the four levels of BPD severity. Nurses and neonatal nurse practitioners provided more detailed descriptions than did neonatologists, and the feeding and developmental specialists

Table 7 Response option rewording after cognitive interviews

Question	Original Response Options	Revised Response Options
How would you describe the infant's general state?	Mainly calm or quiet	Active or quiet sleep
	Restless	Drowsy - eyes open and closed
	Agitated or irritable	Awake
	Distressed	
	Frantic	
How would you describe the infant's general status?*	n/a	Mainly calm or quiet
	n/a	Tired
	n/a	Restless
	n/a	Agitated or irritable
	n/a	Distressed
	n/a	Frantic
How would you describe the infant's tone?	Soft flexion	Soft or neutral flexion
	Some increased extensor tone, fingers splayed	Arms extended
	Increased extensor tone with arching and/or shoulders elevated or retracted	Arms extended with arching and/or shoulders elevated or retracted
		Limp (wiped out)
How do the infant's eyes appear?	Asleep - can't observe	Asleep or closed - can't observe
	Engaged/alert/bright-eyed	Crying
	Easily distracted	Tired
	Panicked/wide-eyed	Engaged or alert
		Easily distracted
		Panicked
How would you describe the infant's endurance during care time? ("Endurance" revised to "stamina")	No fatigue (tolerates care time well)	Sufficient stamina - tolerated care time well
	Minimal fatigue (shows some signs of fatigue with care but recovers quickly)	Tired some with care but recovered quickly
	Moderate fatigue (frequent signs of fatigue with care but recovers with pause)	Tired easily with care but recovered with pause
	Easily fatigued ('wiped out' 3-5 minutes into normal care time)	Tired easily without recovery ('wiped out' 3-5 minutes into normal care time)

* new question broken out of "general state" question as a result of discussion, thus, original response not applicable (n/a)

provided more nuanced responses about feeding and development.

Table 6 shows that, on average, registered nurses, nurse practitioners, neonatologists, and developmental and feeding specialists scored alertness, tone, eyes, eyebrows, and feeding cues mid-range (4-6) on the scale. Desaturation, tachypnea over baseline, time to recover from tachypnea, retractions received high scores (8 or 9). Nurses and specialists were more likely than were physicians to rate aspects of tone and feeding as valuable discriminators of levels of CLD severity.

Respondents reported that pre-assessment data should include information on the clinical environment (eg, parent visits, room noise), administration and timing of medications (eg, timing of last steroid course, dose of caffeine/aminophylline), procedures and tests (eg, laboratory tests, immunizations, radiology visit), and respiratory support (eg, type and magnitude of support).

Workgroup Feedback: The workgroup participants assisted in narrowing multiple terms to a single, best term for 12 items. For example, eyebrow descriptors "furrowed," "scrunched,"

"contracted," and "tense" were narrowed to "furrowed." In addition, participants clarified, defined, or distinguished similar descriptions for eight items. For instance, participants helped discriminate between eyes closed due to stress, described by the term "eyes tightly closed," and eye closure that does not indicate distress, denoted by "closed and sleepy" eyes. In three cases, workgroup participants simplified terms; for example, we reduced descriptions of musculoskeletal tone from four to three because of clinicians' inability to discriminate accurately between four different levels.

Participants also highlighted areas of uncertainty, expressing concern that some of our feeding items (mouth/tongue position; rooting/feeding cues) might be influenced by the feeder's technique and level of experience or the infant's development and feeding skills, rather than by the infant's level of CLD severity. The groups also noted that it is difficult to decipher whether "raised" and "furrowed" eyebrows signal distress related to the infant's CLD.

When we asked workgroup members to rescore after discussion, their responses did not change significantly from what they

Table 8 Examples of question and response option wording changes to the PRPOS

Original	Revision
Question: Does this infant's care plan or orders require or allow an increase in oxygen support during care time? Response options: No, Yes	Split "yes" response option into "yes - required" and "yes - allowed"
Question: How would you describe the infant's general state? Response options: Asleep, Drowsy - eyes open and closed, Awake	Changed "asleep" response option to "asleep (active sleep or quiet sleep)"
Question: How would you describe the infant's color?	Added instruction to ignore jaundice.
Question: How would you describe the infant's breathing?	Reworded question to "How would you describe the greatest degree of retractions you observe?"
Question: How would you describe the infant's tone? Response options: Soft flexion; some increased extensor tone, fingers splayed; increased extensor tone with arching and/or shoulders elevated and retracted	Revised response options to "soft or neutral flexion," "arms extended," "arms extended with arching and/or shoulders elevated or retracted," lip (wiped out)
Question: How do the infant's eyes appear as you begin care? Response options: asleep- can't observe, engaged/alert/bright-eyed, easily distracted, panicked/wide-eyed	Revised response options to "asleep or closed - can't observe," "crying," "tired," "engaged or alert," "easily distracted," and "panicked"

reported before discussion. Overall, most items scored as "moderately" or "pretty closely" reflecting severity of CLD in infants.

Second Survey: Results from the second survey of the modified Delphi process suggested that we had a range of behaviors and actions that would indicate different levels of CLD severity for each domain. For five of the domains (tone and desaturations during the first five minutes of feeding, respiratory rate with feeding, and calming and desaturations during care time), we did not have a descriptive behavior or action that would reflect the absence of disease, or "no CLD." Thus, we added a descriptor that reflected no CLD more clearly. For five domains (sleep, arousal/transition, general state during care time, color change, and feeding cues), we had descriptive behaviors or actions that showed overlap between moderate and severe disease. Most respondents (81%) reported that intercostal, subcostal, and substernal retractions, head bobbing, and nasal flaring were familiar and/or useful terms to describe breathing. A few respondents (16%) noted other degrees to consider between "barely visible" and "pronounced," and a few others (9%) did not find the term "head bob" familiar or useful.

We chose eleven areas for further discussion, expansion, and clarification using focus groups. We eliminated four potential assessment domains (sleep, rooting/feeding cues, mouth/tongue position, and tone during first five minutes of feeding) because of difficulty in defining an appropriate scale (sleep) or low scores on the CLD discrimination question. We also added two areas—retractions and nasal flaring— for inclusion on the tool, but we determined that we did not need to explore these further during the focus groups.

Phase 3: Focus Groups: Eighteen bedside nurses and specialists participated in the two focus groups, with nine participants in each group. All participants had at least three years of experience in the neonatal intensive care unit. The focus group discussions helped us to confirm response options for our items and determine the scale endpoints from no disease to severe CLD. Focus groups also helped us discover which terms should not be used as response options (eg, "mottled" to describe the infant's color, and "floppy" or "hypotonic" to describe the infant's tone). As we note above, we began by presenting the focus groups with eleven areas, arousal, general state during care time, calming, eyes, eyebrows, color, tone, desaturations during feeding, respiratory rate during feeding, desaturations, and tachypnea, and asked group members to

discuss transition/arousal, calming, agitation and energy/activity level, eye appearance, color change, tone, desaturations, and respiratory rate. We also asked focus group members to think about descriptors of general state—mainly calm or quiet, restless, agitated or irritable, distressed, and frantic—and of the ability to calm-self-calms, calms with containment, voice soothing, irritable, not easily calmed, frantic/inconsolable. In the course of listening to focus group discussion, we chose to eliminate the questions about color and tone, and also to eliminate questions about eyebrows, but retain questions on eyes, and add questions about respiratory rate and desaturation during both care time and feeding.

Phase 4: Cognitive Interviews: Six bedside nurses from three academic medical centers, UNC (n=3), Stanford University (n=2), and the University of Iowa (n=1) participated in one-hour cognitive interviews.

Overall, the nurses reported that the questions were easy to answer. Interview respondents found that the tool's instructions were understandable for the overall assessment and the care time portion of it, but they found the instructions less clear for the feeding portion of the assessment. At least one respondent suggested wording changes to the response options of 12 of 20 questions, but half or more of the respondents suggested changes to the response options for only these four questions: (1) How would you describe the infant's general state?; (2) How would you describe the infant's tone?; (3) How do the infant's eyes appear as you begin care?; and (4) How would you describe the infant's endurance during care time?

In response to these cognitive interview results, we changed the response options in four cases about which at least half the respondents had suggestions. The old and new responses to the questions are presented in Table 7. To illustrate the evolving refinement of responses, we initially included two additional response options to the general state question: "sleeping" and "tired." After testing this twice, we realized that the question should actually be divided into two questions— one on "general state" and one on "general status."

Phase 5: Final item revision: We refined the directions for using the scale, particularly for the feeding assessment section. We defined "desaturation" as an oxygen saturation of less than 80%, and we defined "increased respiratory rate" as a respiratory rate above 60 or, if the infant's baseline respiratory rate was already above 60, an "increase" is defined as a respiratory rate above

the baseline. We provided instructions for how to calculate the baseline respiratory rate—count for 30 seconds, then multiply by 2—and we revised other question wording and response options, examples of which can be seen in Table 8.

Discussion

The use of the PROMIS methodology in PRPOS's development assures us that the creation of the instrument has been both transparent and replicable expert clinical judgment from registered nurses, neonatal nurse practitioners, neonatologists, and developmental and feeding specialists has informed all the phases of the development process. We continually refined the scale's potential set of items and response options with the goal of achieving a parsimonious set of items going into the cognitive interviews. We did not have to remove any items during the final scale revision. The prototype scale includes 26 questions about the infant that a nurse assesses before, during, and after a routine care time and feeding, and takes less than 2 minutes to complete.

Our scale development process was similar to, but more broadly inclusive and iterative than, the development of the Premature Infant Pain Profile^{23,24} because of our use of modified Delphi surveys, workgroups, focus groups, and cognitive interviews. We used the more extensive and rigorous modified PROMIS methodology in an attempt to overcome some of the inherent limitations of proxy measures and to accomplish much of the work of establishing valid and reliable items prospectively, rather than depending entirely on retrospective testing of measures. Each phase of the development process produced uniquely valuable information. The initial consultation with expert providers helped us explore and define the domains we needed to measure. The modified Delphi Process, including the two surveys interrupted by workgroup discussion, gave us enormous insight into shared—and unshared—conceptual underpinnings to common terms. The focus groups of end-users—the bedside neonatal intensive care unit nurses who care for infants with BPD—reassured us that we had succeeded in narrowing the domains to the minimum number that adequately describes BPD infants' disease state, to decrease the burden of administration. Finally, the cognitive interviewing gave us an exceptional opportunity to query users' experience with the instrument itself: "Was it understandable? Easy to complete? Effective? Did response categories mean to users what we intended them to mean?" We expect that completion of all these steps will enhance the usefulness of each individual item and enhance the usability of these assessment items across different clinical settings.

Each instrument development phase could not alone lead to a successful product, but no phase was dispensable, and, taken together, they have generated a set of items ready for quantitative assessment. Our development process is limited by the fact that it is performed only in academic medical centers, although it is reasonable to assume that most non-academic center neonatal intensive care units would share many features of the academic medical center environment. Our focus groups were conducted at only two neonatal intensive care units both located in a single state, opening the possibility of limitations by region, or practice culture. Our more geographically dispersed cognitive interviewing and field testing should help us identify any such problems.

The PRPOS is currently undergoing field testing at five academic medical centers, where bedside nurses are applying

the assessment tool to a cohort of 150-200 neonates (25-40 per institution) between 23 and 30-6 weeks gestational age at birth (excluding infants with chromosomal abnormalities) and between 36-0 and 36-6 weeks postmenstrual age. At the conclusion of field testing, we will perform psychometric analyses of the data to test item validity and reliability, for the purpose of further scale refinement.

Conclusions

We expect that use of the PRPOS to assess observable, functional domains will greatly enhance the current unidimensional assessment of BPD severity based on oxygen use alone. For example, the PRPOS might allow clinicians and researchers to test therapies for BPD more effectively by accurately identifying subtle effects on lung function. In addition, refinement in the definition of BPD may allow more accurate prediction of important outcomes such as hospital length of stay and re-hospitalization after discharge, and further refine the relationship between BPD and neurodevelopmental outcome.

Use of a structured approach modeled on the rigorous PROMIS methodology helped us develop and refine a proxy-reported measurement instrument over a short period of time, while maintaining precision, clarity, discrimination, and comprehensiveness balanced with parsimony. This approach will serve as a useful model for others interested in developing proxy-reported outcomes measures.

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A Prospective Cohort Study of the Long-term Effects of CPAP on Carotid Artery Intima-media Thickness in Obstructive Sleep Apnea Syndrome

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Abstract

Objective: To examine the long-term effect of CPAP on carotid artery intima-media thickness (IMT) in patients with Obstructive sleep apnea syndrome (OSAS).

Methods: A prospective observational study over 12 months at a teaching hospital on 50 patients newly diagnosed with OSAS who received CPAP or conservative treatment (CT). Carotid IMT was assessed with B-mode Doppler ultrasound from both carotid arteries using images of the far wall of the distal 10mm of the common carotid arteries at baseline, 6 months and 12 months.

Measurements and results: Altogether 28 and 22 patients received CPAP and CT respectively without significant differences in age 48.8(1.8) vs 50.5(2.0) yrs, BMI 28.2(0.7) vs 28.0(1.2) kg/m², ESS 13.1(0.7) vs 12.7(0.6), AHI 38(3) vs 39(3)/hr, arousal index 29(2) vs 29(2)/hr, minimum SaO₂ 75(2) vs 77(2)% and existing co-morbidities. CPAP usage was 4.6(0.3) and 4.7(0.4) hrs/night over 6 months and 1 year respectively. Carotid artery IMT at baseline, 6 months, and 12 months were 758(30), 721(20), and 705(20) micron for the CPAP group versus 760(30), 770(30), and 778(30) micron respectively for the CT group, $p=0.002$. Among those free of cardiovascular disease ($n=24$), the carotid artery IMT at baseline, 6 months and 12 months were 722(40), 691(40), and 659(30) micron for the CPAP group ($n=12$) with usage 4.5(0.7) and 4.7(0.7) hrs/night over 6 months and 12 months whereas the IMT data for the CT group ($n=12$) were 660(20), 685(10), and 690(20) micron respectively, $p=0.006$.

Conclusions: Reduction of carotid artery IMT occurred mostly in the first 6 months and was sustained at 12 months in patients with reasonable CPAP compliance.

Background

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper airway obstruction causing daytime sleepiness, impaired cognitive function and poor health status. Untreated OSA is associated with increased risks of developing fatal and non-fatal cardiovascular events. Three large prospective cohort studies have shown that untreated OSA is an independent risk factor for all-cause mortality after long-term

follow-up. Untreated OSA is also associated with dysglycemia, systemic inflammation, endothelial dysfunction, platelet activation, and other cardiovascular consequences such as cardiac arrhythmias especially atrial fibrillation (AF), coronary artery disease, asymptomatic early atherosclerosis, and silent brain infarction.

In recent years, carotid artery IMT, measured by B-mode ultrasound, has been shown to be a highly reproducible test and correlate well with traditional vascular risk factors. It may predict the likelihood of acute coronary events and stroke in asymptomatic healthy subjects. Several studies have shown that the severity of OSA is independently related to the carotid artery IMT, with the severity of OSA-related hypoxemia more important than the frequency of obstructive events. One randomized controlled trial (RCT) has shown that continuous positive airway pressure (CPAP) ($n=12$) over 4 months could reduce carotid artery IMT in patients with severe OSAS free of existing cardiovascular diseases versus controls ($n=12$), but another recent RCT of 3 months treatment duration has failed to show any significant change in carotid artery IMT when comparing CPAP ($n=43$) versus sham CPAP ($n=43$). Hence it remains unknown whether CPAP can consistently reduce the carotid artery IMT in patients with OSAS or to a greater magnitude over a longer treatment period. This study examined the long-term effects of CPAP versus conservative treatment (CT) on carotid artery IMT over a period of 1 year.

Methods

We conducted a prospective observational study of the treatment effects on carotid artery IMT in patients newly diagnosed with OSAS. OSAS, as defined by an overnight polysomnography (PSG) showing apnea-hypopnea index (AHI) ≥ 5 /hour of sleep plus excessive daytime sleepiness or two of the following symptoms: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue, and impaired concentration. The patients were recruited from the Respiratory Clinic, Prince of Wales Hospital, Hong Kong. The inclusion criteria of the study included age 20 to 80 yrs, and AHI ≥ 5 /hr on PSG with symptoms of OSA as described above. The exclusion criteria included patients having problems staying awake during driving, professional drivers, shift work, recent myocardial infarction, unstable angina, underlying malignancy, and treatment of hyperlipidemia with statins or other lipid-lowering agents. Our study was approved by the Ethics Committee of the Chinese University of Hong Kong (CRE-2005.135) and appropriate informed written consent was obtained from the subjects.

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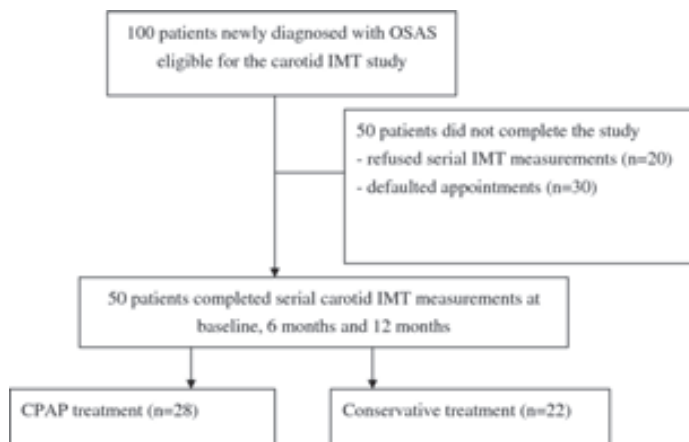


Figure 1 Patient profile. Among the 20 eligible patients who did not consent for the study, 14 had started CPAP treatment at home whereas 6 were subsequently referred for treatment with the mandibular advancement device. Among the 30 patients who had agreed to join the study initially, 22 were started on home CPAP whereas the other 8 opted for conservative treatment. However these 30 patients were unable to return for serial measurements of carotid IMT due to their busy work schedule.

Sleep assessment: Overnight diagnostic PSG (Healthdyne Alice 4, USA) was performed for every subject recording electroencephalogram (EEG), electro-oculogram, submental electromyogram (EMG), bilateral anterior tibial EMG, electrocardiogram, chest and abdominal wall movement by inductance plethysmography, airflow measured by a nasal pressure transducer [PTAF2, Pro-Tech, Woodinville, WA, USA] and supplemented by an oral thermister, and finger pulse oximetry as described in our previous studies. Sleep stages were scored according to standard criteria by Rechtschaffen and Kales. Apnea was defined as cessation of airflow for >10 seconds and hypopnea as a reduction of airflow of $\geq 50\%$ for >10 seconds plus an oxygen desaturation of >3% or an arousal. An arousal was scored if there was a 3 sec or longer abrupt shift in EEG frequency to alpha or theta or >16 Hz, following at least 10 sec of sleep, and if arising in REM there must be a rise in EMG tone.

Following confirmation of OSA, all patients were arranged to undergo an attended overnight autoCPAP titration on the second night of the sleep study. All patients were given a basic CPAP education program by our respiratory nurse supplemented by education brochure. The nurse would fit a comfortable CPAP mask from a wide range of selection for every patient, who was then given a short trial of CPAP therapy with the Autoset (ResMed, Sydney, Australia) CPAP device for approximately 30 minutes for acclimatization in the afternoon. Following the overnight autoCPAP titration study, each patient was interviewed by the physician on duty and invited to participate in the serial carotid IMT study.

Group 1 (CT): After confirmation of significant OSAS and completion of overnight attended autoCPAP titration, patients who were not keen to start CPAP yet were encouraged to a) avoid sleep deprivation by having sufficient hours of sleep every night; b) sleep in lateral positions; c) avoid sedatives and alcohol consumption 4 hours before sleep; and d) lose weight by exercise and diet where appropriate.

Group 2 (CPAP): In addition to the usual advice as given to group 1, patients who had agreed to commence CPAP treatment after completing an overnight autoCPAP titration were subsequently

prescribed CPAP device with a time counter recording machine run time. The CPAP pressure for each patient was set at the minimum pressure needed to abolish snoring, obstructive respiratory events, and airflow limitation for 95% of the night as determined by the overnight AutoSet CPAP titration study.

Carotid artery IMT: Was measured at baseline, 6 months, and 12 months for patients in both groups. The patients were followed up at the Respiratory clinic at 1, 3, 6 and 12, months whereas objective CPAP usage was measured from the time counter for group 2.

Carotid artery IMT was assessed by B-mode ultrasound scanning with an 11-MHz linear phase array transducer (Sonos 5500, Hewlett-Packard, Andover, MA). Bilateral IMT measurements were obtained at the distal 10 mm of common carotid artery as described by our group previously. The IMT was defined as the distance between the leading edge of the luminal echo to that of the media/adventitia echo and analyzed with a computerized edge-detection system (Q-Lab5.0, Xcelera, Phillips, USA). Three end-diastolic frames were selected, digitized, and analyzed for the mean IMT, and the average reading from these 3 frames was calculated for both right and left carotid arteries. The sole carotid scan operator (QS) was blinded to the clinical treatment status of the studied subjects and was not involved in the clinical assessment.

Blood pressure (BP) was measured in the right arm after at least 5 minutes of rest using a standard sphygmomanometer and the Korotkoff sound V was used as the indicator for the diastolic BP at baseline before PSG and at clinic visits at 6 months and 12 months.

Statistical analysis: The sample size was estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS, Kaysville, Utah). Based on the findings of Drager et al, group sample sizes of 28 would achieve 80% power to detect a difference of carotid IMT between the treatment and control groups (645 ± 95 versus 740 ± 150 [micron]) at a significance level (α) of 0.05, using a two-sided paired Student's t test.

The primary end-point was the change in carotid artery IMT. For comparisons between the 2 groups at each time point, unpaired t-test was used for normally distributed variables and Mann-Whitney U test for non-normally distributed variables. To compare the measurements before and after CPAP treatment, paired t-test was used for normally distributed variables and Wilcoxon's signed rank test for non-normally distributed variables. Two-factor ANOVA (group versus time) with repeated measures on the factor time (baseline minus treatment) was used to test for the effect of CPAP versus CT. Data are expressed as mean \pm SE unless stated otherwise. A p-value of <0.05 is considered significant.

Results

We invited 100 patients with newly confirmed OSAS who had met the study criteria to participate in the serial carotid IMT study after completing PSG and an overnight autoCPAP titration. However, 50 eligible patients either refused to participate (n=20) or could not take time off (n=30) for completion of the serial carotid IMT study (Figure 1). There were no significant differences in demographics between patients who completed the carotid IMT study versus those who did not. Among the remaining 50 patients who had completed the carotid IMT

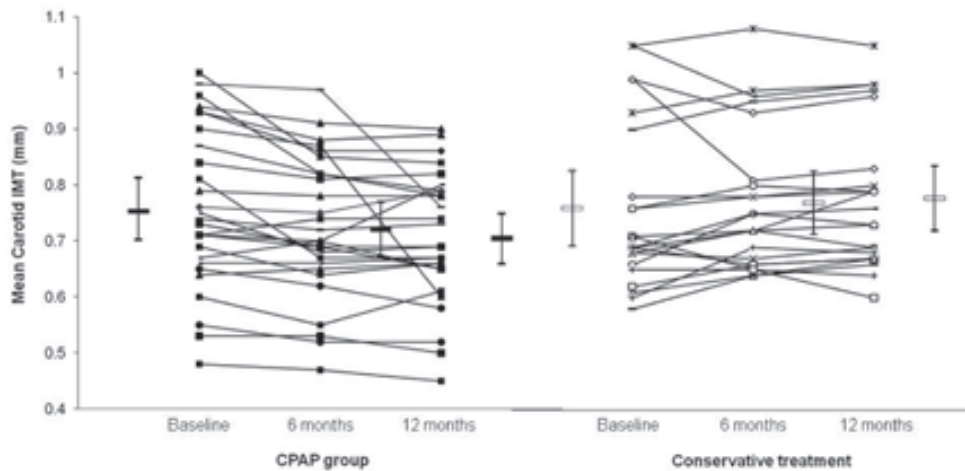


Figure 2 Shows the data plots of OSA patients on CPAP (n = 28) and those on conservative treatment (n = 22). The serial mean carotid artery IMT at baseline, 6 months and 12 months were 757.5(30), 720.9(20) and 704.5(20)micron for the CPAP group versus 760.0(30), 769.8(30), and 777.7(30)micron respectively for those on conservative treatment, p =0.002 (ANOVA for repeated measures).

study, 22 received CT whereas 28 received CPAP treatment. The demographics and severity of OSA between the two groups were similar. The subjects did not alter the dosage of their medications during the study.

Patient profile. Among the 20 eligible patients who did not consent for the study, 14 had started CPAP treatment at home whereas 6 were subsequently referred for treatment with the mandibular advancement device. Among the 30 patients who had agreed to join the study initially, 22 were started on home CPAP whereas the other 8 opted for conservative treatment. However these 30 patients were unable to return for serial measurements of carotid IMT due to their busy work schedule

Comparisons of changes of parameters between CPAP group and CT group: The objective CPAP usage were 4.6(0.3) and 4.7(0.4) hrs/night for the CPAP group over 6 months and 1 year respectively. The serial mean carotid artery IMT at baseline, 6 months and 12 months were 757.5(30), 720.9(20) and 704.5(20) micron for the CPAP group whereas the serial IMT data for the CT group were 760.0(30), 769.8(30), and 777.7(30)micron respectively, p=0.002 (ANOVA for repeated measures).

Figure 2 Shows the data plots of OSA patients on CPAP (n=28) and those on conservative treatment (n=22). The serial mean carotid artery IMT at baseline, 6 months and 12 months were 757.5(30), 720.9(20) and 704.5(20)micron for the CPAP group versus 760.0(30), 769.8(30), and 777.7(30)micron respectively for those on conservative treatment, p =0.002 (ANOVA for repeated measures)

The changes in mean carotid artery IMT between baseline and 6 months were -36.6 (10) versus 9.8(10)micron for the CPAP and CT group respectively, 95%CI (-77, -15.8 micron), p=0.004. The changes in mean carotid artery IMT between baseline and 12 months were -53(20) versus 17.7(10) micron for the CPAP and the CT group respectively, 95%CI (-114.8, -26.7 micron), p=0.002. The changes in mean carotid artery IMT between 6 months and 12 months were -16.4(10) versus 8(10) micron for the CPAP and the CT group respectively, 95%CI (-56, 72.2 micron), p=0.127. There was no correlation between objective CPAP usage and changes in carotid IMT at 6 months, r=-0.185

(p=0.375) and at 12 months, r=-0.018 (p=0.930).

Comparisons of changes of parameters between CPAP group and CT group among those free of existing cardiovascular disease (excluding smoking and alcohol intake): Among those free of existing cardiovascular disease (n=24), there were no significant differences in baseline demographics and severity of OSAS between the two groups including the absence of carotid plaques. The mean carotid artery IMT at baseline, 6 months and 12 months were 721.7(40), 690.8(40), and 659.2(30) micron for the CPAP group (n=12) with objective CPAP usage 4.5(0.7) and 4.7(0.7) hrs/night over 6 months and 12 months whereas the corresponding carotid IMT data for the CT group (n=12) were 660.0(20), 684.6(10) and 690.0(20) micron respectively, p=0.006 (ANOVA for repeated measures).

The changes in mean carotid artery IMT between baseline and 6 months were -30.8 (10) versus 24.6(10) micron for the CPAP and CT group respectively, 95%CI (-89.4, -21.4 micron), p=0.003. The changes in mean carotid artery IMT between baseline and 12 months were -62.5(20) versus 30(20) micron for the CPAP and CT group respectively, 95%CI (-155.4, -29.6 micron), p=0.006. The changes in mean carotid artery IMT between 6 months and 12 months were -31.7(20) versus 5.4(10) micron for the CPAP and the CT group respectively, 95%CI (-87.9, 13.7 micron), p=0.144.

Discussion

In a group of 50 symptomatic patients newly diagnosed with severe OSAS, this prospective observational study has shown that CPAP treatment (n=28) resulted in significant reduction in carotid artery IMT compared to those who had opted for conservative treatment (CT, n=22) over a study period of 12 months. Most of the reduction in carotid artery IMT when comparing CPAP against CT group appeared to have occurred within the first 6 months of treatment whereas there was no significant change from 6 to 12 months while the patients had maintained reasonable CPAP usage objectively throughout the study. Similar observations were noted in patients with and without existing cardiovascular diseases.

Data from the Sleep Heart Health Study (SHHS) have shown that modest to severe levels of OSA are associated with an approximately threefold increased risk of ischemic stroke in community-dwelling men. The Wisconsin Sleep Cohort Study has provided prospective evidence that OSA is related to significantly increased odds of suffering a stroke over the next 4 years after adjustment for age and gender. In an observational sleep clinic study, Yaggi et al have shown that OSA significantly increases the risk of stroke or death from any cause and the increase is independent of other known risk factors. Patients with stroke and OSA have an increased risk of early death over 10 years, whereas sleep apnea is significantly associated with increased risk of stroke among patients with coronary artery disease over a follow-up period of 10 years.

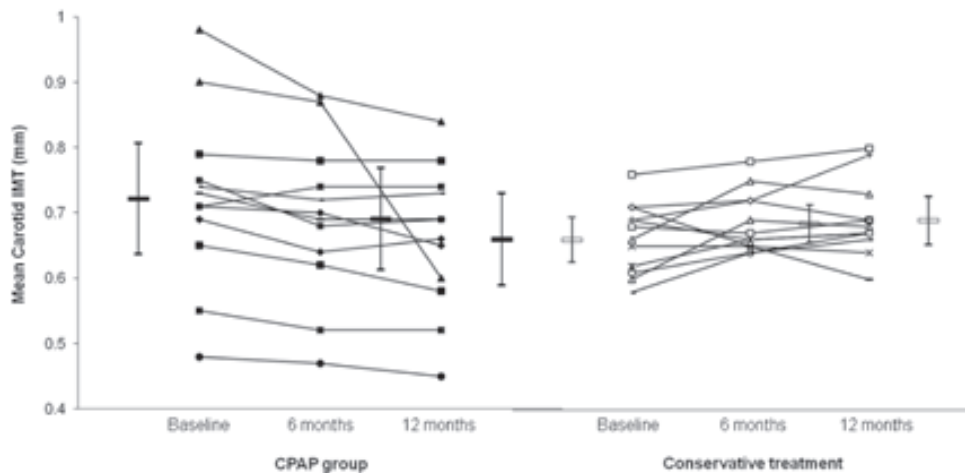


Figure 3 Shows the data plots of OSA patients free of existing cardiovascular diseases (excluding smoking and alcohol consumption). The mean carotid artery IMT at baseline, 6 months and 12 months were 721.7(40), 690.8(40) and 659.2(30) micron for the CPAP group (n = 12) versus 660.0(20), 684.6(10) and 690.0(20) micron respectively for those on conservative treatment (n = 12), $p = 0.006$ (ANOVA for repeated measures).

There are several proposed mechanisms linking OSA and stroke. Snoring-induced vibrational injury may lead to carotid atherosclerosis. There is a strong association between OSA and AF. Platelet activation and silent brain infarction were also more common in patients with moderate to severe OSA than in controls. OSA may accelerate atherosclerosis through the effect of hypertension and other mechanisms such as insulin resistance, diabetes, and dyslipidemia. In addition, OSA can induce direct proatherogenic effects through the mechanisms of systemic inflammation, oxidative stress, vascular smooth cell activation, increased adhesion molecule expression, monocyte/lymphocyte activation, increased lipid loading in macrophages, lipid peroxidation, and endothelial dysfunction.

In recent years, carotid artery IMT has been well accepted as a non-invasive tool which may predict the likelihood of acute coronary events and stroke in asymptomatic healthy subjects. Carotid artery IMT has been applied by several research groups to study different OSA populations. Although cross-sectional analysis of the SHHS has found no evidence that mild to moderate SDB is associated with subclinical atherosclerosis, data from other groups have suggested that OSA may lead to early atherosclerosis, as reflected by increase in carotid artery IMT and occurrence of plaques, in the absence of any significant comorbidity. In one series of OSA patients, severity of oxygen desaturation and BP status were the best

predictors for carotid wall hypertrophy whereas plaque occurrence without known cardiovascular disease was also related to the amount of oxygen desaturation regardless of their BP status. OSA-related hypoxia and systemic inflammation might be associated with progression of atherosclerosis and increased risk of cardiovascular morbidity. Another study has demonstrated a relationship between lipid peroxidation, carotid artery IMT, and intermittent hypoxia in non-obese OSA patients whereas in patients with minimally symptomatic OSA, diverse properties of endothelial function are impaired and arterial stiffness is increased. To date, only one RCT with a small sample size has shown that CPAP therapy (n=12) over 4 months could reduce carotid IMT in patients with severe OSAS free of existing cardiovascular diseases versus controls (n=12) (mean changes of -62 vs 8 micron for the two groups respectively, $p=0.02$).

In this study, there were significant differences when comparing the changes in carotid IMT at 6 months [-36.6 (10) versus 9.8 (10)micron] and at 12 months [-53 (20) versus 17.7 (10) micron] respectively from baseline between CPAP and CT groups. The magnitude of reduction in carotid IMT with CPAP was similar to those patients with OSAS with and without existing cardiovascular disease who received CPAP treatment. A clinical trial comparing rosuvastatin vs placebo among 984 low risk subjects showed no significant difference in the rate of mean maximum carotid IMT progression after 6 months (2.3 vs 10.6 micron/year, $p=0.34$). However, carotid IMT progression rates were significantly different when comparing rosuvastatin vs placebo at 12 months, (3.2 vs 13.3

micron/year, $p=0.049$) whereas the divergence grew with further follow-up (-0.9 vs 13.1 micron/year at 18 months and -1.4 vs 13.1 micron/year after 24 months of treatment, $p<0.001$ for both time points).

Although we did not find any significant correlation between objective CPAP usage and carotid IMT in this study, variability in the individual response may be related to the severity of OSA (AHI, hypoxemia) and CPAP compliance. Although the changes in carotid IMT with CPAP (n=43) versus sham CPAP (n=43) were not significant in the whole study population by Sharma et al, a subgroup analysis among those (n=51) with CPAP usage at least 5 hrs/night showed significant reduction in carotid IMT (34 vs 14 micron, $p<0.05$) when comparing CPAP vs sham CPAP treatment over 3 months.

This study is limited by the fact that it was not a RCT as it would not be ethical to withhold CPAP treatment for symptomatic patients with severe OSAS for a 1-year study in our locality. Only 50% of eligible OSA patients had participated in this study although the demographics and severity of OSA between those who participated in this study were similar to those who did not. Likewise patients who received CPAP and those who opted for CT were similar in terms of demographics and baseline severity of OSA. Lastly only baseline data of glucose, lipids and carotid plaques were available and we did not have serial data to assess the treatment effects.

Conclusion

In summary, this prospective observational study has shown that CPAP treatment resulted in significant reduction in carotid artery IMT whereas no significant change was noted among those who opted for conservative treatment over a study period of 1 year. Reduction in carotid artery IMT within the CPAP group occurred mostly within the first 6 months of treatment in patients with and without existing cardiovascular diseases and the reduction well maintained at 12 months in patients with reasonable CPAP compliance. Patients newly diagnosed with OSAS should be encouraged to comply with CPAP not just to relieve daytime sleepiness but there may be cardio-protective effects. Further studies with the RCT design over short to medium term are warranted to assess the effect of CPAP on carotid IMT.

Two-Year Home-Based Nocturnal Noninvasive Ventilation Added to Rehabilitation in Chronic Obstructive Pulmonary Disease Patients

Marieke L. Duiverman, Johan B. Wempe, Gerrie Bladder, Judith M. Vonk, Jan G. Zijlstra, Huib A.M. Kerstjens, Peter J. Wijkstra

Abstract

Background: The use of noninvasive intermittent positive pressure ventilation (NIPPV) in chronic obstructive pulmonary disease (COPD) patients with chronic hypercapnic respiratory failure remains controversial as long-term data are almost lacking. The aim was to compare the outcome of 2-year home-based nocturnal NIPPV in addition to rehabilitation (NIPPV + PR) with rehabilitation alone (PR) in COPD patients with chronic hypercapnic respiratory failure.

Methods: Sixty-six patients could be analyzed for the two-year home-based follow-up period. Differences in change between the NIPPV + PR and PR group were assessed by a linear mixed effects model with a random effect on the intercept, and adjustment for baseline values. The primary outcome was health-related quality of life (HRQoL); secondary outcomes were mood state, dyspnea, gas exchange, functional status, pulmonary function, and exacerbation frequency.

Results: Although the addition of NIPPV did not significantly improve the Chronic Respiratory Questionnaire compared to rehabilitation alone (mean difference in change between groups -1.3 points (95% CI: -9.7 to 7.4)), the addition of NIPPV did improve HRQoL assessed with the Magerit Respiratory Failure questionnaire (-13.4% (-22.7 to -4.2; $p=0.005$)), mood state (Hospital Anxiety and Depression scale -4.0 points (-7.8 to 0.0; $p=0.05$)), dyspnea (Medical Research Council -0.4 points (-0.8 to -0.0; $p=0.05$)), daytime arterial blood gases (PaCO₂ -0.4 kPa (-0.8 to -0.2; $p=0.01$); PaO₂ 0.8 kPa (0.0 to 1.5; $p=0.03$)), 6-minute walking distance (77.3 m (46.4 to 108.0; $p<0.001$)), Groningen

Activity and Restriction scale (-3.8 points (-7.4 to -0.4; $p=0.03$)), and forced expiratory volume in 1 second (115 ml (19 to 211; $p=0.019$)). Exacerbation frequency was not changed.

Conclusions: The addition of NIPPV to pulmonary rehabilitation for 2 years in severe COPD patients with chronic hypercapnic respiratory failure improves HRQoL, mood, dyspnea, gas exchange, exercise tolerance and lung function decline. The benefits increase further with time.

Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease leading to severe dyspnea at low exercise levels, reduced health-related quality of life (HRQoL) and high mortality rates.¹ Pulmonary rehabilitation (PR) improves dyspnea, exercise capacity, and HRQoL in patients with COPD.² These positive effects can be maintained well if the exercise training is continued at home after initial intensive PR.³ However, in severe COPD patients, PR may be difficult to perform, and effects may be less maintainable at home.⁴ Therefore, there is a need for additive therapies enhancing the effectiveness of PR, especially in patients with severe COPD.

We recently showed that the addition of 3-month nocturnal noninvasive intermittent positive pressure ventilation (NIPPV) to an intensive multidisciplinary rehabilitation program improves the outcomes of PR in severe COPD patients with chronic hypercapnic respiratory failure.⁵ Three other studies have also investigated noninvasive ventilation in combination with PR, but assessed short-term effects only.⁶⁻⁸ A few studies showed conflicting results of long-term effects of NIPPV in COPD.⁹⁻¹¹ However, these studies did not add NIPPV to PR and ventilator settings used were probably too low to provide beneficial effects.¹²

The present study explores whether the initial positive effects of 3-month NIPPV in addition to PR, with the use of sufficient ventilator settings, can be maintained over 2-year home-based follow-up in COPD patients with chronic hypercapnic respiratory failure. Outcome parameters were HRQoL, mood state, dyspnea scores, gas exchange, functional status, pulmonary function, and exacerbation frequency.

Methods

Patients: Patients with COPD GOLD stage III or IV [1] (forced expiratory volume in 1 second (FEV₁)/forced vital capacity < 70% and FEV₁ < 50% predicted), aged between 40 and 76 years,

Authors Duiverman, Kerstjens and Wijkstra are with the Department of Pulmonary Diseases; Duiverman, Bladder and Wijkstra are with the Department of Home Mechanical Ventilation; Wempe is with the Center for Rehabilitation; Vonk is with the Department of Epidemiology; and Zijlstra is with the Department of Critical Care, University Medical Center Groningen, University of Groningen, The Netherlands. The authors thank all participating pulmonologists, doctors, respiratory nurses, and physiotherapists, who contributed to the study and all participating out-of-hospital physiotherapists, nurses and members of their home mechanical ventilation center, pulmonary department and intensive care unit. They would like to thank Prof D.S. Postma for writing advice, and above all, all patients who participated in the study. Dr Wijkstra has received research grants from Respironics in 2009, 2010, and 2011. Reprinted from BioMed Central, Respiratory Research, © 2011 Duiverman et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

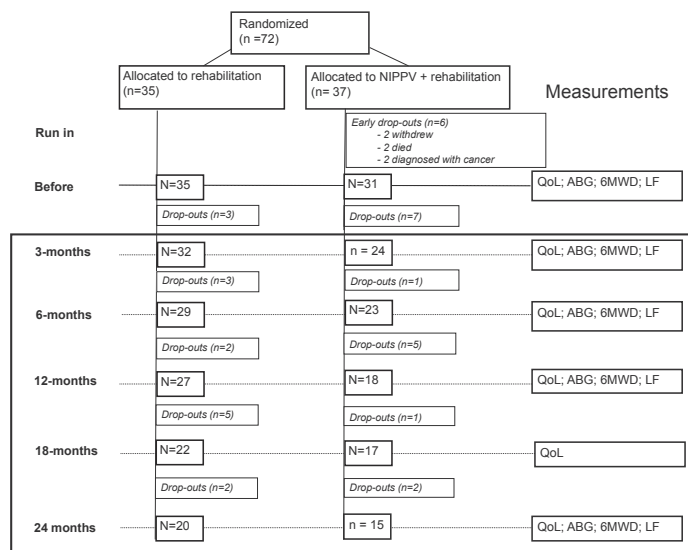


Figure 1: Flow diagram of the study progress. Legend: The present article presents the results of the home-based 3-24 month period, shown with a black square around it. QoL: health-related Quality of Life; ABG: arterial blood gases; 6MWD: 6-minute walking distance; LF: lung function measurements.

in stable clinical condition (no exacerbation in the four weeks prior to study participation together with a $\text{pH} > 7.35$); and with chronic hypercapnic respiratory failure (an arterial carbon dioxide pressure (PaCO_2) > 6.0 kPa at rest while breathing room air) were included. Exclusion criteria were: cardiac or neuromuscular diseases limiting exercise tolerance; previous exposure to a pulmonary rehabilitation program during the previous 18 months or previous exposure to chronic NIPPV ever; or an apnea/ hypopnea index ≥ 10 / hour. An overnight polygraphy (Embletta pds, Medcare Automation BV, Amsterdam, the Netherlands) was performed in all patients with a body mass index ≥ 30 kg/m², and in patients who snored or had complaints of disrupted sleep, excessive daytime sleepiness, or morning headache.

Study design: Randomization: The study design was randomized controlled with parallel-groups. Patients were assigned to nocturnal NIPPV in addition to rehabilitation (NIPPV + PR) or

Table 2 Changes in Chronic Respiratory Questionnaire

	Change up to 24 months
CRQ total - points	
N+R - mean (95% CI)	-3.6 (-10.1 to 2.9)
R - mean (95% CI)	-2.3 (-7.8 to 3.2)
Adjusted difference in change - mean (95% CI)*	-1.3 (-9.7 to 7.4)
CRQ dyspnea - points	
N+R - mean (95% CI)	-1.5 (-4.0 to 0.8)
R - mean (95% CI)	0.0 (-2.1 to 2.1)
Adjusted difference in change - mean (95% CI)*	-1.7 (-4.8 to 1.5)
CRQ fatigue - points	
N+R - mean (95% CI)	-1.5 (-3.6 to 0.4)
R - mean (95% CI)	-1.5 (-2.9 to 0.2)
Adjusted difference in change - mean (95% CI)*	-0.2 (-2.7 to 2.3)
CRQ emotion - points	
N+R - mean (95% CI)	-1.1 (-3.6 to 1.3)
R - mean (95% CI)	-0.4 (-2.5 to 1.7)
Adjusted difference in change - mean (95% CI)*	-0.8 (-4.0 to 2.5)
CRQ mastery	
N+R - mean (95% CI)	-0.8 (-2.5 to 0.6)
R - mean (95% CI)	-0.7 (-2.1 to 0.4)
Adjusted difference in change - mean (95% CI)*	0.0 (-2.1 to 2.1)

Data presented are mean changes (95% confidence intervals). * The differences in change are the treatment effects or between groups differences in change (95% CI), with adjustment for the baseline values. A positive difference in change signifies more improvement over time with NIPPV + PR relative to PR alone.

The CRQ (chronic respiratory questionnaire) contains a total score (score range from best (140) to worst (20)), and 4 different domains: dyspnea domain (score range from best (35) to worst (5)), fatigue domain (score range from best (28) to worst (4)), emotion domain (score range from best (49) to worst (7)), mastery domain score range from best (35) to worst (5)). N+R: NIPPV + rehabilitation group; R: rehabilitation group.

to rehabilitation alone (PR). Randomization was computerized and performed by an independent statistician, with minimization for FEV1 (≤ 1.2 L or > 1.2 L), PaCO_2 (≤ 7.0 kPa or > 7.0 kPa), and body mass index (≤ 30 kg/m² or > 30 kg/m²).¹³

Rehabilitation: After a 12-week multidisciplinary in-hospital rehabilitation program,⁵ all patients continued with a home-based rehabilitation program, with or without nocturnal NIPPV. In the current manuscript results of the home-based period are presented; results of the multidisciplinary in-hospital program have been reported separately.⁵ The home-based program consisted of physiotherapy at a community practice 1-2 times a week during the whole study period, with or without home NIPPV. Most patients visited the physiotherapist two times a week. A few patients (both from the NIPPV + PR group and the PR group) visited the physiotherapist once a week because the distance to travel to the physiotherapy practice was too long. All participating physiotherapists in the study were members of the Northern COPD physiotherapists group, which means that the physiotherapists were regularly taught in COPD exercise programs, and work in a well-equipped environment for COPD patients.

Table 1 Characteristics of the patients included at the start of the follow-up period

Characteristics	NIPPV + rehabilitation	Rehabilitation
Subjects - n	24	32
Gender - M:F	16: 8	17: 15
Age - yrs, mean (SD)	63 (10)	61 (8)
Patients on LTOT - n (%)	14 (58%)	18 (56%)
BMI - kg/m ² , mean (SD)	27.2 (5.1)	27.0 (5.8)
Active smokers, n (%)	5 (21%)	11 (34%)
Pack years - yrs, median (IQR)	42 (31-57)	43 (24-58)
Medication, n (%)		
inhaled corticosteroids	22 (92%)	29 (91%)
oral corticosteroids	10 (42%)	14 (44%)
bronchodilators	24 (100%)	31 (97%)
theophylline	5 (21%)	8 (25%)

Data are means (SD) or median (interquartile range, IQR), unless otherwise indicated. LTOT: long-term oxygen therapy; BMI: body mass index. Health-related quality of life scores, blood gases, exercise tolerance, and lung function data are presented in Figures 2-5 and additional file 1 tables 1-6.

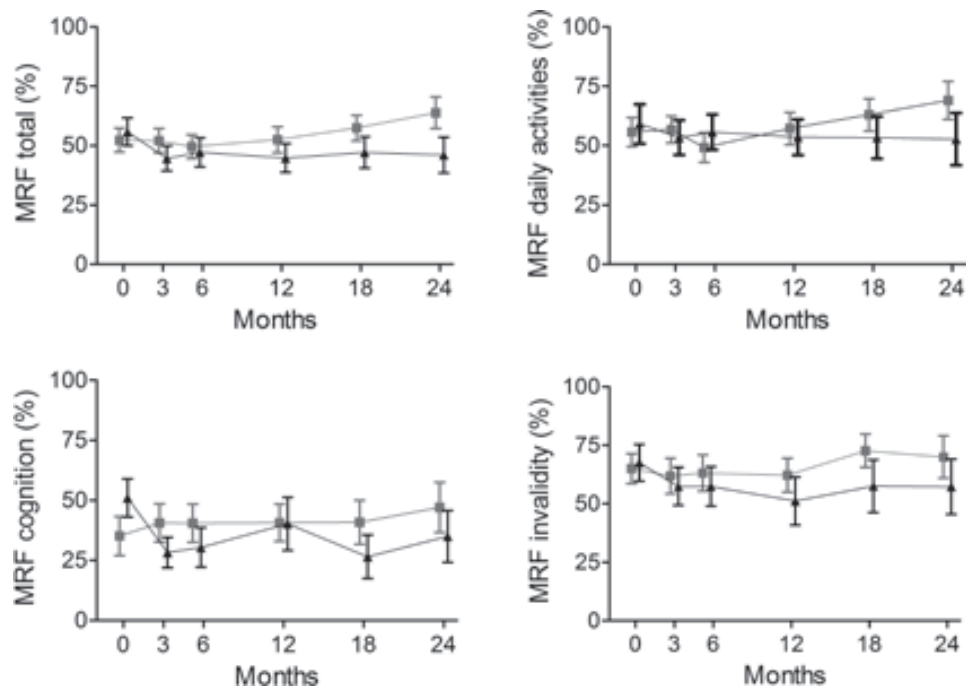


Figure 2: Maugeri Respiratory Failure scores Legend: MRF scores at the different measurement points in the NIPPV + rehabilitation group (black triangles) and the rehabilitation group (grey blocks). Lower scores signify better quality of life. The change was significantly better in the NIPPV + rehabilitation group ($p < 0.02$).

Each session consisted of 30-minute periods of cycling exercises, walking, and inspiratory muscle training each. The cycling protocol consisted of intervals of one minute loaded cycling (aimed at 140% of a patient's initial peak work rate on cycle ergometry), and one minute unloaded cycling, during 30 minutes.¹⁴ Inspiratory muscle training was performed on an inspiratory threshold device at an interval basis (two minutes of loaded breathing, followed by one minute rest), starting with the threshold resistance on 30% of baseline maximal inspiratory pressure (P_{Imax}), increasing the resistance with 5-10% per session until 70% P_{Imax} was reached.¹⁵ In patients with low fat free mass, strength training was added. Patients were also instructed to stay as active as possible at home, they were stimulated to walk at least each day and to train with their inspiratory device. All sessions were noted in a diary in order to monitor the progress and attendances to the program. Furthermore, there was regular contact with the physiotherapists participating in this study. If patients did not show up without a good reason for a longer period they were regarded as drop-outs (3 patients in the PR group and 1 patient in the NIPPV + PR group). Oxygen was used during training to maintain arterial oxygen saturation >90%.

NIPPV: In the NIPPV + PR group, patients were instituted on nocturnal bilevel NIPPV. Noninvasive ventilation was supplied through a pressure cycled ventilator, applying both inspiratory and expiratory pressure (BiPAP; Synchrony, Respironics, Inc, Murrysville, PA). A nasal or full face mask (Mirage mask, ResMed Ltd, UK) of the proper size was used. The ventilator was set in a spontaneous/ timed mode (S/T), with a backup frequency. Inspiratory positive airway pressure (IPAP) was increased up to maximal tolerated pressure and titrated towards an optimal correction of nocturnal arterial blood gases (PaCO₂ < 6.0 kPa and arterial oxygen pressure (PaO₂) > 8.0 kPa). Effectiveness of NIPPV was initially monitored by means of arterial blood gas measurements during the night,⁵ during the home based period NIPPV effectiveness was monitored by means of transcutaneous

O₂-saturation and PCO_{2tc} measurements performed with the TOSCA (Type TOSCA 500, Linde Medical Sensors AG, Basel, Switzerland).^{16,17} Ventilator compliance was determined from the ventilator counter readings. A specialized nurse from our department of home mechanical ventilation supervised the home mechanical ventilation.

Outcomes: Outcome measures of the home-based period were performed just before the start of this period (after 3 months in-hospital rehabilitation), and then after 6, 12, 18, and after 24 months (Figure 1). The primary outcome was predefined to be HRQoL, assessed by the Chronic Respiratory Questionnaire (CRQ).¹⁸ Additionally, HRQoL was measured with the Maugeri Respiratory Failure questionnaire (MRF-28),¹⁹ and Severe Respiratory Insufficiency questionnaire (SRI).²⁰ Secondary outcomes were mood state (Hospital Anxiety and Depression scale (HADS)),²¹ dyspnea scores (Medical Research Council (MRC)),²² gas exchange (arterial blood gases), functional status (6-minute walking distance (6MWD), activity level (Groningen Activity and Restriction Scale (GARS)),²³ pulmonary function (FEV₁, vital capacity, and lung volumes), and exacerbation frequency. An exacerbation was defined as an episode of increased pulmonary complaints for which (an increase in) oral steroids and/ or antibiotics was needed (Figure 1).

Sample size: To detect a clinically relevant change in the CRQ score of 10 points with 80% power, 40 patients per group were needed.²⁴ The target sample size was 50 patients per group, considering a probability of 20% drop-out of randomized patients.

Analyses and Statistics: Continuous variables were summarized with the use of means and standard deviations or medians with interquartile ranges depending on their distribution. Treatment effects or differences in change between the PR and NIPPV + PR group, with the associated 95% CI and p-value, were assessed by a linear mixed effects model with a random effect on the intercept, with adjustment for the values at the start of

Table 3 Changes in Groningen Activity and Restriction Scale (GARS), Hospital Anxiety and Depression scale (HADS), and Medical Research Council (MRC)

	Change up to 24 months
GARS, total - points	
N+R - mean (95% CI)	0.6 (-1.9 to 3.4)
R - mean (95% CI)	4.6 (2.3 to 6.9) †
Adjusted difference in change - mean (95% CI)*	-3.8 (-7.4 to -0.4)‡
HADS, total - points	
N+R - mean (95% CI)	-0.2 (-3.4 to 2.7)
R - mean (95% CI)	3.6 (1.3 to 5.9) †
Adjusted difference in change - mean (95% CI)*	-4.0 (-7.8 to 0.0)‡
MRC - points	
N+R - mean (95% CI)	0.2 (-0.2 to 0.4)
R - mean (95% CI)	0.6 (0.4 to 0.8) †
Adjusted difference in change - mean; 95% CI*	-0.4 (-0.8 to -0.0)‡

Data presented are mean changes (95% confidence intervals). * The differences in change are the treatment effects or between groups differences in change (95% CI), with adjustment for the baseline values. A negative outcome indicates benefit for the NIPPV + rehabilitation group compared to the rehabilitation group.

GARS: Groningen Activity and Restriction Scale (score range from best (18) to worst (72)); HADS: Hospital Anxiety and Depression scale (score range from best (0) to worst (42)); MRC: Medical Research Council dyspnea scale (score range best (1) to worst (5)); N+R: NIPPV + rehabilitation group; R: rehabilitation group.

†: $p < 0.05$, significant difference in change over time within a group or ‡ $p < 0.05$: significant difference in change between groups.

the period.²⁵ Outcomes were screened for linearity by visual inspection of all plots. A full data set analysis was performed, signifying intention-to-treat, with all data of all patients available at the start of the home- based period included for analyses and all available data used for analyses until patients dropped out. A $p < 0.05$ was considered statistically significant. Analyses were performed by an independent statistician (JV) with SPSS 16.0.

Results

Patients: Thirty-two patients in the PR group and 24 patients in the NIPPV + PR group completed the 3-month multidisciplinary program,⁵ and were included in the present report (Figure 1, Table 1). Most patients suffered from one of more comorbidities, the most common being osteoporosis (NIPPV + PR group: 3 patients (13%); PR group: 4 patients (13%)); hypertension (NIPPV + PR group: 7 patients (29%); PR group: 8 patients (25%)); cardiac dysfunction and/or chronic atrial fibrillation (NIPPV + PR group: 8 patients (33%); PR group: 5 patients (16%)); depression (NIPPV + PR group: 4 patients (17%); PR group: 8 patients (25%)); and diabetes mellitus (PR group: 8 patients (25%)). Diuretics were used by 6 patients in the NIPPV + PR group and 11 patients in the PR group at the start of the study period (not significantly different), but were started in significantly more patients in the PR group (NIPPV + PR group: 3 patients; PR group: 10 patients; $p=0.03$), so that at the end of the study period significantly more patients in the PR group used diuretics compared to the NIPPV + PR group ($p=0.003$).

At the start of the study period, 51 patients (91%) used inhaled corticosteroids, and 55 patients (98%) used bronchodilators (inhaled beta-agonist or anticholinergic medication) (Table 1).

Table 4 Changes in Pulmonary function

	Change up to 24 months
FEV ₁ - liters	
N+R - mean (95% CI)	-0.03 (-0.10 to 0.05)
R - mean (95% CI)	-0.14 (-0.20 to -0.08) †
Adjusted difference in change - mean (95% CI)*	0.12 (0.02 to 0.21) ‡
VC - liters	
N+R - mean (95% CI)	-0.01 (-0.19 to 0.17)
R - mean (95% CI)	-0.20 (-0.35 to -0.04) †
Adjusted difference in change - mean (95% CI)*	0.19 (-0.05 to 0.42)
RV%TLC	
N+R - mean (95% CI)	0.8 (-5.3 to 7.1)
R - mean (95% CI)	0.8 (-4.4 to 6.1)
Adjusted difference in change - mean (95% CI)*	0.2 (-8.0 to 8.4)
P _i max - kPa	
N+R - mean (95% CI)	1.1 (0.4 to 2.5)
R - mean (95% CI)	-0.6 (-1.9 to 0.6)
Adjusted difference in change - mean (95% CI)*	1.7 (-0.0 to 3.6)

Data presented are mean changes (95% confidence intervals). * The differences in change are the treatment effects or between groups differences in change (95% CI), with adjustment for the baseline values. Lung volumes and P_imax were measured until 12 months only.

FEV₁: forced expiratory volume in 1 second in L; VC: maximal vital capacity, L; RV%TLC: residual volume as a percentage of total lung capacity; P_imax: maximal inspiratory pressure in kPa. N+R: NIPPV + rehabilitation group; R: rehabilitation group.

†: $p < 0.05$, significant difference in change over time within a group or ‡ $p < 0.05$: significant difference in change between groups.

During the study period no further changes were made, except for the one patient in the PR group who initially did not want to use a bronchodilator but started on tiotropium during the follow up. At the start of the study period, 24 patients (43%) used oral corticosteroids (all at a standard dosage of 5 mg 3 times a week to 10 mg/ day prescribed by their own pulmonologist to prevent exacerbations). Changes in oral steroid use were made in 6 patients: in 2 PR group patients oral steroids were started, in 3 PR group patients the dosage was increased, and in 1 PR patient oral steroids could be stopped. Thirteen patients (23%) were on theophylline, in one patient in the PR group theophylline was started during the study period. At the start of the study period 2 patients were on prophylactic antibiotics, during the study period azithromycin or doxycycline was started in an additional 3 patients in the NIPPV + PR group and 7 patients in the PR group (not significantly different).

Treatment compliance and drop-outs for the complete study period: During the home-based follow-up period, nine patients in the NIPPV + PR group did not complete the study (three patients withdrew from follow-up, one patient had an aorta dissection, and five patients (21%) died; two from a COPD exacerbation, two suddenly at home without further cause verification, and one patient without further information). In the NIPPV + PR group, drop-outs had a significantly lower baseline PaO₂ compared to completers (PaO₂ 7.2 (0.8) kPa vs 8.2 (1.0) kPa; $p=0.02$).

During the home-based period, 12 patients in the PR group did not complete the study (three patients were non-compliant, one

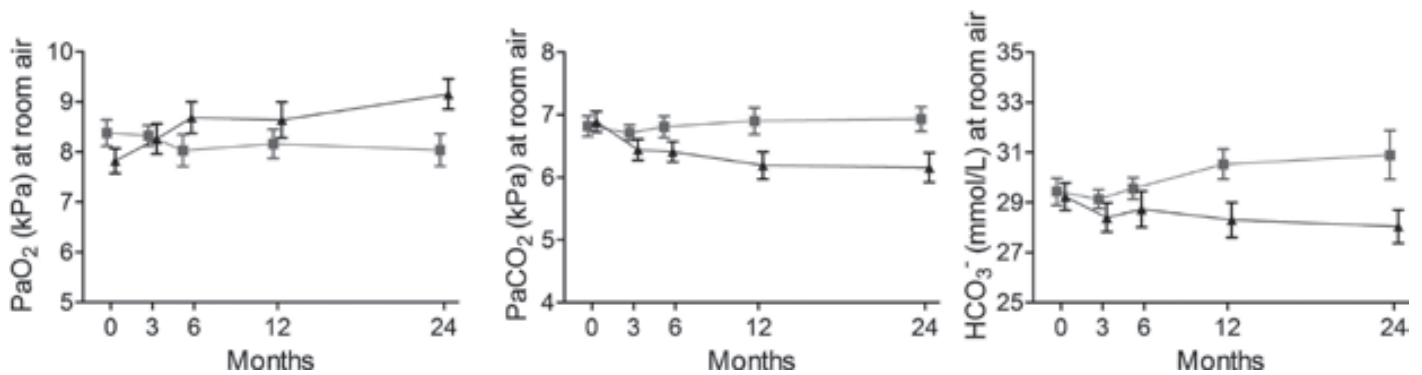


Figure 3: Daytime arterial blood gases Legend: Daytime arterial blood gases without additional oxygen at the different measurement points in the NIPPV + rehabilitation group (black triangles) and the rehabilitation group (grey blocks). The change was significantly better in the NIPPV + rehabilitation group ($p < 0.02$).

received a lung transplantation, one got an ischemic stroke, one patient's clinical condition deteriorated making further measurements impossible, one was treated with CPAP by his own pulmonologist, and five patients (16%) died, all from a COPD exacerbation). In the PR group, at baseline, drop-outs had a significantly higher RV/%TLC ratio (63 (7) vs. 57 (8); $p=0.04$), a worse 6MWD (232 (98) m vs. 347 (99) m; $p=0.004$), and worse HRQoL (CRQ total, 69 (11) vs 86 (20) points; $p=0.005$) than those who completed the study.

There were no significant differences between the groups at the start of the study period (Table 1), except for slightly better HRQoL scores in the NIPPV + PR group compared to the PR group (CRQ total score 96.8 (15.3) vs 87.1 (18.9) points; $p=0.044$; CRQ fatigue score 18.8 (3.9) vs. 15.4 (5.6) points, $p=0.015$; SRI attendant symptoms: 71.1 (19.6) vs 60.2 (19.6) %, $p=0.032$). When the analysis was repeated with only patients who completed the whole study, there were no baseline differences. The number of patients that died during the study was the same in both groups (five patients).

NIPPV settings: The mean IPAP at the start of the home-based follow-up period was 23 (4) cm H₂O, with a mean EPAP of 6 (2) cm H₂O, mean respiratory rate on NIPPV of 18 (3) breaths/min, an inspiration time of 1.0 (0.1) seconds, and a rise time of 1.2 (0.6) seconds. Fourteen patients used oxygen during the day (median flow rate of 2 L/min (range 0.75 to 4)), they also used oxygen while on the ventilator (median flow rate of 1.75 L/min (range 1 to 4 L/min)). Only minor adjustments were made during the study period in order to improve (daytime) arterial blood gases more. In 6 patients IPAP was increased by a median of 4 cm H₂O (range 2 to 5 cm H₂O), in three patients IPAP was decreased by a median of 2 cm H₂O (range 1 to 3 cm H₂O) to optimize comfort). Daytime of the nocturnal transcutaneous measurements (TOSCA) are presented in additional file 1, Table S3. After two years, mean IPAP in the 15 remaining patients was 23 (4) cm H₂O, mean EPAP 6 (2) cm H₂O, mean respiratory rate on NIPPV 18 (3) breaths/min, inspiration time 0.9 (0.2) seconds, and rise time 1.2 (0.6) seconds. Seven patients used oxygen during the day (median flow rate of 1.5 L/min (range 1 to 3)), however only four of them needed oxygen when on the ventilator (median flow rate of 2 L/min (range 2 to 4 L/min)).

One patient was ventilated through a nose mask, the remaining through a full face mask. Compliance was good, after two years patients used their ventilator 94% of the days (range 75 to 100%), with a median use per day of 6.9 hours (range 40 minutes to 11.4 hours/ 24 hours).

Health-related quality of life, mood state, and dyspnea: The change in CRQ total and domain scores did not differ between both groups (Table 2). The MRF-28 total score, and its domains daily activities and invalidity, improved more in the NIPPV + PR group than the PR group (difference in change for MRF-28 total score: -13.4 % (95% CI -22.7 to -4.2; $p=0.005$), Figure 2). The SRI physical functioning domain improved more in the NIPPV + PR group than the PR group (difference 10.7 % (95% CI 3.8 to 17.6; $p=0.003$)). The HADS and MRC scores improved more in the NIPPV + PR group than the PR group (Table 3).

Daytime arterial blood gases: Arterial blood gases improved more in the NIPPV + PR group than the PR group (PaO₂ 0.8 kPa (95 % CI 0.0 to 1.5; $p=0.032$); PaCO₂ -0.4 kPa (95 % CI -0.8 to -0.2; $p = 0.011$); HCO₃⁻ - 3 2.7 mmol/L (95 % CI -4.4 to -1.1; $p=0.002$); Figure 3).

Functional status: The 6MWD was maintained in the NIPPV + PR group, while it deteriorated in the PR group, the difference in change being significant (77.3 m (95% CI 46.4 to 108.0; $p<0.001$; Figure 4, additional file 1, Table S6). The GARS scores improved more in the NIPPV + PR group than the PR group (Table 3).

Pulmonary function: In the NIPPV + PR group, mean FEV1 stabilized or even slightly increased from 0.89 to 0.95 over time, which was significantly different from the mean reduction in FEV1 from 0.81 to 0.69 L in the PR group, the difference between the groups being 115 ml (95% CI 19 to 211; $p=0.019$; Figure 5, Table 4). There was no difference in VC or RV/%TLC, although the latter was measured only until the 12-month time point. There was no difference in change in maximal inspiratory muscle pressure (P_{imax}) between the groups (Table 4).

Exacerbation frequency: The median exacerbation frequency was 3.0 exacerbations/year in both groups, the median hospitalization rate varied between 0–2 hospitalizations/ year; both were not significantly different over time or between groups. Also, the median number of hospitalization days/year was also not significantly different over time or between groups.

Discussion

Our study shows for the first time that home-based NIPPV + PR provides long-term benefit as to HRQoL, mood state, dyspnea, gas exchange, exercise tolerance, and FEV1 over PR alone in patients with severe COPD with chronic hypercapnic respiratory failure. We believe the present RCT to be unique being the first to show that the addition of NIPPV improves FEV1 over 2-year follow-up compared to rehabilitation alone. The rehabilitation

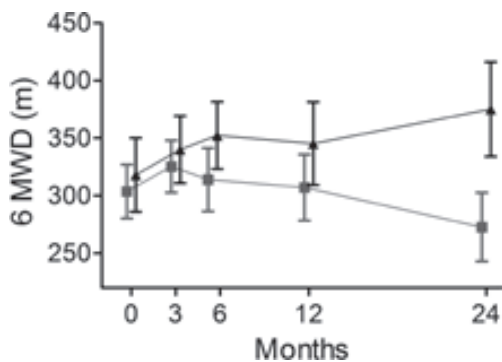


Figure 4: 6-minute walking distance Legend: 6MWD in meters at the different measurement points in the NIPPV + rehabilitation group (black triangles) and the rehabilitation group (grey blocks). The change was significantly better in the NIPPV + rehabilitation group ($p < 0.001$).

group had an average decline in post-bronchodilator FEV1 of 83 ml/yr, while in the NIPPV + PR group this was 17 ml/yr. Except for smoking cessation²⁶ and, in some studies, the use of inhaled corticosteroids,²⁷ no interventions have been shown to slow down FEV1 decline in COPD. Notably, effects found with smoking cessation and inhaled corticosteroids were smaller compared to the difference found in our study of 66 ml/year, which is a large effect in these severe COPD patients. We speculate that NIPPV stabilizes FEV1 either by volume expansion and/or a decrease in airflow obstruction. We were unable to show volume expansion, as we did not show significant changes in vital capacity, lung volumes or hyperinflation. However, lung volumes were measured until 12 months, so that volume expansion could still have occurred during the last year. Independently from changes in lung volumes, FEV1 stabilization is probably caused by a decrease in airflow obstruction. We speculate that a reduction in hypercapnia achieved with NIPPV reduces salt and water retention thereby reducing air wall edema.²⁸ Although speculative, reduced air wall edema might also exhibit a positive effect on airway wall remodeling by reducing inflammation when muscle fibers become less overstretched. An increase of FEV1 at short-term has been previously reported in studies using high inflation pressures with significant reductions in hypercapnia.^{29, 30} The high pressures might be of essential importance to improve of lung function.¹²

This is the first randomized clinical trial to demonstrate that NIPPV is effective in improving daytime arterial blood gases at the longer term. This requires that effective ventilation during the night was achieved. Although it is obvious that effective ventilation is the first condition that should be met with NIPPV, it appears that in most NIPPV studies rather low positive pressure were used, so that outcomes have often been difficult to interpret.^{6,8,9-11} We believe that close monitoring during the night is essential in improving gas exchange and that higher pressures are important to achieve good compliance²⁹ and effective ventilation.^{12,29-31} High compliance as we achieved is essential. This all will have contributed to the positive clinical effects we found.

Exercise tolerance remained stable in the NIPPV + PR group, while it deteriorated in the PR group. A gradual loss of exercise tolerance at long term has been shown before in moderate to severe COPD patients, despite a out-of-hospital maintenance rehabilitation program.^{3,32-34} Probably, positive effects of NIPPV on arterial blood gases give patients a more favorable condition to train and thus prevent deterioration in their physical

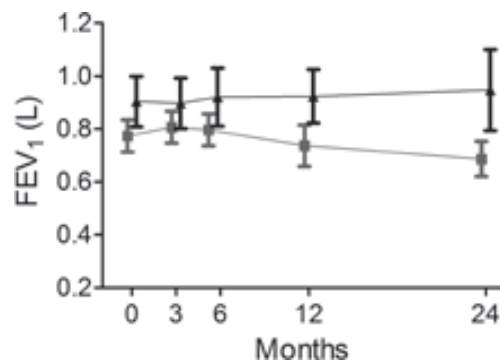


Figure 5: Forced expiratory volume in 1 second (FEV1) Legend: FEV1 in liters (L) at the different measurement points in the NIPPV + rehabilitation group (black triangles) and the rehabilitation group (grey blocks). The change was significantly better in the NIPPV + rehabilitation group ($p < 0.02$).

condition, thus stressing the importance of additional therapies in COPD patients with chronic respiratory failure at long term.

Although these outcomes are promising, we have to notify that the results of our primary outcome, HRQoL, showed uncertain results, with the primary endpoint, CRQ, not showing any improvement. However, in hindsight, we have debated whether the CRQ is the optimal instrument to assess HRQoL in patients with chronic respiratory failure. By contrast, the MRF-28 and SRI were especially developed for patients with chronic respiratory failure improved, and are therefore probably more responsive in these patients.^{12,35} Furthermore, we showed improvements in dyspnea scores and depression scores, both being an important determinant of HRQoL.

Chronic long-term NIPPV is a costly intervention. In a next study it would be interesting to add a true costs-benefit-analysis, as this may play a role in the further implication of NIPPV in chronic COPD patients. We did not find a difference between groups in overall exacerbation frequency, hospitalization rate for a COPD exacerbation or the number of hospitalization days. However in our cohort exacerbations did not occur frequently and the majority of the exacerbations occurred in a minority of the patients, so that large inter-individual differences occurred and data were not normally distributed.

The present study has some limitations. We did not use sham-ventilation in our control group, hence patients and investigators were not blinded. Sham-ventilation is difficult to implement at home during the long study period. Secondly, only 72 patients were included while according to the power calculation 40 patients per group were needed to find a 10-point change in CRQ total score. Due to the difficult recruitment and financial constraints we were unable to further extend the inclusion period. This may have influenced our results due to a type-II error for false negative outcomes, such as might have occurred with the CRQ. This does not, however, affect the observed significant improvements in our study. Finally, our study was not powered to find a difference in survival. While survival benefit of noninvasive ventilation has been shown one controlled study,¹¹ clear evidence of improved survival is still lacking and should be investigated in larger studies.

Conclusions

In conclusion, the present study is the first RCT to show that, with long-term, 2-year NIPPV in addition to PR as compared to PR alone, positive effects can be maintained in HRQoL and gas

exchange, while additional effects can be achieved in functional status (exercise tolerance), mood state, dyspnea scores, and FEV1 in severe COPD patients with chronic hypercapnic respiratory failure. Although larger long-term studies have to confirm our results and give additional evidence on survival benefit and cost-effectiveness, with the present study evidence is provided for a rational use of NIPPV as an additional intervention next to pulmonary rehabilitation in severe COPD patients with chronic hypercapnic respiratory failure. Close monitoring of ventilatory support and the use of sufficiently high inspiratory pressures are probably crucial in obtaining these positive effects. This study shows that interventions that need a long period to reach their maximal effect like NIPPV should be studied over a long time scale, especially in slowly progressive diseases like COPD. Beneficial effects may require much time to develop fully and can therefore easily be underestimated.

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A Challenging Patient: approaches to controlling FiO₂ during highly unstable oxygen saturation

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Following the critical phase of their care, some infants experience frequent episodes of significant oxygen desaturation. Maintaining good control of SpO₂, while at the same time weaning oxygen, can be most challenging. We present this case study of such an infant. We include information on the relative effectiveness of a new closed loop FiO₂ control system (Avea-CLiO₂, CareFusion Yorba Linda CA) and two manual FiO₂ titration approaches. While this infant was unusually challenging, we have been using CLiO₂ routinely for about 1 year and have found it to be very effective in a broad range of patients. Based on this general clinical experience and on our controlled trial,¹ we have found Avea-CLiO₂ to likely be more effective than the best manual care and to result in a significant reduction in nursing labor.

This female was born at another hospital at an estimated gestational age of 27 weeks, weighing 800 grams. Having experienced intrauterine asphyxia, she required cardiopulmonary resuscitation in the delivery room. Subsequently after not responding to NCPAP, she was intubated and transferred to our center at 4 hours of age. Upon arrival she was stabilized with surfactant but required an FiO₂ of 80%.

Her primary diagnosis was RDS with grade II IVH and hypothermic syndrome. The early course of treatment was complicated with a PDA and hemodynamic instability, both treated medically. By the 10th day of SIMV (20/5 rate 50) her FiO₂ had been weaned to below 30%, but she was experiencing frequent severe episodic desaturation spells (9/hour < 80% SpO₂). For this reason she was placed on the Avea-CLiO₂ ventilator with automated FiO₂. Two days later she was enrolled in a study¹ to compare automated CLiO₂ control to two protocol-driven FiO₂ adjustment strategies implemented by a dedicated operator to CLiO₂ for approximately 7.5 hours. As can be seen in Figure 1 during CLiO₂ use, SpO₂ control was much more effective than during the periods of manual adjustment. The frequency and severity of episodes of severe hyper and hypoxemia were markedly reduced with CLiO₂. Following this study period, she was placed back under CLiO₂ FiO₂ control, and the course over the next 14 hours is documented in Figure 2. During this period her SpO₂ remained very unstable but FiO₂ was, nevertheless, automatically weaned. She remained on Avea-CLiO₂ until she was extubated 9 days later. She was then placed

on SiPAP and weaned to NCPAP over the next 11 days. She was discharged home without the need for supplemental oxygen, mild BPD and grade II ROP.

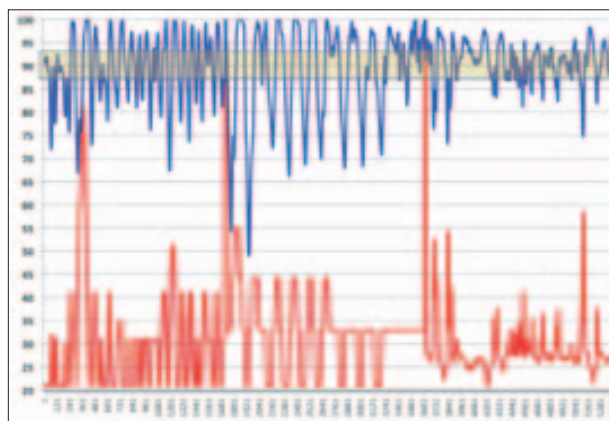


Figure 1. Comparison of CLiO₂ and Two Methods of Manual FiO₂ Control – 7.5 hours. The chart shows the FiO₂ (red) and SpO₂ (blue) based on 1 minute rolling averages of 5-second data points. Each tick on the time axis represents 10 minutes. The vertical red bars represent the 2.5 hour time demarcation between the three FiO₂ control approaches. (Attentive, Routine, and CLiO₂, respectively). The yellow horizontal band represents the intended target range (87%-93% SpO₂). The FiO₂ adjustments in response to desaturations during manual control, regardless of the strategy, were larger and longer compared to the faster more proportional control of CLiO₂. During Attentive control the swings in saturations were more frequent but of shorter duration than during Routine control. The difference in overshoot of SpO₂ in response to FiO₂ increases is also markedly less during use of CLiO₂. CLiO₂ also found a baseline FiO₂, in which to return to after desaturations of about 25%, which was apparently an FiO₂ that better suited the infant's needs.

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CLiO2 Theory of Operation

CLiO2 utilizes a sophisticated patented control system. While monitoring SpO2 virtually continuously, CLiO2 compares the SpO2 to the clinician selected target range. Every 1 second CLiO2 considers a change to the FiO2. If the SpO2 is outside the target range, the FiO2 change is based not only on the duration and magnitude/depth of the episode but also on the trajectory of the SpO2.

CLiO2 considers a baseline FiO2 level to facilitate returning to the target range as quickly as possible and minimizing overshoot beyond the target range. The baseline FiO2 is initially set by the clinician and updated automatically based on the infant's course. The time constant of the update is based on the infant's SpO2 stability. That is, the more stable the more quickly the baseline is changed.

In addition, when the SpO2 is within the upper half of the desired target range, the FiO2 is slowly weaned down to bring it to the mid-point of the desired range. Furthermore, even when in the target range, CLiO2 identifies rapid changes in SpO2 and responds in anticipation of a significant excursion.

Finally, in addition to traditional SpO2 alarms, CLiO2 also offers two other safety features. First, should CLiO2 need to increase FiO2 significantly to maintain SpO2 in the target range, an alert is provided to the clinician. Second, should the oximeter signal drop out, or be of poor quality, CLiO2 returns the FiO2 to the clinician set backup FiO2 or the most recent FiO2, whichever is higher.

CLiO2 has been shown in two controlled trials,^{2,3} when compared to routine care, to markedly increase time in intended SpO2 target range, to reduce time in severe hyperoxemia without increasing time in severe hypoxemia and to reduce the level of inspired oxygen.

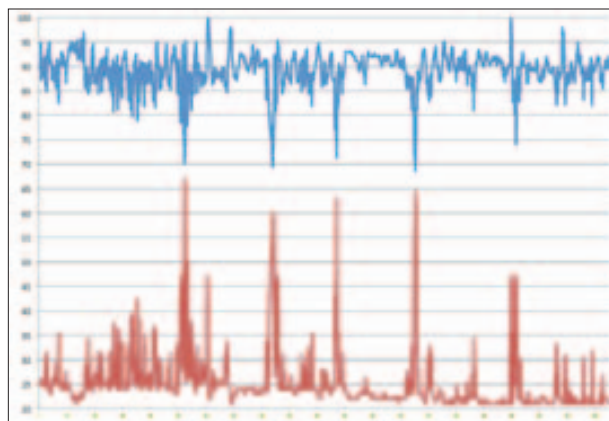


Figure 2. Subsequent CLiO2 Control – 14 hours. The chart shows the FiO2 (red) and SpO2 (blue) based on 1-minute rolling averages of 5-second data points. Each tick on the time axis represents 45 minutes. In this chart CLiO2's response to acute hyper and hypoxemia episodes remains apparent, but the longer period of time also affords the opportunity to see CLiO2's response to less acute trends in SpO2. In the early part of this period, at a time when the SpO2 was relatively stable but drifted above the control range, the FiO2 was reduced to 21%. Immediately following this, the FiO2 was increased when the SpO2 deteriorated. Over this 14-hour period of time, however, CLiO2 automatically reduced the FiO2 from a baseline of 25% to 21%.

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Lactate*

Comparison instrument	Slope and intercept	Bias	Corr. coeff. [r]	No. of samples
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