

Volume 8 Number 3 June-July 2013

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The Journal of Pulmonary Technique

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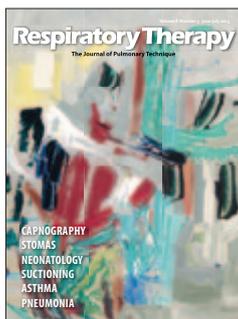
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**References:** 1. Castro M, et al, for the AIR2 Trial Study Group. *Ann Allergy Asthma Immunol.* 2011;107:65-70. 2. Castro M, et al, for the AIR2 Trial Study Group. *Am J Respir Crit Care Med.* 2010;181:116-124.

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June-July 2013

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## Editorial

### RTs vs Docs

Here's a study you might find of interest, in case you missed it: The journal *Respiratory Care* published a paper on physician-ordered aerosol therapy vs respiratory therapist-driven aerosol protocol.

According to the abstract, the utilization of RT driven protocols for single interventions, such as oxygen titration and bronchopulmonary hygiene, and protocols consisting of multiple interventions have been associated with improvements in resource utilization. Based on this, the researchers started a quality improvement project to transition the delivery of respiratory care services from physician-ordered treatments to RT-driven protocols.

During the first phase of the quality improvement project, they compared the frequency of bronchodilator administration and its associated costs between a physician-ordered bronchodilator strategy and a RT-driven bronchodilator protocol strategy. Over a period of 2 weeks, RTs administered physician-ordered bronchodilator treatments. During this time they assessed the subjects' clinical status and what they would have recommended in regard to bronchodilator treatment frequency following an RT-driven protocol.

Forty-eight subjects were ordered bronchodilator treatments, which resulted in 88 assessments. The utilization of a protocol would have resulted in 42 (47.7%) bronchodilator orders administered every 6 hours, as needed, and 27 (30.6%) orders administered every 8 hours, compared with 2 (2.2%) and 2 (2.2%), respectively, in the physician-ordered group. Conversely, physician-ordered treatments were prescribed every 4 hours in 56 (63.6%) cases, compared with 10 (11.3%) in the RT-driven protocol group. Total bronchodilator therapy cost in the physician-ordered group was \$1,672.85, whereas it would have been \$904.53 in the RT-driven one. Per patient costs were \$19.0 ± 6.9 in the physician-ordered group, and would have been \$10.3 ± 9.4 in the RT-driven bronchodilator protocol group.

The authors concluded – The application of an RT-driven bronchodilator protocol can hypothetically reduce the frequency of bronchodilator treatments, compared with a physician-ordered strategy, resulting in a theoretical reduction of costs in patients who require bronchodilator therapy.

Les Plesko  
Editor

Source: Physician-ordered aerosol therapy versus respiratory therapist-driven aerosol protocol: the effect on resource utilization. Kallam, et al, *Respir Care*. 2013 Mar;58(3):431-7.



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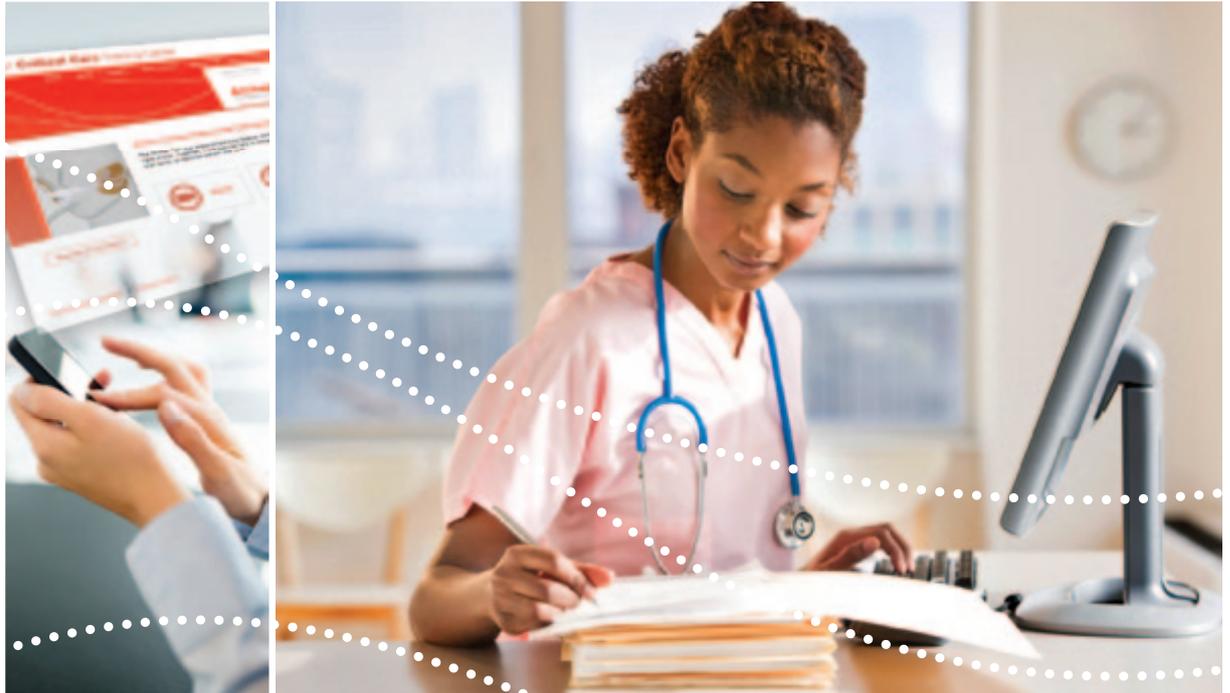
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## COPD

June 14 and 15 are the dates for the COPD8USA conference, hosted by The COPD Foundation. The content for this conference is designed to provide important clinical and scientific knowledge no matter what your role is in the healthcare provider team. The program is designed for primary care physicians, pulmonologists, advanced and registered nurses, physician assistants and respiratory therapists, medical directors, care coordinators and others who are involved and/or interested in the management of individuals with COPD. COPD8USA is dedicated to highlighting the changes in the current healthcare landscape and capitalizing on those changes to positively impact patient care. In order to address the new healthcare environment and educate physicians and healthcare providers about how to best utilize the new system to positively impact patient care, COPD8USA will include 3 tracks: Clinical, Research, and Care Delivery. Visit [www.copdconferencesusa.org](http://www.copdconferencesusa.org).

## BMC NEWS

The Research Councils UK (RCUK) policy on open access goes into effect on 1 April 2013. The policy states that all peer-reviewed published research articles and conference proceedings funded by RCUK must be open access. BioMed Central has over 250 science, technology and medicine open access journals, many with high impact factors at the top of their fields. All articles are published CC-BY and fully compliant with RCUK's open access policy. To help institutions support open access publishing, BioMed Central is working closely with UK research institutions and RCUK, and as part of this has produced a helpful video (<http://www.biomedcentral.com/funding/rcuklpf>). Through BioMed Central's partnership with Edanz, it is aiming to support authors to select the journal that best suits their research from the 350+ open access journals published by BioMed Central, Chemistry Central and SpringerOpen... The Journal Selector uses semantic technology to help authors quickly choose the open access journal that is right for their manuscript. Authors can enter an abstract or description of their research and the Journal Selector provides a list of relevant open access journals. Matches to a journal are based on the similarity of the entered text to articles already published in that journal. To see how it works, go here: <http://www.biomedcentral.com/authors/authorfaq/findout>.

## POOR SCIENCE

Ben Goldacre writes on Huffington Post as part of TedTalks:

“Doctors need the results of clinical trials to make informed choices, with their patients, about which treatment to use. But the best currently available evidence estimates that half of all clinical trials, for the treatments we use today, have never been published. This problem is the same for industry-sponsored trials and independent academic studies, across all fields of medicine from surgery to oncology, and it represents an enormous hidden hole for everything we do. Doctors can't make informed decisions when half the evidence is missing. Most people react to this situation with incredulity, because it's so obviously absurd. How can medics, academics, and legislators have permitted such a huge problem to persist? The answer is simple. This territory has been policed – and aggressively – by the pharmaceutical industry. They have worked hard to shut down public discussion on the topic for several decades, with great success... They only demanded information about new trials, and this is hopeless. Anything that only gets us the results of studies completing after 2008 does nothing to fix medicine today, because more than 80% of all treatments prescribed this year came to the market more than ten years ago. We need the results of clinical trials from 2007, 2003, 1999, and 1993, to make informed decisions about the medicines we use today. This isn't about catching companies out for past misdemeanors, it's a simple practical matter of making medicine optimally safe and effective... Sometimes they pretend that the academic journals are the bad guys for rejecting papers with negative results, when this was barely ever an issue, and in any case, there are now endless open access journals, specifically designed to accept negative results.” Goldacre, a doctor who is the author of the book *Bad Pharma*, has started a petition at AllTrials (you can google it) that calls for the release of basic information (including brief summary results, and the long “Clinical Study Report” where available) for all trials, on all treatments currently in use, whether past or future. Over 40,000 people have signed, as well as 200 organizations.

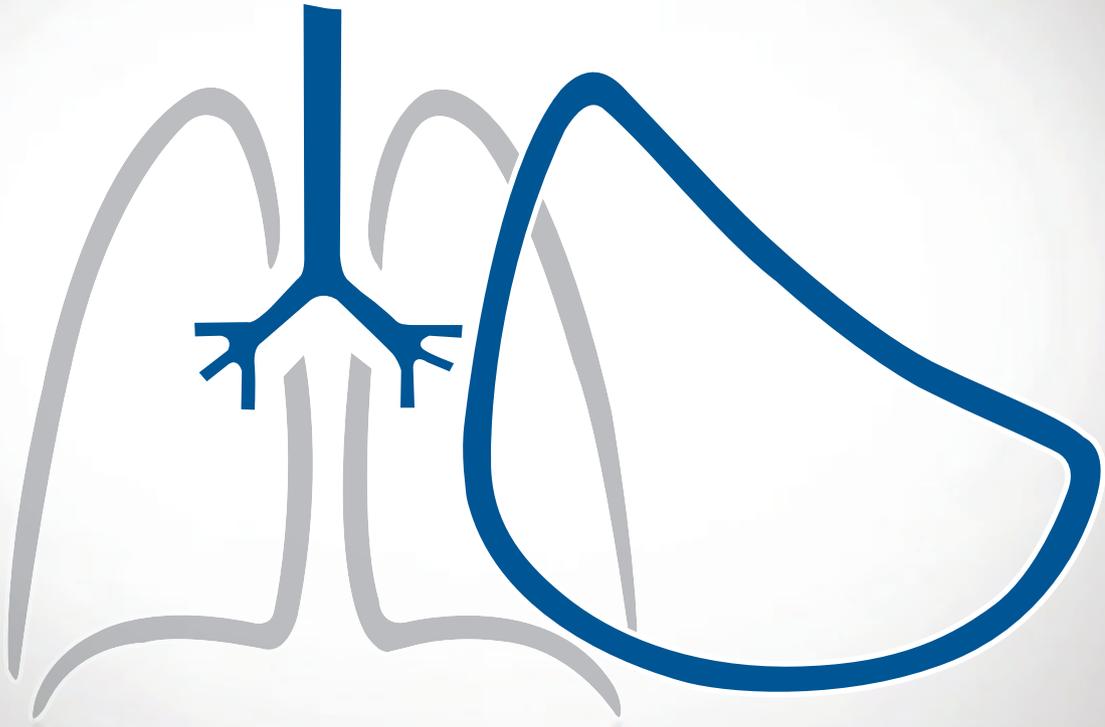
## NEW DEADLY VIRUS

A new deadly virus has popped up, first identified by a Saudi virologist who was fired for reporting on it. A new strain of the coronavirus, which is also responsible for the common cold, has now been identified in a number of countries. As we report on this, the number of cases is at 15, and more than half had died. As of now, according to a report by the news blog Raw Story, from information published by the Guardian newspaper, there are no signs that the virus spreads from person to person, but scientists are worried that the virus will mutate and adapt to spread more readily. The source of the virus is unknown, but researchers are looking at a matching strain in pipistrelle bats, which were also the source of the Sars virus, which then spread to humans via infected civet cats. Scientists suspect that this current coronavirus is carried to humans by some intermediary animal. In one case, a patient noted that his goats had been sick before he fell ill, and the goats' keeper also fell ill with a respiratory infection. Researchers want countries in the Middle East to test goats, sheep, camels and horses for the virus, but nothing is happening on that front so far. The above story was reported by Raw Story, copyright Guardian News and Media 2013, with additional reporting by Mark Smith.

## KILLER CELLS

Scientists from Brigham and Women's Hospital have discovered two new drug targets in the inflammatory response pathway responsible for asthma attacks. Researchers studied the lungs and blood of 22 people with mild and severe asthma. They saw that immune cells called natural killer cells and type 2 innate

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lymphoid cells played significant roles in airway inflammation in study participants with severe asthma. Natural killer cells decreased airway inflammation by encouraging programmed cell death in immune cells called eosinophils, whereas type 2 innate lymphoid cells promoted airway inflammation by secreting the cell-signaling molecules interleukin-13. Both mechanisms were controlled by a molecule called lipoxin A4 which is responsible for resolving inflammation. To achieve this, lipoxin A4 acted in both pro-resolving and anti-inflammatory ways. The researchers saw that lipoxin A4 encouraged natural killer cells to decrease inflammation by facilitating eosinophil cell death. Lipoxin A4 also discouraged type 2 innate lymphoid cells from promoting inflammation by blocking interleukin-13 secretion.

## LIARS

Douglas Farrago reports on his Authentic Medicine blog: "Patients lie. That's just a reality. [According to an article in the Wall Street Journal] 'Common lies include everything from diet and exercise regimens to medication adherence, sexual histories, and taking alternative medicines.' Over the years, I think I have seen it all. I have seen a lot of illicit drug use that was only admitted to me after years of someone being my patient. I have seen lies about med use that have made me look bad when I increased the dose. The numbers are staggering. A physician survey referenced in the article states the 77% said that one-fourth or more of their patients omitted facts or lied, and 28% estimated it was half or more of their patients. The truth of the matter is that all people lie a little bit. Not all of it is malicious. I never took it personally unless they were trying to manipulate something from me. Heck, even doctors shade the truth sometimes. 'A study published last year in the journal Health Affairs found that just over one-tenth of more than 1,800 physicians surveyed had told patients something untrue in the previous year.'"

## BLOOD CLOTS

The frequency of vena cava filter use to prevent migration of blood clots to the lungs in patients with acute venous thromboembolism appears to vary widely and be associated with which hospital provides the patient care, according to researchers at the University of California, Davis, who noted that the use of VCFs continues to increase despite uncertainty about the relative benefits vs risks. The study included 263 hospitals where 130,643 acute VTE hospitalizations occurred with the placement of 19,537 VCFs (14.95%). Researchers found that the range in frequency of VCF use was between 0% and 39%. The hospital characteristics associated with VCF use included having a small number of beds, a rural location and being a private

hospital. The researchers said the use of VCFs was based on the local hospital culture. "Taken together with the results of another recent study that reported no clear indication for VCF use in approximately 50% of patients who received a VCF, the findings suggest that use of VCFs is based substantially on the local hospital culture and practice patterns. The absence of reliable data indicating a clear benefit (or clear harm) associated with VCF use likely contributes to the wide variation in use that we observed," the authors concluded.

## EPIDEMIC

Asthma is becoming an epidemic in the United States, according to a study in a recent issue of *Annals of Allergy, Asthma & Immunology*, which noted that 26 million Americans are currently affected. But a more surprising finding of the study is that 75% of asthmatic adults between 20 and 40 years old, and 65% of asthmatic adults 55 years old and older have at least one allergy. A total of 2,573 adults were studied in a National Health and Nutrition Examination Survey (NHANES). A panel of 19 allergens was used to detect allergy among asthmatics. While asthma is frequently associated with children, it is not uncommon among adults 60 years and older, affecting three to seven percent. This number is likely higher, however, because asthma is often under-diagnosed in older adults.

## ANTIBIOTIC AND HEART PROBLEMS

Clarithromycin may be associated with an increased risk of heart problems, according to researchers at the University of Dundee, who analyzed data on 1,343 patients admitted to hospital with acute exacerbations of COPD and 1,631 patients admitted with community acquired pneumonia. Seventy-three out of 281 of the patients prescribed clarithromycin during acute exacerbations of COPD had at least one cardiovascular event over the next year compared to 195 out of 1,062 of the patients who didn't get the antibiotic. Among patients given clarithromycin for community acquired pneumonia, 123 out of 980 had at least one cardiovascular event compared to 48 out of 651 not on the drug. For COPD, a significant association was also found between clarithromycin use and cardiovascular mortality, but not all-cause mortality. For community acquired pneumonia, no association was found between clarithromycin use and cardiovascular mortality or all-cause mortality. Longer durations of clarithromycin use were associated with more cardiovascular events. However, use of other types of antibiotics, such as  $\beta$ -lactams, showed no association. The researchers suggested that there will be an additional cardiovascular event for every eight patients given clarithromycin compared to patients not given the drug (or one in 11 for pneumonia). The data also suggest that the increased risk may persist beyond the time when clarithromycin is stopped.

## WORSE THAN A HEART ATTACK

The long-term consequences of pneumonia can be worse than having a heart attack, especially for older adults, according to researchers at the University of Michigan Health System and University of Washington School of Medicine. Patients who were treated for pneumonia, even those hospitalized just once in a nine-year period and who did not require critical care, were more than twice as likely to develop new cognitive impairments that often led to disability and nursing home admissions. After treatment for pneumonia, patients also had nearly double the risk of substantial depressive symptoms. Like people who had heart attacks, following hospitalization, patients with pneumonia also had an increased risk of losing the ability to maintain daily

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### IMBALANCE

Increased respiratory symptoms and loss of asthma-related quality of life in obese people may be due to an imbalance in the metabolism of the amino acid arginine rather than allergy or airway inflammation, according to a study at the University of Pittsburgh School of Medicine. Researchers pointed to the conundrum that those with severe asthma may require frequent steroid treatments and need to limit their activity, resulting in weight gain, and that obesity aggravates or initiates asthma symptoms. The researchers collected blood samples from 155 adults, half of whom had severe asthma and half who were obese. They found that compared to early-onset asthma patients, late-onset obese asthma patients had lower plasma levels of the arginine and higher levels of the arginine metabolite ADMA, which interferes with NO production.

### PREEMIE LUNGS

Researchers at Yale School of Medicine have located key molecules that switch on stress pathways in preterm lung disorders, and also found that when parts of these pathways were blocked with a Cox2 inhibitor, lung damage was prevented or reversed. The researchers studied the lung tissue of newborn mice and found that when this tissue was exposed to hyperoxia, there was a marked increase of cyclooxygenase 2 in the lung's stress pathways. With the Cox2 inhibitor, they were able to reverse BPD in mice.

### DOWN SYNDROME AND OSA

Researchers at the University of Southampton will investigate tests for OSA that affects babies and children who have Down syndrome, with an eye on introducing an affordable and simple routine screening. Studies suggest that three-fourths of Down syndrome babies will have OSA. The screening tests will comprise a sleep questionnaire and pulse oximetry.

### IT'S ALIVE

Surgeons at the University of Pittsburgh Medical Center performed a "breathing lung" transplant using a portable machine that provides a constant supply of blood and nutrients to the donor organs. The double-lung transplant used the Organ Care System, also known as the OCS lung, by TransMedics Inc. The 53-year-

old patient had suffered from pulmonary fibrosis and pulmonary hypertension. Using the OCS device, the lungs are immediately placed in the machine after donation and kept functioning at body temperature while in transit to the recipient. The surgeons plan to enroll ten patients in a clinical trial which will randomize five participants to get the OCS device and five to be treated using the traditional method of care. The OCS machine resembles a small cart on wheels, and monitors the organ's arterial pressure, gas exchange ratio, vascular resistance and other data through embedded sensors so doctors can get an immediate snapshot of the organ's viability.

## PRODUCTS

### PURCHASE

Nonin Medical, Inc announced that the company's EQUANOX Advance Cerebral/Somatic Oximetry System has been selected for use by Poland's five university-based pediatric hospitals. EQUANOX is a near infrared spectroscopy (NIRS)-based monitoring device that noninvasively and continuously detects oxygen saturation status in brain and other tissue. The purchase was made possible by the Great Orchestra of Christmas Charity (GOCC) organization, one of the largest non-government charity organizations in Poland. Each year the GOCC meets with hospital leaders to determine what the biggest needs are for medical equipment. Contact [noninequanox.com](http://noninequanox.com).

### APP OVERSIGHT

MediSafe Project version 2.0 has launched, giving doctors better patient oversight between office visits via an in-app list of personalized medication adherence statistics users can send them. Adherence rates are color coded to help users easily understand how well they're taking medications as prescribed. Users can email their personalized list as an Excel spreadsheet to doctors, caretakers or family members. To protect their privacy, no patient identity information is included in the spreadsheet, but users can add it to the email if they choose. As the first medication reminder to use cloud sync technology, MediSafe Project sends alerts to users' family, friends and caretakers when they miss a dose. Since its November 2012 launch, MediSafe Project users have an average self-reported medication adherence rate of 79% – twenty-nine points higher than

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the World Health Organization's estimated average medication adherence of 50%. More than 35,000 people have downloaded MediSafe Project on Android and iOS. Users have visited the app a total of 900,000 times and recorded taking over 750,000 medication doses as directed. iOS users can expect the update to arrive in iTunes this June. Contact [medisafeproject.com](http://medisafeproject.com).

### **IMPROVED OUTCOMES**

Hospital General Universitario Santa Lucia, and Masimo announced that the hospital has become the first in Spain to deploy Masimo Patient SafetyNet, clinically shown to help improve patient outcomes and reduce costs. General Universitario Santa Lucia installed the Patient SafetyNet system to provide advanced monitoring of its most vulnerable patients in the neonatal basic care unit. Patient SafetyNet can help ensure patient safety by noninvasively and continuously measuring a patient's physiological conditions and detecting changes or abnormalities that signal declining health status in real-time. When changes occur in the measured values, which may indicate deterioration in the patient's condition, the system automatically sends wireless alerts directly to clinicians, prompting a potentially lifesaving response to the patient's bedside. The Masimo Patient SafetyNet system consists of Masimo SET Measure-Through Motion and Low Perfusion pulse oximetry, with choice of patient-tolerant and easy-to-use ventilation monitoring with rainbow Acoustic Monitoring or standard capnography, and remote monitoring and notification to help keep clinicians connected to patients. Patient SafetyNet has been clinically shown to help reduce rapid response activations, intensive care unit (ICU) transfers, and deaths related to opioid-induced respiratory depression. Contact [masimo.com](http://masimo.com).

### **OSA MANAGEMENT**

Philips Respironics, a unit of Royal Philips Electronics, announced significant advancements to its medSage obstructive sleep apnea patient management and resupply solution. The medSage service is a web-based voice and email software that has helped OSA patients achieve compliance with their sleep therapies while helping homecare providers to efficiently manage and grow their mask resupply businesses since 2004. The new version 3.0 enhancements represent a major re-launch, incorporating the most extensive updates to date based on best practices of homecare providers. The changes reduce by half the number of steps and time needed to perform functions such as adding and viewing comments, patient searching, finding and editing reorders, and resolving patient notifications. The medSage service features include automated eligibility determination, customizable patient call scripts designed to assist with reimbursement documentation and other industry requirements including CMS reports. It also allows for the patient's preferred method of communication such as pre-recorded voice recognition surveys, email, live calls, or after-hours hotline with fulfillment service providers. The medSage service is intended for larger homecare providers and is part of Philips Respironics Fit for Life comprehensive resupply sleep apnea mask solution. Fit for Life also offers the EncoreResupply patient compliance management and ongoing supply replenishment service for small to mid-size homecare providers and sleep labs. Contact [respironics.com](http://respironics.com).

### **TAPPED**

HealthTap, the mobile health platform for health answers and tips, announced that its popular patient-doctor question and answer service is now extended to doctor-doctor

communications. With over 600 million doctor-answers served to patients to date, HealthTap now offers doctors the ability to ask questions of one another within the same network that's already providing members with the highest-quality health information available. HealthTap's Doc2Doc messaging platform opens up the knowledge of the country's best doctors to one another and to patients. This enables physicians practicing in 128 specialties to instantaneously exchange best practices, resulting in better outcomes and higher quality patient care. Doc2Doc leverages the high engagement of doctors on the HealthTap platform to provide a friendly online social setting for exchanging expert medical knowledge beyond conferences, seminars and hospital cafeterias. Contact [healthtap.com](http://healthtap.com).

### **GO GREEN**

Electromed, Inc, maker of the SmartVest Airway Clearance System, announced the expansion of its product line with Ginkgo Green, a new SmartVest garment color. In addition to Ginkgo Green, Electromed's garment line includes SmartVest Teal, Powerful Purple, Brilliant Blue, Seriously Pink, and Racing Red. Every in-home patient has an option to select a colored SmartVest garment, personalizing their treatment experience. Contact [electromed.com](http://electromed.com) or [smartvest.com](http://smartvest.com).

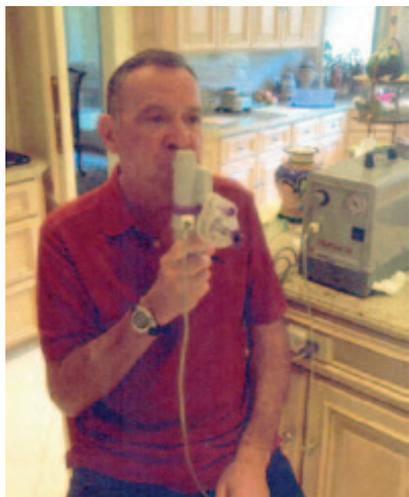
### **AGREEMENT**

Terumo Cardiovascular Systems announced it has entered into a multi-year distribution agreement with Nonin Medical, Inc. Terumo CVS will distribute Nonin's EQUANOX Model 7600 Regional Oximetry System to adult and pediatric cardiovascular hospitals in the US; Nonin's direct sales force will focus on certain non-cardiovascular applications in those hospitals, and applications in all other US hospitals. Terumo CVS manufactures and markets medical devices for the global cardiac surgery market. The Nonin EQUANOX Model 7600 Regional Oximetry System is a noninvasive medical monitoring system that continuously detects oxygen saturation status in the brain and tissue beneath the sensor during surgical procedures and in intensive care environments such as pediatric and neonatal intensive care units. The system allows anesthesiologists, perfusionists, cardiovascular surgeons, and other clinicians to quickly react to reverse tissue ischemia events before they become critical. Contact [noninequanox.com](http://noninequanox.com) or [terumomedical.com](http://terumomedical.com).

### **ENDORSEMENT**

A patient using the Vortran Percussive Nebulizer [Vortran Medical Technology 1, Inc] sent the company the following letter: To Whom It May Concern, I was diagnosed with lung cancer and underwent surgery July 2006 to remove the right upper lobe. In September 2006 I had viral pneumonia followed by chronic asthma and COPD. Over a period of time the regular nebulizer was not sufficient for me to deliver medication deeper into the bronchials to assist in bring up the secretions. I started using the Vortran July 2011 which had given me excellent relief helping to mobilize the secretions to keep me from being hospitalized. The Vortran is vital to my daily treatment regimen which is anywhere from two to our times a day. I would like to commend and express my sincere appreciation to Lynn Weddington and Jeremy for their polite and caring persistence in helping me. Sincerely yours, Jim Decker... The patient's physician wrote an accompanying letter: My patient, James Decker, has had a problem with mucus plugging for several years. He's had excellent relief from the Vortran Percussive Nebulizer, which has helped greatly in mobilizing his secretions and keeping him out

of the hospital. It is vital to his well being to continue these treatments indefinitely.  
– Dennis R. Novak, MD, FCCP.



*James Decker using the Vortran Percussive Nebulizer*

### THE FUTURE

World renowned physicians and respiratory therapy leaders met on February 12, 2013 at Banner Desert Hospital's Rosati Education Center in Phoenix, AZ to present innovative approaches that may help define the future of respiratory therapy. The complementary conference, Current Concepts in Critical Care Ventilation – 2013, was sponsored by Dräger, a leading provider of perioperative, monitoring, neonatal care, and mechanical ventilation systems. More than 125 respiratory therapists, registered nurses, and RT students attended the event. Attendees had the opportunity to confer with conference faculty and colleagues from more than 16 states and were given the opportunity to experience the latest in mechanical ventilator technology using Dräger's ventilation and monitoring systems, including the newest releases such as the Evita Infinity V500 and Savina 300. Through hands-on product demonstrations, therapists were able to practice using these advanced ventilators and monitors to optimize gas exchange and oxygenation to potentially minimize patient time on ventilators and prevent ventilator-induced lung injuries. Research and studies included: a historical view of mechanical ventilation, alveolar physiology, ventilator waveform analysis and intervention, latests findings during APRV mode of ventilation, lung recruitment techniques, and case studies in ARDS. Due to the success of

the program, Dräger will host a similar conference on June 28 in Newport Beach, Calif. at the Marriott Resort & Spa. For more information, contact Ed Coombs at (215) 660-2322, draeger.us.

### ERGONOMIC

AG Industries offers high quality, comfortable Full Face & Nasal mask options, ergonomically designed in small, medium, and large sizes. The AG Full Face & Sopora Nasal Masks feature soft and odorless, replaceable medical grade silicone cushions and a quiet exhalation port, positioned upward, to prevent disrupting partners. A standard 22mm connection allows both masks to be used with the AG Flex Tube to reduce torque between the tube and mask. In addition to the superior qualities of the mask, the soft neoprene headgear features "quick snap" buckles that make getting the mask off and on a "snap." Contact [agindustries.com](http://agindustries.com).

### MRI CLEARED

Impact Instrumentation, Inc received FDA 510(k) clearance in 2012 to market its new MRI conditional ventilator, the Eagle II MR. This full featured ventilator, weighing less than 10 lbs, offers AC, SIMV and mask CPAP-NPPV, volume and pressure targeted breaths and both invasive and noninvasive ventilation modes. Features of the new Eagle IITM MRI Ventilator include: • Automatic leak compensation - helps mitigate mask CPAP leaks while improving patient comfort. • Pressure Support - minimizes your patient's work of breathing. • MRI Circuits - low dead space 12 ft patient circuits allow users to place the Eagle II MRI as close as 2 m (~6.6 ft) to the magnet's bore. • Roll Stand - an MRI conditional, 5 locking wheel roll stand is available to secure the ventilator in place. • Enhanced power - 10 hour battery life with two-hour charge time compared with current industry standard of 1- 4-hour battery life. • Built-In Compressor - no need for auxiliary oxygen. • Smart-Help - provides care givers with alarm resolution support. • Wide patient range - can be used on infants (5kg) through adults. • Automatic apnea backup - begins ventilation when spontaneous ventilation ceases. The Eagle II MRI Portable Ventilator can be used in MRI suites that operate 3 Tesla magnets or less. It is manufactured in the USA by New Jersey-based Impact Instrumentation, Inc a medical device developer and manufacturer of respiratory products and measuring instrumentation. Contact [impactii.com](http://impactii.com).

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# BLOOD GAS ROUNDTABLE

## Nova Biomedical

### Tell us about the blood gas products you offer.

Nova Stat Profile 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, co-oximetry tests, and metabolites including lactate, BUN and Creatinine. No other blood gas/critical care analyzer can match the clinical value of pHox Ultra to effectively manage high acuity, critically ill patients.

### Describe the applications for your products.

*Applications in the OR and ICU:* Test menu is one of the most important criteria in selecting a whole blood point-of-care analyzer for use in the ICU. ICUs require a comprehensive menu of stat tests to effectively manage the higher acuity of today's critically ill patients. pHox Ultra is the only point-of-care analyzer to provide a comprehensive stat menu including blood gases and Chem 8 plus lactate, ionized magnesium, hematocrit, hemoglobin, and measured SO<sub>2</sub>%.

*Applications in the ED:* One successful strategy to reduce ED overcrowding, improve patient satisfaction, and expedite triage involves reducing waiting times for essential laboratory tests such as a Chem 8 profile, electrolyte profile, blood gas profile, Hct and Hb profile, or a combination of these tests.

These are among the most commonly ordered and useful tests for evaluating, triaging, or discharging patients in the ED. • Stat Profile analyzers can perform a Chem 8 profile plus pH, lactate, Hct and Hb from 2 drops of whole blood in only 2 minutes. • Having the Stat Profile whole blood test menu available in the ED has been shown to be effective in reducing patient waiting times to see a clinician to less than 30 minutes, and improving patient satisfaction with the ED.

*Stat Profile analyzers in the Stat Lab:* A strategy that has effectively addressed the need for critical care testing in numerous hospitals has been use of a Stat Profile analyzer in a centralized stat testing location. Stat Profile is an all-in-one solution for providing rapid turnaround time to multiple departments from a single stat lab: • The 20-test menu meets the diverse test menu needs of multiple departments such as Surgery, ICU, NICU, ED, and Respiratory Therapy with a single analyzer. • The 2 minute analysis time and whole blood capability provide the rapid turnaround time necessary for a stat lab. • Custom test panels can be set up to handle the specific test menu needs of each department. • The high sample throughput (up to 38 samples per hour) can handle the workload of multiple departments with a single analyzer.

### Discuss training and support for the use of your products.

Immediately following analyzer installation, training of operators is provided by Nova training and applications staff. Correlation 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.

### Discuss point of care testing as it applies to your products.

As the acuity of patients seen in the hospital increases, more and more critical care analyzers are being placed at the point of care. For example, Stat Profile 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. Historically, respiratory therapists have overseen blood gas testing as it directly relates to their patient care. Now that Stat Profile point of care analyzers can provide full critical care testing results, respiratory therapists, with their unique knowledge of these devices, become even more valuable to the critical care team. Stat Profile analyzers enhance this value as the only whole blood analyzers to provide a comprehensive panel of tests including ionized magnesium and BUN/Creatinine. Increased use of point-of-care testing also demands that devices be more automated. Nova analyzers feature fully automated operation and analysis of selected test menus with just a touch 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. Snap-in sensors and reagent cartridges make maintenance easy.

## Roche Diagnostics

### Tell us about the blood gas products you offer.

Roche Diagnostics' blood gas portfolio includes the **cobas b 123** POC system, cobas b 221 system, and **cobas bge link** software for hospital point-of-care. The cobas b 123 POC system is a mobile, near patient blood gas analyzer with a broad assay menu including lactate. Blood clots are commonplace for most blood gas analyzers and it can be time consuming to return the analyzer to reliable performance. The cobas b 123 POC system features an unparalleled system of four levels of clot protection to help prevent pack failures. This next generation blood gas analyzer is designed to help provide optimal reliability, allowing you to spend more time providing quality care to your patients. Analyzer downtime due to pack failure and blood clots and inability to control costs with existing devices are major user issues for Respiratory Managers requiring a near patient blood gas analyzer. The cobas b 123 POC system reagent pack requires no refrigeration and offers excellent reliability. In addition, the cobas b 123 POC system has consumables with

smart chips allowing them to be easily transferred between like devices which help customers control costs and spend more time providing quality care to their patients. The cobas b 221 system was uniquely designed to help provide virtually uninterrupted performance. The analyzer has a powerful fluidic system that includes both peristaltic pump and vacuum pump mechanics that can remove the source of trouble and help minimize downtime. The cobas b 221 system configurable menu has options for blood gas (pO<sub>2</sub>, pCO<sub>2</sub>, and pH), electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, Ca<sup>+</sup>, Hematocrit), metabolites (glucose, lactate, BUN), and Co-oximetry (O<sub>2</sub>Hb, HHb, COHb, MetHb, tHb, Bilirubin). It was the first blood gas system 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. Both analyzers use cobas bge link software enabling the user to monitor and control multiple, decentralized units from one location. Cobas bge link software 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.

#### Describe the applications for your products.

The cobas b 123 POC system and cobas b 221 system analyzers can be used in a wide variety of hospital settings including the central laboratory, respiratory therapy department, intensive care units, emergency department, STAT Lab, operating room, NICU, Cath Lab and patient floor. Both analyzers can use a variety of sample input devices including syringe, capillary, test tubes, and MICROSAMPLER PROTECT. The cobas b 123 POC system is FDA approved for analysis of whole blood samples. The cobas b 221 system is FDA approved for analysis whole blood, serum plasma, dialysate solution and pleural fluid.

#### Discuss training and support for the use of your products.

Roche Diagnostics provides a variety of educational materials to help healthcare professionals operate the cobas b 221 POC system and cobas b 221 system properly and help maintain operator certification. These educational materials include: • Onboard video tutorials and a customer-based training DVD along

with instruction manuals that provide detailed descriptions to help operators avoid errors using the equipment. • Roche offers on-site blood gas analyzer and cobas bge link software training at the customer facility. Roche also offers a two-day training program at its Indianapolis headquarters for two operators for the cobas b 221 system. • 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. • 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.

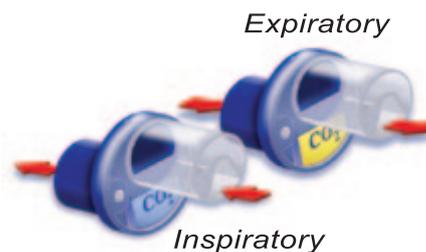
#### Discuss point of care testing as it applies to your products.

The cobas b 123 POC system can help improve patient care testing by delivering accurate results for up to thirty patient tests per hour. The analyzer has a Micro Mode feature that uses only 37 µl sample for blood gas parameters, 55 µl for blood gas parameters and COOX, and 25 µl for COOX only. The cobas b 123 POC system has been designed with a mobile cart for ease of use in the OR, ER, ICU, RT area and Lab. The cobas b 221 system can help improve point of care testing by delivering accurate test 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 system, 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 system 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.

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## Siemens Healthcare Diagnostics

### **Tell us about the blood gas products you offer.**

Siemens Healthcare Diagnostics offers a comprehensive portfolio of blood gas solutions with our RAPIDSystems analyzers, designed to produce fast, accurate results so that clinicians can rapidly and confidently make critical treatment decisions. Further, with our breadth of products, we are able to provide solutions that meet a range of customer needs, both in low volume critical care settings and high-throughput environments. Additionally, Siemens blood gas systems integrate with our RAPIDComm Data Management System, enabling point-of-care (POC) coordinators to manage and control testing quality over multiple analyzers on their network. The RAPIDComm system also provides the ability to manage operator access, set operator certification requirements, manage quality control (QC) results, and remotely troubleshoot devices on the network.

### **Describe the applications for your products.**

Siemens blood gas analyzers are used to deliver fast, accurate results in many critical care environments, such as emergency rooms, intensive care units, respiratory therapy, and operating rooms, and can be used to enhance blood gas testing efficiency in the clinical laboratory. Additionally, our blood gas analyzers feature comprehensive critical care testing menus. The most recent addition to our blood gas system portfolio is the RAPIDPoint 500 System, which delivers test results for blood gas, electrolytes, glucose, lactate and full CO-oximetry, including neonatal total bilirubin (nBili) and total hemoglobin (tHb) in approximately 60 seconds.

### **Discuss training and support for the use of your products.**

Siemens provides both live and virtual training for customers, as well as its Personalized Education Plan (PEP), a competency-based clinical laboratory educational tool conveniently available online. PEP allows healthcare professionals to easily plan a wide variety of product-specific, professional development, and job-relevant courses. Siemens also recognizes that physicians and clinicians treating patients at the point of care can greatly benefit from easy access to educational resources via mobile devices. With this in mind, we recently launched two complimentary mobile blood gas reference tools for smart phones and tablets. The 135-page “Rapid Analysis – Blood Gases and More” e-book is a comprehensive reference manual that reviews the history of blood gas testing, pre-exam considerations, acid base metabolism, electrolytes, and metabolites. The “ABC Guide” app is an interactive tool for use on iPhone or iPad to identify normal and abnormal ranges for pH, arterial blood gas, electrolyte, and analyte results. Download instructions are available at <http://healthcare.siemens.com/point-of-care/mobile-resources>.

### **Discuss point of care testing as it applies to your products.**

Siemens blood gas solutions help meet the growing demand for near-patient testing by providing clinicians with fast, reliable, laboratory-quality results. In addition to blood gas results from Siemens RAPIDSystems, the Siemens RAPIDComm Data Management System also enables POC coordinators to remotely monitor and manage diabetes testing results via the DCA Vantage analyzer and urinalysis via the CLINITEK Status Connect System. This connectivity helps enhance oversight, improve results reliability, maximize instrument uptime, streamline workflow, and simplify compliance.

## TELCOR

### **Tell us about the blood gas products you offer.**

TELCOR's industry-leading QML point of care software is designed to provide online, real-time, paperless processing of results to the electronic health record and comprehensive data management and reporting. QML integrates blood gas, electrolyte and co-oximetry results from these industry-leading blood gas manufacturers: Abbott Point of Care, Alere, Instrumentation Laboratory, International Technidyne Corporation, Nova Biomedical, OPTI Medical Systems, Inc, Radiometer America Inc, Roche Diagnostics and Siemens Healthcare Diagnostics. We understand that point of care devices come in all shapes and sizes, each with unique integration requirements. That's why TELCOR's system was designed to develop a unique piece of software, called a driver, for each specific device type. These device-type drivers do three main things: talk to the vendor's proprietary software or directly to the device, remap the data into a common TELCOR import format, and return data to the vendor's proprietary software or devices, if they are capable of receiving electronic data. Our blood gas interfaces (results, ADT and orders) are the most flexible in the industry and include hundreds of configuration options. Our comprehensive system allows for patient result management, quality control results, operator competency and reporting.

### **Describe the applications for your products.**

QML can be installed just for respiratory labs, just for point of care clinical labs, or for a combination of both. It can also be implemented in a single-hospital use model or an enterprise multi-hospital model with multiple interfaces where access to results is limited by operator login. QML has the functionality to send results to multiple systems where organizations have multiple LISs or want to send results to both the EMR/HIS and LIS.

### **Discuss training and support for the use of your products.**

Through the use of technology, TELCOR pioneered and continues to refine remote software installation and implementation activities. All of TELCOR's 1,400+ hospitals have been implemented through this methodology. We have a well-defined process, which includes two formal training sessions, along with a great deal of informal teaching that occurs throughout the implementation process. We also provide one post-live training session for the review of workflow, system operations and reporting. TELCOR provides 24 x 7 x 365 support once the customer goes live with the system. TELCOR's customer service is unmatched, and TELCOR's point of care customers have unlimited access to the customer service staff. Our customer support specialists can answer questions, provide configuration assistance, troubleshoot and offer general product support. All support is provided from our corporate offices in Lincoln, NE, where we are staffed 7 am to 7 pm Central except weekends and holidays and then via an on-call analyst after hours. New features and functionality are constantly being developed for the system based on customer requests, regulatory requirements and the evolution of the ever-changing point of care industry, with millions of dollars being reinvested each year into research and development for TELCOR's products. These upgrades, along with hardware migrations and reinstallations, are all included with the support agreement.

## **Discuss point of care testing as it applies to your products.**

Developed by TELCOR and first installed in 2001, TELCOR's industry-leading point of care information and interface management solution was designed specifically to support the management and reporting requirements of the expanding point of care testing market. TELCOR's solution can effectively eliminate errors, omissions and delays that are associated with manual charting. It also allows for future growth of the point of care program. QML supports multiple simultaneous result interfaces when blood gases from a non-lab department are added to an existing QML system. TELCOR provides connectivity to more POCT testing devices and LIS/EMR systems than anyone in the industry. Because we are a truly open vendor, we don't limit the device types that can be connected through QML. Our software connects to 90-plus device types, including blood gases, and is used in more than 1,400 hospitals in North America. We also provide the widest array of point of care configuration options in the industry. Most point of care tests are interfaced without requiring a pre-existing order in the LIS/EMR/HER, which is commonly referred to as unsolicited result processing. With the recent increase in Clinical Physician Order Entry (CPOE), the need to link point of care results to an existing and specific order in the EMR/HIS is increasing. This type of result reporting is commonly referred to as solicited result processing. Though the majority of interfaces are industry standard HL7, TELCOR does support scripted (aka terminal emulation, screen scraping) interfaces to systems that are unable to accept unsolicited results. Founded in 1995, TELCOR is dedicated to the development and delivery of software that integrates all laboratory results performed outside the main clinical laboratory into the electronic health record.

## **SLEEP ROUNDTABLE**

### **3B Medical, Inc**

#### **Tell us about the sleep products.**

3B Medical, Inc offers a full feature/full function line of CPAP and Auto-CPAP devices, as well as a line of interfaces. Our product line is unique as it offers features usually associated with higher end models at a price point designed to meet the challenging demands of reduced reimbursements.

#### **Describe the venues where your products are used.**

3B Medical, Inc's products are versatile and currently being used in patient homes, hospitals, and sleep labs.

#### **Discuss the education and training you provide about your product, for professionals and/or patients.**

3B Medical, Inc provides full support and inservicing to DME companies and professionals, as well as telephone tech support.

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

All of 3B Medical, Inc's devices come standard with our remote access compliance reporting using iCode. ICode is an easy to use web based program requiring no software installation or direct cable connection. ICode can be accessed anywhere at any time, by the DME homecare provider, physician or patient, allowing easy monitoring of patient adherence. ICode helps with reimbursement by providing a Best 30 Day Adherence score. The best 30 day is a percentage of the best consecutive 30 days of usage that meets the CPAP LCD.

## **ResMed**

#### **Tell us about your company's sleep products.**

Obstructive sleep apnea (OSA) is a dangerous disease involving the collapse of the upper airway during sleep, resulting in disrupted sleep and oxygen deprivation. The first effective treatment for OSA, the continuous positive airway pressure (CPAP) machine was developed in 1981. ResMed was founded in 1989, only eight years later, so ResMed has been a part of the treatment of obstructive sleep apnea from the beginning. ResMed develops and markets flow generators for CPAP and Automatic Positive Airway Pressure (APAP), along with a full range of masks including full face, nasal, and nasal pillow masks, and masks designed specifically for women, as well as pediatric masks for children.

#### **Where can your sleep products be used?**

ResMed products for the treatment of sleep-disordered breathing (SDB) may be used in sleep centers and in private homes. They are also portable to accommodate travelers. ResMed's respiratory therapy and ventilation products may be used in hospitals, acute care facilities, and at home.

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

There are two important factors in ensuring patient compliance. The first is creating a product that patients will want to use, because CPAP treatment is only effective if it is used consistently. ResMed makes flow generators that are sleek, quiet, and unobtrusive, so that using therapy is not a hassle. They also have an intuitive use interface that mimics that of computers and cell phones, so that learning to use a flow generator is not stressful. ResMed masks are comfortable and rest lightly on the face, while still offering a good fit and seal. ResMed flow generators also record the quality of mask fit and sleep, so that patients can see right away if everything is working properly. Patient compliance also comes from increased accountability. ResMed flow generators can save and wirelessly transmit data through the ResTraxx online monitoring system about the frequency of treatment so that doctors can see, at a glance, whether a patient is being compliant. This allows clinicians to know if a patient is following their treatment plan and to ensure that their treatment is effective.

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

Each product comes with a Welcome Guide to enhance the instruction on product use that the patient receives from their doctor and home medical equipment provider. ResMed also provides YouTube videos that can help with maintenance, cleaning, and fitting their mask and flow generators. In addition, Wake Up To Sleep ([wakeuptosleep.com](http://wakeuptosleep.com)) ResMed's online sleep apnea support community, offers patients a way to connect with other patients and coaches on a peer to peer level. This helps patients get the most out of their OSA treatment, and to offer their own stories in a supportive, understanding, community. ResMed also offers training for clinicians, including clinical guides, and the ResMed eLearning Academy which focuses on continuing clinical education.

## **Sleepnet Corporation**

#### **Tell us about your company's sleep products.**

Sleepnet Corporation is a US based designer and manufacturer

of AIR°gel masks for the sleep-disordered breathing (SDB) and acute care product industry across 43 countries worldwide. Producing American-made masks since 1997, Sleepnet offers high quality masks such as the Mojo, iQ and Phantom for SDB patients and the MiniMe, MiniMe 2 and Veraseal for the pediatric and disposable non-invasive ventilation mask markets respectively. *Mask Solutions:* Only Sleepnet offers AIR°gel masks. AIR°gel is the softest and most reliable gel mask in the market today, providing superior seal and comfort to the user. We also provide the only custom-fit masks (Mojo, iQ, MiniMe & MiniMe 2). Our patented Custom Fit Technology allows the user to shape and mold the mask for a customized fit that maximizes comfort.

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

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

We pride ourselves on designing easy to use sleep care products. Our masks come with illustrated step-by-step instructions. We also provide how-to videos and other educational material on our website ([www.sleepnetmasks.com](http://www.sleepnetmasks.com)).

### **Discuss any issues relevant to reimbursement.**

Sleepnet is focused on providing cost effective solutions that provide a high standard of care. We incorporate technologies that are easy to use and cover the needs of a broad spectrum of patients. Our Custom Fit Technology allows our masks to fit a large portion of the population (iQ Nasal Mask, Mojo Full Face Mask, MiniMe, & MiniMe 2). Our AIR°gel combined with A.C.T. create comfortable reliably sealing masks that reduce compliance issues. While offering new technology, we work hard to ensure that our devices meet current insurance standards so that our customers can be confident in reimbursement.

## **COMPANY PROFILE**

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*Continued on page 21...*

# Comparing Lung Oxygen Delivery with Three Different High FiO<sub>2</sub> Masks

Henry Chang, BME; Martin Stegenga, BEng; Manhim Tsang, BSEE

## Introduction

Effective delivery of high concentrations of oxygen depends on the ability of oxygen delivery masks to provide adequate oxygen flow to meet the inspiratory demands of the patient and without allowing entrainment of room air into the inspired flow that would dilute the oxygen.<sup>1</sup> For most oxygen masks on the market, their basic “open” design, which might include the side ports holes provided for exhalation, allows room air to enter the inspired gas stream throughout inspiration, particularly at high inspired flows.

Several publications have compared the Hi-Ox High FiO<sub>2</sub> oxygen mask to the standard non-rebreathing mask and have demonstrated its ability to deliver higher inspired oxygen concentrations at any matching flow.<sup>2-9</sup> More recently, two oxygen masks with different designs than the standard non-rebreathing mask have entered the market with suggestions that they can deliver high inspired oxygen concentrations at modest oxygen flow rates.

We therefore performed a study to compare the oxygen delivery capability of the recently reintroduced Ceretec Hi-Ox High FiO<sub>2</sub> Oxygen Mask against the BLS FLO2MAX Oxygen Mask and the Southmedic 1425-8 Oxygen Mask to determine if there were performance differences.

## Background on the Measurement of Actual FiO<sub>2</sub>

When monitoring inspired oxygen concentration, many investigators simply monitor the concentration of oxygen at the mouth and determine that this represents the inspired oxygen concentration. However, without measuring actual inspired flow, there is no way to determine the “volume” of oxygen that is inspired. If a subject holds their breath, the concentration at their lips might reach 100% if monitoring only the oxygen concentration at their lips, while no oxygen actually entered their lungs. Therefore, the only way to understand the effectiveness of any oxygen delivery system is to measure the concentration that leaves the lungs at the end of an exhalation (the alveolar concentration). That is a truer measure of inspired oxygen.

The inspiratory flow of patients is not a square wave, constant flow. There are higher flows early in the breath and slower flows towards the end of the breath. Therefore more volume enters the lungs early in the breath and dilution effects are greater than late in the breath.



Figure 1. Oral sampling port, side view.



Figure 2. Oral sampling port, front view.

We do note that the exhaled oxygen concentration will be a few percentage points below the actual inspired oxygen as the exhaled concentration doesn't account for the uptake of oxygen by the blood in the lungs. However, at the very least, it represents the lowest alveolar oxygen concentration. In summary, measuring inspired oxygen entering the lungs (concentration only) is a misrepresentation of the actual oxygen delivery capabilities of a mask.

## Methods

A Teledyne ultra-fast oxygen sensor (model UFO-130-2) was connected to a vacuum sample pump drawing gas for analysis at 275 ml/min. The analyzer was calibrated with a 2-point calibration at 21% with room air and at 100% with a pure oxygen cylinder source.

The 1/16th inch diameter sample line was connected to an adapter placed between the teeth of the subject, just in front of their lips for side-stream sampling of inspired and expired oxygen (Figures 1 and 2). The adapter barely extended beyond the lips and created a patent pathway to the lungs for gas analysis. The output of the analyzer was connected to a LabView Data Acquisition BNC-2120 sampling at 100 Hz.

With several publications for the performance of the Hi-Ox throughout a wide range of oxygen flows already in the peer reviewed literature, it was only tested at an oxygen flow of 8 LPM to confirm the performance under this test configuration.

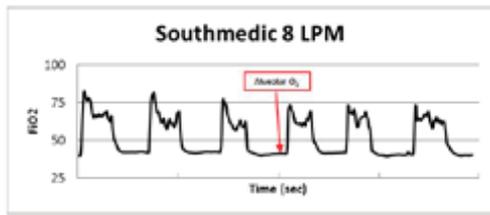


Figure 3. Southmedic: Alveolar oxygen 40-41%

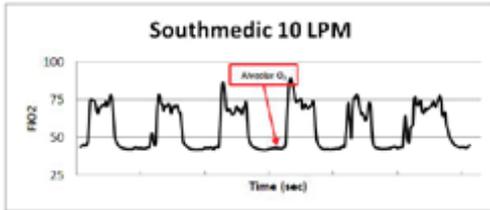


Figure 4. Southmedic: Alveolar oxygen 43%

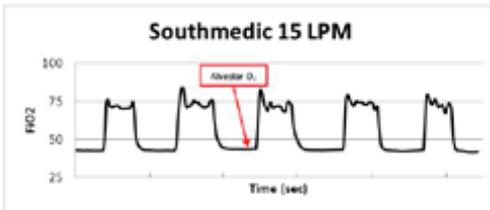


Figure 5. Southmedic: Alveolar oxygen 43%

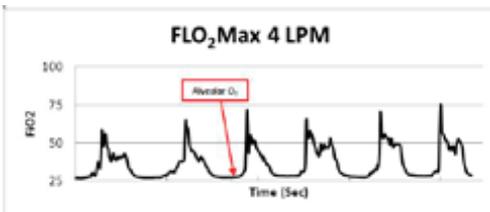


Figure 6. FLO2MAX: Alveolar oxygen 28%

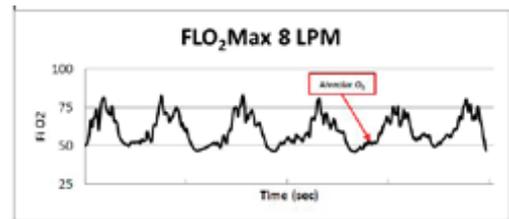


Figure 7. FLO2MAX: Alveolar oxygen 52%

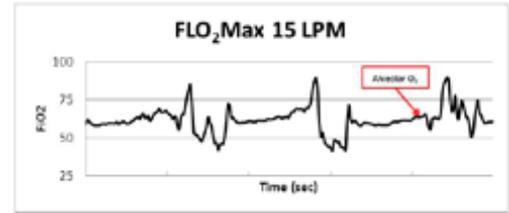


Figure 8. FLO2MAX: Alveolar oxygen 62%

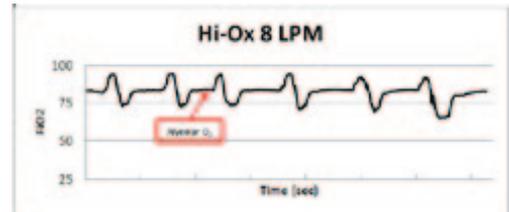


Figure 9. Hi-Ox: Alveolar oxygen 84%

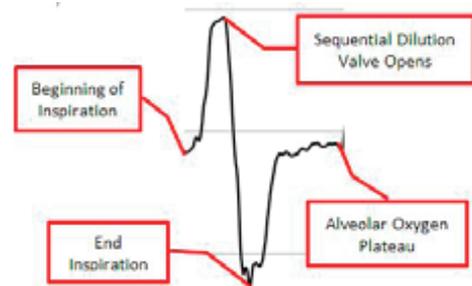


Figure 10. Single Hi-Ox breath

The Southmedic mask was tested at 8, 10 and 15 LPM and the BLS mask was tested at 4, 8 and 15 LPM.

After breathing on each mask at a resting ventilation level for seven minutes to allow for washout of nitrogen from the lungs and establish a steady state end-tidal oxygen concentration, the oxygen waveforms from several breaths were collected and analyzed on each mask and at each flow rate.

The end-tidal oxygen concentration for each breath was determined as the oxygen plateau just prior to inspiration where the oxygen concentration started on its next rise.

## Results

Figures 3, 4 and 5 are data from the Southmedic mask at 8, 10 and 15 LPM respectively.

Measurements from these graphs demonstrate that although the “inspired oxygen” reached up to the 80% range at some point in the breath, the actual concentration in the alveoli never exceeded 45%.

Figures 6, 7 and 8 are data from the BLS mask at 4, 8 and 15 LPM respectively. Measurements from these graphs demonstrate that

although the “inspired oxygen” reached up to the 80% range at some point in the breath, the actual concentration in the alveoli ranged from 28 to 62%.

Figure 9 is the data from the Hi-Ox at 8 LPM. Measurements from this graph demonstrate that the Hi-Ox delivers at least 80% oxygen at 8 LPM and the data is consistent with the previous publications describing its performance.

## Discussion

To explain the differences between performance of the Ceretec Hi-Ox and BLS or Southmedic mask, we found the important difference being that the Hi-Ox is a sequential dilution mask. That means the patient inhales only oxygen from the flow meter and the reservoir until the reservoir is empty. Towards the end of the breath and following the collapse of the inspiratory reservoir, the sequential dilution valve opens and then allows room air to enter the mask. This dilution at the end of the breath dilutes the oxygen in the airways and mouth, but limits dilution in the alveoli. Therefore as the tracing in Figure 10 shows, there is a high inspired oxygen early in the breath, which drops lower as the dilution valve opens. On exhalation, the first gas exhaled is the diluted oxygen at a lower concentration from the airways followed by the alveolar gas

representative of the effectiveness of the mask. In the case of the Hi-Ox, it is above 80%.

This data supports the previous publications that no other oxygen mask can deliver the same FiO<sub>2</sub> as the Hi-Ox at the same or even higher flows. Figure 10 describes the timing of actions of the Hi-Ox throughout a single breath. It can be observed that the time between the sequential dilution valve opening and the end of inspiration is fairly short. Additionally, this is towards the end of inspiration when the inspiratory flow is also low. Therefore the volume of diluted oxygen is also small and has little effect on the alveolar concentration.

These characteristics of the Hi-Ox explain why it is able to deliver these high oxygen concentrations. The almost 40% difference in alveolar concentration with the Hi-Ox when compared to the Southmedic mask represents a 280 mmHg higher PiO<sub>2</sub> and creates a situation whereby patients in respiratory distress may be able to avoid intubation solely to treat hypoxemia. In the case of the BLS mask, at matching flow rates, it's a 228 mmHg difference and even with the BLS running on 15 LPM, it's a 156 mmHg difference.

### Conclusion

We have demonstrated that the published data on the Hi-Ox can be repeated on Ceretec Hi-Ox High FiO<sub>2</sub> mask. It is also clear from this data that the Ceretec Hi-Ox is significantly better than the Southmedic or BLS oxygen masks at delivering inspired oxygen to the alveoli for the treatment of hypoxic patients.

### References

- 1 Redding JS, McAfee DD, Gross CW. Oxygen concentrations received from commonly used delivery systems. *South Med J.* 1978 Feb;71(2):169-72.
- 2 Somogyi R, Preiss D, Veseley A, Prisman E, Tesler J, Volgyesi G, Fisher JA, Sasano H, Iscoe S. Case Report: behind the mask. *Resp Ther* 2002; 5:24-26.
- 3 Somogyi R, Vesely A, Sasano H, Prisman E, Fisher JA. Evaluation of a New 3-Valve Non-Rebreathing Mask (Hi-Ox) for the Delivery of High FIO<sub>2</sub> at Low Flows — Comparison with the Hudson Type Non-Rebreathing Mask. *Can J Emer Med.* 2002; 4 Abst 068
- 4 Slessarev M, Somogyi R, Preiss D, Vesely A, Sasano H, Fisher JA. Efficiency of oxygen administration: sequential gas delivery versus “flow into a cone” methods. *Crit Care Med.* 2006 Mar;34(3):829-34
- 5 Hinkelbein J, Glaser E. Evaluation of two oxygen face masks with special regard to inspiratory oxygen fraction (FiO<sub>2</sub>) for emergency use in rescue helicopters. *Air Med J.* 2008 Mar-Apr;27(2):86-90.
- 6 Bouak F, Eaton DJ. Possibilities for mass casualty oxygen systems in search and rescue missions. Part 1: the VIASYS Hi-Ox80. *Defence R&D Canada-Toronto Technical Report 2005; DRDC Toronto TR 2005-207*
- 7 Bouak F, Michas B, Eaton DJ. Assessment of the Pulmanex Hi-Ox for aeromedical evacuation at 8000 feet. *Defence R&D Canada-Toronto Technical Report 2007; DRDC Toronto TR 2006-2007.*
- 8 Bouak F. Oxygen therapy: description and advances in oxygen delivery systems. *Defence R&D Canada-Toronto Technical Report 2004; DRDC Toronto TR 2004-112.*
- 9 Bouak F, Eaton DJ. New advanced mass casualty breathing system for oxygen therapy. *Defence R&D Canada-Toronto Technical Report 2006; DRDC Toronto TR 2006-2001*

*Company profile...continued from page 18*

can be reduced to less than 2%, which in turn minimizes the negative impact to your data and your budget.

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# Identifying and Correcting Patient-Ventilator Asynchrony with NAVA in an Adult Critically Ill Patient

Daniel D. Rowley, MS, RRT-ACCS, NPS, RPFT, FAARC; Frank J. Caruso, RRT; Stuart M. Lowson, MD

## Abstract

Patient-ventilator asynchrony during adult mechanical ventilation is associated with negative outcomes and physiologic sequelae. Conventional airway pressure and flow waveform monitoring is used to evaluate for trigger and cycle asynchrony. The prevalence of asynchrony may be underestimated when compared to diaphragmatic electrical activity monitoring. We report a case of a 76-year old mechanically ventilated patient who failed multiple weaning attempts. Signs of asynchrony were undetected by conventional waveform analysis, but marked asynchrony was identified and corrected with diaphragmatic electrical activity monitoring and neurally adjusted ventilatory assist mode. *Key words:* diaphragm electrical activity; mechanical ventilation; patient-ventilator interaction; spontaneous breathing trial; trigger asynchrony; waveform graphics; weaning.

## Introduction

Patient-ventilator asynchrony (PVA) is receiving increased awareness and recognition as a potential source of adverse patient outcomes,<sup>1,3</sup> increased duration of mechanical ventilation, and hospital costs.<sup>4</sup> PVA is usually diagnosed by patient observation and airway pressure and flow scalar graphic waveform assessments. Several authors have noted that pressure and flow scalar graphic waveform assessments do not result in reliable detection of all forms of PVA and that a mechanism to record diaphragmatic electromyography (Edi) may be a more sensitive means of diagnosing PVA.<sup>3</sup>

Edi monitoring is possible with the use of the esophagogastric catheter used for Neurally Adjusted Ventilator Assist [NAVA] (Maquet, Solna, Sweden). The Edi catheter has bipolar electrodes embedded into the distal end and is inserted into the patient, either through the nasal or oral route, and it is advanced until the electrodes are positioned at the crus of the diaphragm.<sup>5</sup> When the diaphragm contracts, an Edi signal is detected and relayed to the ventilator where the information is filtered, amplified, and converted into clinically useful Edi waveform that is displayed on the ventilator's monitor. In NAVA preview, the Edi signal is displayed simultaneously with conventional

airway pressure and flow waveform graphics in a manner that may result in rapid detection of PVA if it is present. This is based on the assumption that the Edi signal is a reliable measure of the respiratory center output and that neuro-ventilatory coupling is intact.

We are presenting a case of a difficult to wean patient in whom PVA was present but difficult to diagnose using conventional pressure and flow scalar graphic waveforms. The Edi catheter and activation of NAVA preview during conventional ventilation helped us to identify PVA clearly in a patient who was receiving volume controlled continuous mandatory ventilation (VC-CMV). The undiagnosed PVA may have contributed to the patient's difficulty in weaning from mechanical ventilation.

## Case Summary

A 76-year old, 72 kg (ideal body weight [IBW]), African American male with congestive heart failure, chronic obstructive pulmonary disease (COPD), and hypertension was transferred to our medical center after having been involved in a motor vehicle collision. He was electively intubated in the field with an 8.0-mm inner diameter endotracheal tube (ETT) secondary to loss of consciousness and respiratory distress. Upon arrival to our emergency room, the patient was hemodynamically stable with a pulse oximetry (SpO<sub>2</sub>) measurement of 97% on the following ventilator (LTV 1200, Care Fusion, Yorba Linda, CA) settings: VC-CMV mode, FIO<sub>2</sub> 1.0, respiratory rate (f) 16, tidal volume (V<sub>T</sub>) 400 mL (6 mL/kg IBW), and PEEP 5 cm H<sub>2</sub>O. A chest radiograph confirmed good ETT positioning in the trachea, in addition to multiple right-sided rib fractures (2 through 7) and a pneumothorax. A chest tube was inserted into the right side of the patient's chest wall to relieve the pneumothorax. Computed tomography of the head and chest was negative for additional injuries with the exception of a transverse process fracture at the seventh thoracic vertebra. The patient was transferred to the adult surgical/trauma intensive care unit (ICU) for further medical management.

The patient's medical course in the adult surgical/trauma ICU was complicated by multiple failed attempts to wean him from mechanical ventilation. VC-CMV was our preferred mode for unloading the respiratory muscles when he failed to pass a daily continuous positive airway pressure (CPAP) spontaneous breathing trial (SBT) lasting up to 120 minutes. We use standard criteria for adult SBT failure criteria that includes evidence of accessory muscle use, change in heart rate or systemic blood pressure by > 10% of pre-SBT values, f > 30 breaths/min, and

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Figure 1.



Figure 2.

evidence of impending respiratory failure when comparing pre and post-SBT arterial blood gas (ABG) results. His resting VC-CMV settings included FIO<sub>2</sub> .30, f 18, V<sub>T</sub> 400 mL, inspiratory time 0.9 seconds, PEEP 5 cm H<sub>2</sub>O, and pressure trigger -2 cm H<sub>2</sub>O. His intrinsic breathing pattern remained active during VC-CMV as measured by a total respiratory rate exceeding the ventilator's set rate of 18 breaths/min. VC-CMV on the Maquet Servo-i permits assisted breaths when the ventilator detects spontaneous breaths.

By ICU day seven, the patient had already failed planned SBTs on five occasions. Ninety minute SBTs were associated with increased respiratory distress, worsening hypercarbia (PaCO<sub>2</sub> increased from 31 to 57 mm Hg), and oxygenation (PaO<sub>2</sub> decreased from 73 to 58 mm Hg). Discussion about correctable factors that may be precluding this patient from passing the SBT occurred during multidisciplinary patient care rounds. The patient's COPD was described as mild. He did not require home oxygen, used bronchodilator inhalers intermittently, had never been hospitalized for an exacerbation of COPD, and had good exercise tolerance pre-trauma admission. With the exception of an unresolved small, intermittent, chest tube leak that resulted from the original blunt chest trauma, the only other issue was his pain control manifesting from the multiple rib fractures. Analgesia had been provided with a Dilaudid PCA and intermittent IV Tylenol. Unfortunately, an epidural was not placed because of the patient's spine fracture. An end-expiratory hold maneuver to diagnose intrinsic PEEP was not performed because of the presence of a chest tube leak and active spontaneous breathing efforts, both of which may have produced unreliable clinical measurement data. However, the flow waveform graphic demonstrated gradual expiratory airflow return to baseline prior to each triggered breath (Fig 1). A related comfort issue was the question of how well the patient appeared to be "resting" on VC-CMV. No significant PVA appeared to be present on the airway pressure and flow waveform graphics (Fig 1). A bedside physical examination revealed well defined accessory muscles with mild intercostal and abdominal contractions during inhalation and exhalation, respectively. The patient denied feeling short of breath during our bedside examination in the ICU.

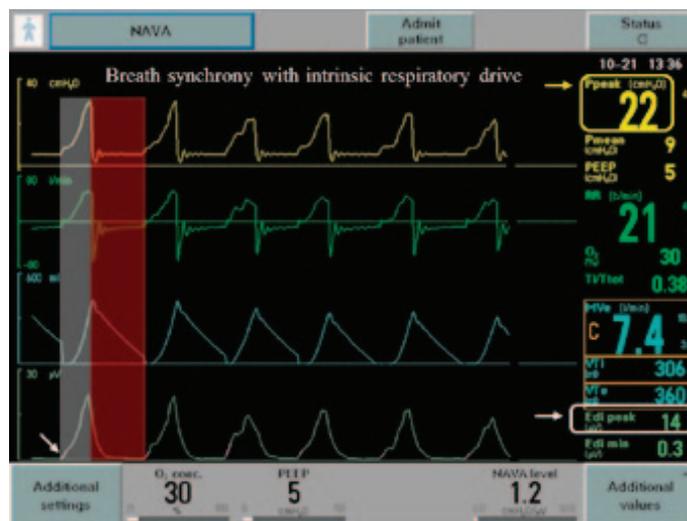


Figure 3.

On ICU day eight, the patient received a 6.0-mm internal diameter cuffed percutaneous tracheostomy tube in keeping with the trauma unit policy of early tracheostomy in patients having failed at least three SBTs. A 16 Fr/125 cm long Edi catheter was inserted through the patient's nasal cavity without difficulty or complications. NAVA mode was started post-tracheostomy, and the NAVA level was set to deliver a targeted tidal volume of 5-6 mL/kg (IBW). The interface between the Edi catheter and ventilator allowed us to assess for patient-ventilator synchrony using NAVA pre-view that, unlike conventional airway pressure and flow scalar waveform graphics (Fig 1), demonstrated significant PVA. The patient's PVA included marked trigger delays, prolonged airway insufflation with inspiratory flow, and cycle delays that extended beyond the patient's intrinsic inspiratory effort. These asynchronies were identified with the superimposed airway pressure and Edi scalar waveform graphics (Fig 2). Pneumatic trigger and cycle delays are present in three of four breaths depicted in Figure 2. The fourth intrinsic respiratory effort did not result in a ventilator assisted breath despite evidence of neuro-ventilatory coupling resulting in diaphragm contraction (Edi peak 40  $\mu$ V).

We placed the patient on NAVA with the hope of improving PVA. The initial Edi during NAVA preview was 40  $\mu$ V, which is significantly above the normal value of 5 to 10  $\mu$ V that would be expected in a patient without increased diaphragmatic workload. When we changed the patient from VC-CMV to NAVA, both PVA and Edi peak improved. The Edi peak decreased 65% from 40 to 14  $\mu$ V, indicating decreased diaphragmatic workload. Peak airway pressure also decreased by 35% when compared to VC-CMV (Figs 2 and 3). Adequacy of ventilation and oxygenation was confirmed by ABG results within one hour after changing to NAVA mode: pH 7.40, PaCO<sub>2</sub> 44 mm Hg, and PaO<sub>2</sub> 91 mm Hg.

Our patient remained on NAVA and the sequence of loading and unloading the diaphragm continued for four days before he passed a SBT. The patient progressed to trach collar with supplemental oxygen. He remained in the ICU for an additional three days before being transferred out of the ICU.

## Discussion

Improving patient-ventilator interaction has been a focus for advances in mechanical ventilation over the past decade.<sup>6,7</sup> Improvements in ventilator triggering and cycling have been associated with significant improvements in patient-ventilator interactions. However, as our case report demonstrates, significant PVA can still be present despite these advances. Recognized forms of PVA include ineffective efforts (most common), delayed triggering, auto triggering, double triggering, premature cycling, delayed cycling, and flow asynchrony.<sup>1</sup>

In the absence of Edi monitoring, bedside physical examination, clinical observation, and visual inspection of airway pressure and flow scalar waveform graphics are standard methods used to diagnose and evaluate for PVA.<sup>8,9</sup> Classic signs of PVA during VC-CMV are depicted on airway pressure waveforms by marked negative pressure deflections during patient inspiratory efforts, signs of negative pressure deflection on the ascending part of the inspiratory waveform as pressure increases in the airways, and sharp peaking of the waveform at the end of an assisted breath. Flow waveforms will typically reveal a sluggish rise to the clinician-set flow. A secondary rise in flow may also be observed during the inspiratory flow waveform plateau if a patient's inspiratory flow demands are not met with the set inspiratory flow. Ineffective efforts may be recognized by an abrupt decrease in airway pressure ( $> 0.5$  cm H<sub>2</sub>O) during the expiratory period with a simultaneous decrease in expiratory flow, not producing an assisted breath.<sup>3</sup>

In the present case, the patient's PVA was not evident on conventional airway pressure and flow scalar waveform graphics. The patient had the normal predicted inspiratory airway pressure and flow waveforms that are characteristic during VC-CMV (Fig 1). His intrinsic respiratory efforts resulted in enough negative intra-thoracic pressure to meet the set pressure trigger threshold of -2 cm H<sub>2</sub>O. When the ventilator triggered, a set inspiratory flow entered rapidly into the patient's airways and remained constant until the volume-cycled breath ended. There was no evidence of ineffective triggering on the pressure and flow waveform graphics prior to the ineffective diaphragmatic contraction (Fig 2). Others have noted the lack of sensitivity of waveform analysis to detect PVA,<sup>10</sup> and this reinforces the need for improved methods of reliable bedside detection.

By contrast, Edi monitoring revealed significant PVA, indicating

that conventional airway pressure and flow scalar graphic waveform monitoring may identify only the more obvious asynchronies.<sup>3,8,9</sup> In Fig 2, the superimposed airway pressure waveform that appears with the conventional airway pressure waveform mimics the patient's intrinsic breathing pattern. Each time rhythmic electrical discharges are transmitted from the dorsal respiratory unit of the medulla to the diaphragm, cyclic neuronal action potentials of varying magnitude results in diaphragmatic contraction.<sup>11</sup> When the diaphragm contracts, an Edi signal is detected by the Edi catheter's electrodes. An Edi waveform and corresponding numerical values for quantifying the strength of the diaphragm's action potential is also included on the ventilator's screen. This physiologic monitoring tool provides clinicians with an opportunity to trend how the diaphragm responds to interventions that load and unload dominant respiratory system myofibers during assisted and unassisted ventilation.

Factors that may have contributed to the patient's PVA include over-assistance, intrinsic PEEP, the intermittent chest tube air leak, pain/agitation issues, and the choice of VC-CMV. The patient's baseline PaCO<sub>2</sub> was 31 mm Hg, suggesting over-assist. However, the clinician set tidal volume was 5-6 ml/kg (IBW) and the patient was breathing over the set rate of 18 breaths per minute, suggesting that the patient was hyperventilating possibly as a result of pain/agitation or auto-triggering. Measures to improve pain control, including a PCA, did not improve the patient's respiratory status. The patient did have a history of mild COPD, and therefore intrinsic PEEP was a possible cause of ineffective triggering. However, as noted above, the patient's scalar graphic flow waveform demonstrated expiratory flow returning to baseline prior to the next triggered breath (Fig 1).<sup>8</sup> The chest tube air leak was identified as a source of auto-triggering. This is why pressure as opposed to flow trigger was selected. It has been suggested that VC-CMV is associated with a higher incidence of PVA than pressure support ventilation (PSV). Thille et al found that double triggering was more common with VC-CMV,<sup>9</sup> whereas we found that VC-CMV was associated with a higher incidence of diaphragmatic inactivity reflected in absent or abnormally low Edi measurements.<sup>12</sup> In contrast, Leung et al found no significant difference in the percentage of ineffectively triggered breaths when comparing VC-CMV and PSV modes.<sup>13</sup> It appears that either volume or pressure modes may be associated with PVA, and it is perhaps the level of over-assist (tidal volume with VC-CMV and PS level with PSV), rather than the mode per se, that increases the risk of PVA.<sup>1</sup> In the present case, tidal volume was set at 5-6 ml/kg (IBW) thereby minimizing the risk of over-assist induced PVA. We therefore had no obvious etiology for the patient's PVA.

Changing to NAVA resulted in decreased PVA, decreased diaphragm load (as shown by a decrease in the Edi Peak from 40 to 14  $\mu$ V), and decreased airway pressure (Fig 3). These improvements continued while the patient remained on NAVA. The ventilator's ability to respond immediately to the patient's intrinsic respiratory efforts during NAVA is attractive considering that the diaphragm may not always produce adequate force generating capacity to trigger a breath during conventional modes of ventilation. The inability of clinicians to detect or correct PVA may induce diaphragmatic fatigue and structural derangement if an excessive load is sustained.<sup>14-17</sup> The diaphragm is composed of slow-twitch and fast-twitch smooth muscle fibers. The slow-twitch myofibers account for just over 50% of the diaphragm's muscular composition.<sup>16</sup> Slow-twitch fibers

are highly resistant to low-level workload fatigue, but they are incapable of producing high-force generating muscular contractility when respiratory demands escalate. Fast-twitch myofibers, consisting of Type 2a and Type 2b, are recruited sequentially during increased work of breathing in an attempt to temporarily increase the contractile force of the diaphragm. While fast-twitch myofibers are capable of producing higher levels of contractile force,<sup>16</sup> it is important to recognize that they will eventually become fatigued under conditions of sustained muscular load. Perhaps even more important in terms of musculature recovery time is the risk of diffuse structural injury to slow-twitch myofibers when excessive muscular load persists. Slow-twitch myofiber injury can take several days to heal.<sup>16</sup> By decreasing the risk of PVA, NAVA may allow us to decrease the workload associated with assist ventilation and thereby decrease the incidence of ventilator-induced diaphragmatic dysfunction.<sup>15</sup>

While frequent PVA has shown to be associated with prolonged mechanical ventilation, we do not know whether this relationship is causal. A number of factors are associated with an increased frequency of PVA, but it is our personal observation that PVA is seen most commonly in the “sickest” patients (ie, those patients most likely to experience a prolonged course of mechanical ventilation). It is therefore possible that PVA may be associated with, but not the cause of, adverse outcomes such as prolonged mechanical ventilation. Several studies have demonstrated that the incidence of PVA is significantly decreased with NAVA compared to conventional ventilator modes,<sup>18-20</sup> and therefore NAVA and Edi monitoring may help us to better examine the relationship between PVA and difficult ventilator weaning. A prospective randomized controlled trial is required to investigate the hypothesis that NAVA, by decreasing PVA and excess diaphragm workload,<sup>1</sup> results in less time on mechanical ventilation when compared to conventional ventilator modes.

We recognize that Edi monitoring and NAVA is proprietary to the Servo-i ventilator. However, we believe that our case is instructive in terms of appreciating how PVA continues to impose significant challenges for clinicians caring for adult mechanically ventilated patients. Clinicians should search for subtle signs of PVA when they are unable to liberate patients from mechanical ventilation. The clinical importance of trying to optimize patient-ventilator synchrony is evident when considering negative clinical and physiologic outcomes associated with this under recognized and sometimes difficult to correct condition in the ICU. This case report suggests that NAVA preview and NAVA mode may improve the ability to diagnose and correct PVA, respectively.

## References

- Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? *Respir Care*2011;56(1):25-38.
- de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation. *Crit Care Med*2009;37(10):2740-2745.
- Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med*2006;32(10):1515-1522.
- Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med*2005;33(6):1266-1271.
- Sinderby, C., Beck, J. Neurally adjusted ventilatory assist: An update and summary of experiences. *Neth J Criti Care*2007;11(5):243-252.
- Kacmarek RM. The mechanical ventilator: past, present, and future. *Respir Care*2011;56(8):1170-1180.
- Branson RD. Patient-ventilator interaction: the last 40 years. *Respir Care*2011;56(1):15-24.
- MacIntyre NR. Patient-ventilator interactions: optimizing conventional ventilation modes. *Respir Care*2011;56(1):73-84.
- de Wit M. Monitoring of patient-ventilator interaction at the bedside. *Respir Care*2011;56(1):61-72.
- Younes M, Brochard L, Grasso S, Kun J, Mancebo J, Ranieri M, et al. A method for monitoring and improving patient:ventilator interaction. *Intensive Care Med* 2007;33(8):1337-1346.
- Guyton AC, Hall JE, Ralph Erskine Conrad Memorial Fund. Textbook of medical physiology. In: Philadelphia: Elsevier Saunders; 2006:514-515.
- Lowson SM, Rowley DD, Caruso FJ, Clarke L, Beck J, Sinderby CA. Application of NAVA after a failed spontaneous breathing trial in patients initially treated with conventional ventilation. *Am J Resp Crit Care Med* 2011;183:A3205.
- Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort and dyspnea. *Am J Resp Crit Care Med* 1997;155(6):1940-1948.
- Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med*2004;169(3):336-341.
- Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med*2004;169(3):336-341.
- Kallet RH. Patient-ventilator interaction during acute lung injury, and the role of spontaneous breathing: part 1: respiratory muscle function during critical illness. *Respir Care*2011;56(2):181-189.
- Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*2001;164(9):1734-1739.
- Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P. Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. *Intensive Care Med*2008;34(11):2010-2018.
- Piquilloud L, Vignaux L, Bialais E, Roeseler J, Sottiaux T, Laterre P, et al. Neurally adjusted ventilatory assist improves patient-ventilator interaction. *Intensive care medicine*2011(37):263-271.
- Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, et al. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Crit Care Med*2010;38(2):518-526.

# Using Volumetric Capnography to Enhance Clinical Practice

Melissa Turner, BA, RRT, RCP; Paul Garbarini, MS, RRT

In clinical practice today concerning ventilator care, it is becoming common practice to use some application of end-tidal CO<sub>2</sub> monitoring. While this capability can certainly give clinicians a better overall picture of patient conditions, it may also be misleading. End-tidal CO<sub>2</sub> with volumetric information will give a better picture of patient condition and information than end-tidal CO<sub>2</sub> alone. Information that is produced with volumetric measurements can alert to certain patient conditions as well as help with setting optimal PEEP and weaning. Too often, clinicians may rely on hemodynamic measurements in situations that, by the time hemodynamics have changed, the patient's condition has already deteriorated. Volumetric measurements in many instances will change faster than hemodynamics. In order to alert clinicians to unfavorable situations, adjustments can be made sooner, or better therapy implemented.

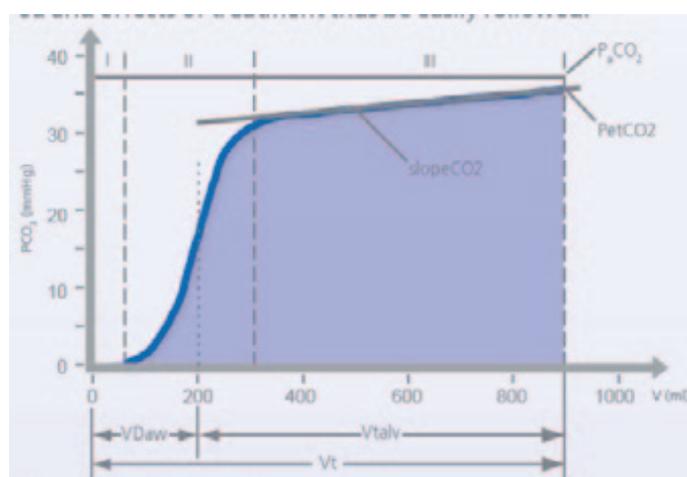
There are many bits of information we receive from volumetric monitoring. V<sub>daw</sub> is airway dead space. V<sub>daw</sub> is composed of the anatomic dead space (V<sub>Danat</sub>) and any mechanical dead space, such as an HME.

Alveolar dead space (V<sub>Dalv</sub>) is the areas of the lung which are ventilated but not perfused, V<sub>d</sub>/V<sub>t</sub> is the physiologic dead space fraction; it is the sum of the alveolar dead space and airway/mechanical dead space.

So, for example, if the V<sub>d</sub>/V<sub>t</sub> is 33% (considered normal), then 33% or 1/3 of the tidal volume is dead space or "wasted" ventilation. The degree of physiologic dead space correlates with the severity of lung disease and has been shown to be predictive of mortality in ARDS patients, V̇CO<sub>2</sub> or volume of CO<sub>2</sub> excreted from the lungs per minute. V̇<sub>alv</sub> is alveolar minute ventilation or the volume of CO<sub>2</sub> per minute that participates in gas exchange. V<sub>E</sub> is the total ventilation per minute which is the respiratory rate x the tidal volume. If the dead space per tidal volume is subtracted from the tidal volume then knowing the breath rate, we can calculate the effective or alveolar minute volume. Slope CO<sub>2</sub> gives shape of slope for Phase III in capnogram. PetCO<sub>2</sub> (partial pressure of CO<sub>2</sub>) and FetCO<sub>2</sub> (fraction or percent CO<sub>2</sub>) are end-tidal CO<sub>2</sub> measurements. Becoming familiar with these measurements and their departures from baseline can give the clinician a good road map of what is happening with their patient.

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First, let's talk about slope CO<sub>2</sub>, which refers to the shape of a capnogram in Phase III. Phase III is the alveolar plateau. The shape of the plateau is relatively flat in most post-op patients. There is normally a small incline to this plateau under normal conditions. If that slope becomes steep it is indicative of COPD, asthma, or another obstructive situation, or an indication of ineffective ventilation. This is certainly something easy to assess as it is only "eyeballing" the shape of the plateau on the capnogram.



**Description of volumetric capnogram:**  
Phase I: Pure airway dead space, from point of measurement of CO<sub>2</sub> toward the lungs  
Phase II: Weighted average of alveolar gas from different lung spaces, at the sensor location; measurement is V<sub>Daw</sub>  
Phase III: Alveolar plateau; measurement is slopeCO<sub>2</sub> together with end-tidal CO<sub>2</sub>.

Since gas exchange takes place in alveolus, V̇<sub>alv</sub> is the best representation of adequate ventilation. It gives the best indication if CO<sub>2</sub> removal was adequate. The differences between V<sub>E</sub> and V̇<sub>alv</sub> are not always consistent. It is better to use V̇<sub>alv</sub> when assessing ventilation adequacy. V̇<sub>alv</sub> used in combination with other volumetric measurements will also be helpful when assessing patients during weaning, as will be mentioned later in this writing.

V̇CO<sub>2</sub>, as mentioned earlier, is the volume of CO<sub>2</sub> excreted from the CO<sub>2</sub> produced by the body. There are three things that can affect CO<sub>2</sub> elimination and they are diffusion, perfusion, and

ventilation. These are three ways in which the body eliminates CO<sub>2</sub> and a change to any one or more will affect V̇CO<sub>2</sub> and PaCO<sub>2</sub>. If perfusion or ventilation decreases, V̇CO<sub>2</sub> will decrease and PaCO<sub>2</sub> will increase. The relationship of PaCO<sub>2</sub> to V̇CO<sub>2</sub> is generally a stable or inverse relationship. Any changes that occur because of metabolic activity are gradual changes. Changes that occur as a result of ventilation or perfusion happen more quickly. V̇CO<sub>2</sub> can increase with such things as paralytic/sedative weaning, sepsis, and tetanus. V̇CO<sub>2</sub> will decrease because of fever breaking, blood loss, or low cardiac output.

PaCO<sub>2</sub> to PetCO<sub>2</sub> gradient should also be assessed. PetCO<sub>2</sub> is more commonly expressed as EtCO<sub>2</sub>. On the capnogram, if there is no plateau in Phase III of the alveolar plateau, then the gradient is large. An increased gradient will indicate a sicker patient. As that gradient becomes smaller, the patient is getting better. Also, with respect to setting an optimal PEEP level, the PaCO<sub>2</sub> to PetCO<sub>2</sub> gradient will be narrow. If the gradient widens with increasing PEEP, it is likely that pulmonary perfusion is being compromised by the increased PEEP level. As to whether PaCO<sub>2</sub> to end tidal gradient changes or changes in V̇CO<sub>2</sub> reduce the potential for ventilator induced lung injury is not proven.

The EtCO<sub>2</sub> value is for those new to EtCO<sub>2</sub> monitoring, often assumed to be equivalent to the PaCO<sub>2</sub> or arterial CO<sub>2</sub>. But now that we have a better understanding of dead space, we understand that the measured EtCO<sub>2</sub> in the patient's exhaled gas is dependent on the degree of dead space and to some extent, shunt. So, in patients without lung disease or cardiac failure, the EtCO<sub>2</sub> will be close to arterial PaCO<sub>2</sub>, within 2-4 cm. If the EtCO<sub>2</sub> is much lower than the PaCO<sub>2</sub>, this is not an indication that EtCO<sub>2</sub> measurements are inaccurate, but rather is telling us that there is increased dead space or other derangement in gas exchange that should be assessed.

Many times when a patient is having a pulmonary embolism (PE), there is little to no effect on hemodynamics initially. If monitoring that same patient's CO<sub>2</sub>, one would immediately notice a rapid decrease in PetCO<sub>2</sub> as well as V̇CO<sub>2</sub>. Bigger PE, cardiac output decreases, and more of a decrease one will see in PetCO<sub>2</sub> and V̇CO<sub>2</sub>. It is a great indication that something is going on well before one would get an indication hemodynamically. During CPR, sustained very low EtCO<sub>2</sub> levels are prognostic of unsuccessful or inadequate CPR and a sudden elevation of EtCO<sub>2</sub> indicates the return of spontaneous circulation.

Let's take a look at some other clinical situations that involve EtCO<sub>2</sub> and V̇CO<sub>2</sub>. In a hypermetabolic state, both EtCO<sub>2</sub> and V̇CO<sub>2</sub> would increase. An example is during sepsis. During CPR, it has been proven that EtCO<sub>2</sub> has a good correlation with cardiac output. Patients that had a PetCO<sub>2</sub> of 10mmHg or less were not successfully resuscitated. EtCO<sub>2</sub> is a good predictor of survival as an outcome during CPR. One can also use EtCO<sub>2</sub> and V̇CO<sub>2</sub> to help with optimizing PEEP for a patient. Optimal PEEP will be exceeded when V̇CO<sub>2</sub> decreases (although V̇<sub>alv</sub> may remain the same). As mentioned before, PaCO<sub>2</sub> to PetCO<sub>2</sub> gradient will increase and oxygenation can also decrease once optimal PEEP is exceeded. Both of these can easily be seen in trends.

During weaning, here are a few helpful things to look for that help stop weaning trials before failure/fatigue occur, ensuring that patients don't require several days to recover,

especially since there is some objective data that provides more information. When a decrease in V̇CO<sub>2</sub> is followed by a decrease in spontaneous tidal volume, this indicates weaning failure. In this scenario, one will find a decrease in spontaneous V̇<sub>alv</sub>. An increase in V̇CO<sub>2</sub> suggests there is an increase in metabolic activity due to additional work the patient is doing in order to take over his own ventilation. This is in fact a good indication of successful weaning. Here, one will notice an increase in spontaneous V̇<sub>alv</sub>.

Lastly, let's take a look at arterial blood gasses (ABGs) and how volumetric capnography can help to evaluate when the best time to draw an ABG will be. Remember, ABG's are only a snapshot in time. They give a picture of what numbers were at a particular time (time one drew ABG), but it does not reflect energy required to keep these numbers normal. Since PaCO<sub>2</sub> is an indicator of ventilation adequacy, patients must be in a steady state to get an accurate measurement. You should tag V̇CO<sub>2</sub> value to V̇<sub>alv</sub> value. From there, adjust ventilator settings to an appropriate V̇<sub>alv</sub> before drawing ABG. When the V̇CO<sub>2</sub> has stabilized, the patient's ABG values have also stabilized. This is a good time to draw the ABG. If it is determined that the ABG is acceptable, as long as the V̇CO<sub>2</sub> remains stable, the V̇<sub>alv</sub> should be the parameter that is monitored closely. As long as the V̇CO<sub>2</sub> and V̇<sub>alv</sub> remains stable at this determined baseline, the ABG will also remain stable and there is no need to draw repeated ABGs. At this point, you would only want to draw ABGs at an appropriate time, for example, when the V̇CO<sub>2</sub> moves from the baseline.

Volumetric monitoring can really be an asset to enhance ventilator clinical practice. When clinicians know what they are monitoring and are alert to changes that can happen during volumetric monitoring, it makes it easier to manage patients and give the care that they need in a more timely fashion. Not only are clinicians better able to pick up on certain changes in condition faster, but also able to see when they have exceeded an optimal PEEP level and also can assess objective data for weaning purposes. Knowing volumetrics and applying them correctly can enhance current ventilator practice and the care we give to our patients.

# ECG-based Monitoring of Sleep Quality in Chronic Pain Patients

Greg Essick, DDS, PhD

Over 35 years ago, Moldofsky found that healthy individuals reported symptoms of musculoskeletal pain and fatigue when their slow-wave sleep was experimentally disrupted (Moldofsky et al, 1975). Today, non-restorative sleep associated with sleep disruption and fragmentation is a commonly recognized symptom of patients with chronic pain conditions, such as fibromyalgia syndrome (FMS). Patients with FMS often report difficulty falling asleep or waking too early, and 75% of patients complain of unrefreshing (non-restorative) sleep (Stuifbergen et al, 2010, Moldofsky 2008). However, only recently have patient-reported measures of sleep been included in the diagnostic criteria for FMS (Wolfe et al, 2010). For decades, diagnosis was based solely on the presence of chronic widespread pain across the four body quadrants with pain to palpation of 11 or more anatomically defined, tender points (Wolfe et al, 1990).

Fibromyalgia syndrome, as well as co-morbid conditions such as “disorder, is associated with central nervous system dysfunction known as ‘central sensitization,’” characterized by exaggerated or amplified responses to sensory stimulation, particularly noxious sensory stimulation (Petzke et al, 2003; Yunus, 2007). Sleep fragmentation may lead to central sensitization via dysfunction of central inhibitory processes, and the lowered sensory arousal threshold characteristic of central sensitization may, in turn, lead to sleep fragmentation (Smith et al, 2007; Spaeth et al, 2011). In addition, there is mounting evidence that many individuals with FMS have sleep-disordered breathing resulting in sleep fragmentation (Shah et al, 2006). It is also possible that a lowered arousal threshold, such as observed in FMS and other chronic pain conditions, leads to respiratory instability and sleep-disordered breathing (Wellman et al, 2013).

The possibility that therapies that improve sleep quality could lessen the pain and disability of FMS has led clinical investigators to recommend sleep assessment of patients with FMS (Spaeth et al, 2011; Shah et al, 2006). In-home methods have been limited largely to use of diaries and questionnaires (eg, the Pittsburgh Sleep Quality Index, PSQI) for subjective measures of sleep and of actigraphy for objective measures (Menefee et al, 2000). Although sleep measures from actigraphy correlate highly with comparable measures from gold standard polysomnography, they may not correlate with fibromyalgia clinical pain (Anderson et al, 2012). In contrast, measures of nocturnal heart rate variability have been shown to not only

discriminate groups of subjects with and without FMS but to correlate with patients’ clinical pain (Chervin et al, 2009; Thomas et al, 2010; Lerma et al, 2011).

The SleepImage recorder provides a simple-to-use non-intrusive tool, based on heart rate variability, to measure the sleep quality of patients with chronic pain in the home environment. At bedtime, the small SleepImage recorder is secured to the upper right chest with a single ECG electrode. An ECG lead from the recorder connects to a second electrode across the chest. Upon detection of a heartbeat, the device begins recording a high resolution ECG signal until it is removed by the subject in the morning. Five or six nights (total of 48 hours) of data can be recorded before uploading to the secure SleepImage website.

Analysis of the data is based on algorithms developed at Beth Israel Hospital in Boston by Dr Robert Thomas and colleagues (Thomas et al, Sleep 2005). Heart rate variability is combined with an ECG-derived signal of the respiratory cycle based on the amplitude of the R wave as described in Baker and Schramm (2008). The cross-power and coherence between both cardiac and respiratory signals are quantified to generate a spectrogram that illustrates the moving average of the dominant oscillatory ECG frequencies of autonomic nervous system drive coupled with respiration during sleep. A high proportion of power in the high frequency coupling (HFC) band (0.1-0.4 Hz) is associated with physiologic respiratory sinus arrhythmia and stable sleep; whereas, a high proportion of power in the low frequency coupling (LFC) band (0.0-0.1 Hz) is associated with unstable or periodic sleep behaviors. Elevated broad band, low-frequency coupling is a subset of LFC that correlates with scored apneas and hypopneas in patients with sleep apnea. However, Thomas et al (2012) showed that this band is elevated also in individuals with FMS who do not have sleep-disordered breathing and correlates with their pain ratings, implicating a more general role in signifying arousals from sleep and sleep fragmentation. In contrast, narrow band, low-frequency coupling is a subset of LFC that is elevated by the presence of periodic breathing, central sleep apnea or complex sleep apnea. Periodic limb movement disorder can also result in elevated narrow band, low-frequency coupling but at a different frequency than associated with periodic respiratory disorders (Denbar et al, 2012). A third frequency identified as very low-frequency band (0.0-0.01) correlates with periods of wakefulness or REM sleep. In addition to the single lead ECG, the SleepImage recorder measures body position, snoring, and actigraphy from which total sleep time and sleep

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This work with the SleepImage M1 at the University of North Carolina is directed by Greg Essick, DDS, PhD. The article was provided by SleepImage.

efficiency can be estimated. As such, the four-channel sleep recorder provides a potentially valuable tool in characterizing and monitoring sleep quality in patients with chronic pain.

At the Regional Center for Neurosensory Disorders at the University of North Carolina at Chapel Hill, we are using the SleepImage system to evaluate sleep quality in FMS. Thirty female participants who meet the 1990 criteria of the American College of Rheumatology (Wolfe et al, 1990) for FMS and 30 pain-free control participants, matched by group for age and gender, are being studied. The subjects are recruited to participate in an NIH-supported study entitled "Mechanisms of Sensory Processing in Fibromyalgia" (1R01AR054895; Dr Richard H. Gracely, principal investigator; Drs Inna E. Tchivileva and Estephan Moana, co-investigators). The project aims to better understand the role of mechanisms mediating sensations of pain and distress in patients with fibromyalgia. During three visits to the Center, subjects participate in sensory testing and behavior paradigms during which their individual choices in avoiding painful pressure stimuli applied to the thumb nail and unpleasant auditory stimuli are studied. In a final session, the subject's brain activity in response to the auditory and pressure stimuli is assessed using functional magnetic resonance imaging. Moreover, subjects respond to a battery of medical and psychosocial questionnaires including the Pittsburgh Sleep Quality Index (PSQI). The subject's extended participation over a three week period provides the opportunity to obtain, additionally, objective measures of sleep quality using the SleepImage system.

During the first visit, each participant is given a SleepImage recorder and instructions on its use for five, preferably consecutive, nights. For this part of the study the subject is also instructed to keep a sleep calendar, by which she rates on a daily basis the least, average, and the highest pain experienced; the percentage of the waking day pain was experienced; sleep duration on the previous night; and whether caffeine or alcohol (substances that affect sleep quality) was consumed after 2 pm. Once all data are collected, analyses will be undertaken to determine if the findings of Thomas et al (2010) from 14 subjects with FMS and 13 healthy controls can be replicated in our larger (2x) sample of highly characterized subjects and to investigate correlations with multiple measures of the patients' pain on the day of, and on the day after, each night's sleep assessment. We also plan to take advantage of the data provided in the SleepImage report about total sleep time, sleep efficiency and number of arousals from sleep to more fully characterize the quality of sleep in patients with FMS.

## References

- Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosomatic Medicine* 1975; 37(4): 341-351.
- Stuijbergen AK, Phillips L, Carter P, Morrison J, Todd A. Subjective and objective sleep difficulties in women with fibromyalgia syndrome. *Journal of American Academy of Nurse Practitioners* 2010; 22(10):548-556.
- Moldofsky H. The significance, assessment, and management of nonrestorative sleep in fibromyalgia syndrome. *CNS Spectrums* 13: 22-26, 2008.
- Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Research (Hoboken)* 2010; 62(5):600-610.
- Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis & Rheumatism* 1990; 33(2):160-172.
- Petzke F, Clauw DJ, Ambrose K Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. *Pain* 2003; 105(3): 403-413.
- Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Seminars in Arthritis & Rheumatism* 2007; 36(6): 339-356.
- Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 2007; 30(4): 494-505.
- Spaeth M, Rizzi M, Sarzi-Puttini P. Fibromyalgia and sleep. *Best Practice & Research Clinical Rheumatology* 2011; 25:227-239.
- Shah MA, Feinberg S, Krishnan E. Sleep-disordered breathing among women with fibromyalgia syndrome. *Journal of Clinical Rheumatology* 2006; 12: 277-281.
- Wellman A, Edwards BA, Sands SA, Owens RL, Nemati S, Butler JP, Passaglia CL, Jackson AC, Malhotra A, White DP. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *Journal of Applied Physiology* 2013. Jan 24 [Epub ahead of print]
- Menefee LA, Cohen MJM, Anderson WR, Doghramji K, Frank ED, Hochang L. Sleep disturbance and nonmalignant chronic pain: A comprehensive review of the literature. *Pain Medicine* 2000; 1(2):156-172.
- Anderson RJ, McCrae CS, Staud R, Berry RB, Robinson ME. Predictors of clinical pain in fibromyalgia: Examining the role of sleep. *Journal of Pain* 2012; 13(4):350-358.
- Chervin RD, Teodorescu M, Kushwaha R, Deline AM, Brucksch CB, Ribbens-Grimm C, Ruzicka DL, Stein PK, Clauw DJ, Crofford LJ. Objective measures of disordered sleep in fibromyalgia. *Journal of Rheumatology* 2009; 36(9):2009-2016.
- Thomas RJ, Mietus JE, Peng CK, Goldberger AL, Crofford LJ, Chervin RD. Impaired sleep quality in fibromyalgia: Detection and quantification with ECG-based cardiopulmonary coupling spectrograms. *Sleep Medicine* 2010;11:497-501.
- Lerma C, Martinez A, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. *Arthritis Research & Therapy* 2011; 13:R185.
- Baker D, Schramm P. The future of sleep disorder breathing testing. *Sleep Diagnosis and Therapy* 2008; 3.3:24-26.
- Denbar MA, Essick GK, Schramm P. A case study using hybrid therapy to treat a patient with obstructive and central sleep apnea. *Sleep Review* June 2012.

## Are you connected?

Greg Doll

One of the most frightening moments beyond the actual accident itself, said actor Christopher Reeves, occurred one night when he was alone in his bedroom and the circuitry on his life sustaining ventilator disconnected from his tracheostomy tube. Mr Reeves, a quadriplegic and ventilator dependent, unable to move after suffering his catastrophic neck injury while horseback riding in 1995, could not reconnect the circuitry himself. Mercifully, after 2 agonizing minutes in fear, a caretaker finally came to his aid.

To help reduce the chance of these catastrophic events, Pepper Medical has designed and patented the Vent-Tie - Combination Ventilator Antidisconnect Strap and Trach Tie, which is a cost effective and easy to use product offering a margin of safety to the patient and caregiver. An FDA Health Care Message entitled Accidental Breathing Circuit Disconnections in Critical Care Settings notes that “Antidisconnect Devices can be effective in reducing the occurrence of accidental disconnections.”

Dangerous episodes like what occurred to Mr Reeves happen far too frequently, not only in home settings, but also in well controlled acute care facilities with the most advanced equipment and well trained clinicians.

In fact, the FDA reports that approximately 200 deaths as well as numerous injuries and liability cases occur each year in hospitals alone due to accidental ventilator disconnections. The reasons for these life-threatening events are numerous and generally involve the 15 mm connector site where the circuitry meets the tracheostomy tube. This male/female connector is subject to significant forces leading to dangerous conditions if not monitored or secured properly. The tubes tapered 15 mm cannula and circuitries connections are constantly bathed in moisture, humidity and secretions that supply a perfect lubricant. The rapidly changing pressure fluctuations and weight of the ventilator circuitry also combine to negatively impact tubing securement. Additionally, the patient's tugging movements, rotations in bed and constant handling lead to added conditions of peril.

Beyond brain injury and death, the consequences of frequent ventilator disconnections can widely affect not only the patient's well being but also the facility staff and an institution's financial stability and community reputation.

The Centers for Disease Control (CDC) has stated that unintentional disconnections of ventilator dependent patients are a potential cause of VAP.<sup>3</sup> The National Institutes of Health (NIH) also reports that accidental drainage of condensation into the patient's airway and contamination of caregivers during ventilator disconnections add to the risk of VAP and cross contamination.<sup>2</sup> With recent changes in Medicare and private insurance coverage, nosocomial infections (ie VAP)

are no longer reimbursable, leading to significant financial burden on institutions. Coupled with extended stays in hospital and intensive care units, reducing disconnections can reduce added costs.

Other consequences from accidental ventilator disconnections are pernicious alarm events. With increasingly high tech equipment in ICUs there is even more opportunity for alarm fatigue to cloud or mask clinicians' awareness of a potentially catastrophic event. James P. Keller, MS, Vice President, Health Technology Evaluation and Safety, ECRI Institute states that they “routinely see deaths associated with alarm fatigue problems” and rated alarm management as the number one most hazardous health technology issue in 2012.<sup>1</sup> FDA is so concerned about ventilator disconnections and alarm fatigue that they issued an ALERT in the fall of 2011 to caregivers warning that ventilator alarms are going unheard. The FDA cautioned that nurses in particular have become dependent on alarms in caring for patients.

These accidental disconnections result in clinical risk to patients and financial risk to staff and facilities. For example, one claim was settled for more than \$22 million against an unnamed Kansas hospital involving a 38 year old female who disconnected from the ventilator, resulting in severe brain injury. Her attorney, James Howell of Wichita, KS said various hospital committees had previously discussed The Joint Commission's recommendations for improving safety but never implemented them.<sup>4</sup>

Pepper Medical's patented Vent-Tie, combination trach tie and ventilator anti-disconnect strap, is one method to secure the trach tube and the circuitry at the 15 mm connector. The Vent-Tie standardizes quality of care throughout your institution is elegant in its simplicity. The integral anti-disconnect strap can be wrapped and secured to any tubing connector interface, T-piece, Elbow or Closed Suction device to offer an added margin of safety. The Vent-Tie strap allows for clear, easy visualization of the connector site to assure proper monitoring at all times.

The FDA registered Vent-Tie is a two-in-one device compatible with all types of trach tubes and ventilator systems. Commercially available and individually packaged in a convenient bag, it eliminates the use of such unprofessional and improvised devices as rubber bands and strings.

### References

- 1 ECRI Institute, “2012 -10 Most Hazardous Health Technologies” [https://www.ecri.org/Forms/Pages/Alarm\\_Safety\\_Resource.aspx](https://www.ecri.org/Forms/Pages/Alarm_Safety_Resource.aspx)
- 2 NIH, Ventilator Associated Pneumonia, April 6, 2006 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1540438/>
- 3 CDC, Healthcare-associated Infections (HAIs), Strategies to Prevent Ventilator-associated Pneumonia in Acute Care Hospitals, 2008 <http://www.cdc.gov/HAI/vap/vap.html>
- 4 The Boston Globe, December 11, 2011 <http://www.bostonglobe.com/lifestyle/health-wellness/2011/12/11/ventilator-errors-are-linked-deaths/4T1bK11KP2kIIWYEedxX3M/story.html>

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Greg Doll is with Pepper Medical.

# Sleep update

Laszlo Sandor

## OSA SCREENING

The Journal of Sleep Research published the paper, Added value of a mandible movement automated analysis in the screening of OSA, [Maury et al, 2012 European Sleep Research Society (Wiley Online Library)] Highlights from the abstract: In-laboratory polysomnography is the gold standard for diagnosing obstructive sleep apnea syndrome, but is time consuming and costly, with long waiting lists in many sleep laboratories. Therefore, the search for alternative methods to detect respiratory events is growing. In this prospective study, we compared attended polysomnography with two other methods, with or without mandible movement automated analysis provided by a distance-meter and added to airflow and oxygen saturation analysis for the detection of respiratory events. The mandible movement automated analysis allows for the detection of salient mandible movement, which is a surrogate for arousal. All parameters were recorded simultaneously in 570 consecutive patients visiting a sleep laboratory. The most frequent main diagnoses were: obstructive sleep apnea (344; 60%); insomnia/anxiety/depression (75; 13%); and upper airway resistance syndrome (25; 4%). The correlation between polysomnography and the method with mandible movement automated analysis was excellent ( $r: 0.95$ ;  $P < 0.001$ ). Accuracy characteristics of the methods showed a statistical improvement in sensitivity and negative predictive value with the addition of mandible movement automated analysis. This was true for different diagnostic thresholds of obstructive sleep severity, with an excellent efficiency for moderate to severe index (apnea-hypopnea index  $\geq 15$  h-1). The addition of mandible movement automated analysis significantly improves the respiratory index calculation accuracy compared with an airflow and oxygen saturation analysis. This is an attractive method for the screening of obstructive sleep apnea syndrome, increasing the ability to detect hypopnea thanks to the salient mandible movement as a marker of arousals.

## NONINVASIVE ALGORITHM

The journal SLEEP published the paper, Evaluation of a noninvasive algorithm for differentiation of obstructive and central hypopneas. [Randerath, et al, SLEEP 2013;36(3):363-368.] Highlights from the abstract: The clear discrimination of central and obstructive hypopneas is highly relevant to avoid misinterpretation and inappropriate treatment of complicated breathing patterns. Esophageal manometry is the accepted standard for the differentiation of the phenotypes of sleep apnea. However, it is limited in its use due to poor acceptance

by patients and therefore rarely performed in routine clinical practice. Flattening of the inspiratory airflow curve, paradoxical breathing, arousal position, sleep stages, and breathing pattern at the end of the hypopnea can each give hints for the classification of hypopnea. The aim of this study was to evaluate a standardized algorithm combining these polysomnographic parameters for the discrimination of hypopneas in everyday practice. Polysomnography and esophageal manometry were performed in 41 patients suspected of having sleep apnea. Hypopneas were independently discriminated by blinded investigators based on esophageal pressure and the PSG-based algorithm. Only those hypopneas that could be differentiated with both methods were evaluated. There were 1,175 of 1,837 hypopneas (64%) that could be defined by esophageal pressure, 1,812 (98.6%) by the PSG-based algorithm. Using esophageal pressure as a reference, the new algorithm correctly defined 76.9% of central and 60.5% of obstructive hypopneas. The overall accuracy was 68%. The isolated analysis of single PSG parameters revealed a lower accuracy compared with the combined algorithm. The PSG-based algorithm allows for discrimination of most hypopneas. It is advantageous in comparison with esophageal pressure because it is noninvasive and less impaired by artefacts. Therefore, it is a potentially helpful tool for sleep specialists.

## MORBIDITY

The Journal of Clinical Sleep Medicine published the paper, Morbidity prior to a Diagnosis of Sleep-Disordered Breathing: A Controlled National Study, [Jennum et al, J Clin Sleep Med. 2013 Feb 1;9(2):103-8.] Highlights from the abstract: Sleep-disordered breathing (SDB) causes burden to the sufferer, the healthcare system, and society. Most studies have focused on cardiovascular diseases (CVDs) after a diagnosis of obstructive sleep apnea (OSA) or obesity hypoventilation syndrome (OHS); however, the overall morbidity prior to an SDB diagnosis has not been evaluated. The aim of this study was to identify morbidity prior to a SDB diagnosis to identify patients at risk for having/developing SDB. Using data from the Danish National Patient Registry, we identified all patients nationwide given a diagnosis of OSA (19,438) or OHS (755) in all hospitals and clinics. For each patient, we randomly selected 4 citizens matched for age, sex, and socioeconomic status from the Danish Civil Registration System Statistics. Patients with OSA or OHS presented with increased morbidity at least 3 years prior to their SDB diagnosis. The most common contacts with the health system for OSA/OHS [in descending order] were due to musculoskeletal system, endocrine, nutritional, and

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metabolic diseases; diseases of the nervous system, respiratory system, skin and subcutaneous tissue, gastrointestinal, infections, genitourinary system, and ear, nose, and throat. Patients with SDB show significant morbidities several years prior to a diagnosis of OSA or OHS. OSA should be considered in all medical specialties as an important comorbidity. In our study, evidence points to particular emphasis for considering this diagnosis in endocrinology and metabolic specialties.

### **OSA RISK**

The Journal of Clinical Sleep Medicine published the paper, Evaluation of a Single-Channel Nasal Pressure Device to Assess Obstructive Sleep Apnea Risk in Laboratory and Home Environments, [Crowley, et al. Evaluation of a single-channel nasal pressure device to assess obstructive sleep apnea risk in laboratory and home environments. *J Clin Sleep Med* 2013;9(2):109–116.] Highlights from the abstract: [The purpose of the paper is] to evaluate the sensitivity and specificity of a portable single-channel (intra-nasal pressure) sleep apnea device (ApneaLink) (Resmed) in both the laboratory and at home for assessment of sleep apnea risk in comparison with standard polysomnography (PSG). Fifty-five participants underwent simultaneous recordings of standard PSG and ApneaLink in the laboratory. Of these, 38 participants also used the ApneaLink device in their own homes for one night. PSG respiratory events were scored using standard criteria. Intra-nasal pressure signals were analyzed using the ApneaLink automated computerized algorithm provided to yield estimates of airflow for detection of apneas and hypopneas. Apnea-hypopnea indices (AHI) were compared. There was high sensitivity and specificity for the ApneaLink AHI when compared to simultaneous PSG at comparable AHI levels (AHI  $\geq 15$  events/h; sensitivity 100%, specificity 92%; positive and negative predictive values 70% and 100%, respectively). Home-measured ApneaLink AHI sensitivity and specificity were also reliable when compared with PSG (AHI  $\geq 5$ , 81% and 77%, respectively; AHI  $\geq 15$ , 67% and 91%), and improved slightly when two nights' data were used (AHI  $\geq 5$ , 88% and 85%; AHI  $\geq 15$ , 67% and 93%). The ApneaLink demonstrated good sensitivity and specificity in quantifying AHI when compared to PSG in a population with and without confirmed OSA. This simple, easy-to-use device may be useful in de novo large-scale occupational or underserved community OSA diagnostic programs to identify those with unambiguous disease who need immediate treatment or indicate those who may be at increased risk of OSA.

### **TRAINING**

The above referenced journal also published the paper, High-Fidelity Simulation Training for Sleep Technologists in a Pediatric Sleep Disorders Center [Avis, et al, High-fidelity simulation training for sleep technologists in a pediatric sleep disorders center. *J Clin Sleep Med* 2012;8(1):97-101.] Highlights from the abstract: Severe events of respiratory distress can be life threatening. Although rare in some outpatient settings, effective recognition and management are essential to improving outcomes. The value of high-fidelity simulation has not been assessed for sleep technologists (STs). We hypothesized that knowledge of and comfort level in managing emergent pediatric respiratory events would improve with this innovative method. We designed a course that utilized high-fidelity human patient simulators (HPS) and that focused on rapid pediatric assessment of young children in the first 5 minutes of an emergency. We assessed knowledge of and comfort with critical emergencies that STs may encounter in a pediatric sleep center utilizing a

pre/post-test study design. Ten STs enrolled in the study, and scores from the pre- and post-test were compared utilizing a paired samples t-test. Mean participant age was  $42 \pm 11$  years, with average of  $9.3 \pm 3.3$  years of ST experience but minimal experience in managing an actual emergency. Average pretest score was  $54\% \pm 17\%$  correct and improved to  $69\% \pm 16\%$  after the educational intervention ( $p < 0.05$ ). Participant ratings indicated the course was a well-received, innovative educational methodology. A simulation course focusing on respiratory emergencies requiring basic life support skills during the first 5 min of distress can significantly improve the knowledge of STs. Simulation may provide a highly useful methodology for training STs in the management of rare life-threatening events.

### **WOMEN ARE GRUMPIER**

The Daily Mail reported that there is now evidence that women are grumpier in the mornings than men. According the paper's online edition, "Women are more angry and hostile if they get insufficient sleep, say North Carolina scientists. Sleep deprivation also increases women's risk of heart disease, stroke and depression. But a man's health is barely affected by lack of sleep. As inflammation markers are also linked to pain, sleep expert Dr Michael Breus explained that women can literally be in more pain when they wake up. By contrast, the state of a man's health does not appear to be closely linked to how much he sleeps. In the study, carried out by scientists at Duke University in North Carolina, men showed no increased risk of developing the ailments that affect women when they are losing sleep." The cure? According to Breus, is to take strategic naps, though these need to be either 25 minutes or 90 minutes long. Any other length will make you feel worse when you wake up. The Daily Mail article also noted, "One of Britain's leading authorities on sleep found that women actually need 20 minutes more shut-eye. This is because of the female multi-tasking brain... The more of your brain you use during the day, the more of it that needs to recover and, consequently, the more sleep you need."

# Oxygen update

Laszlo Sandor

## VALUES

The journal *Resuscitation* recently published the paper, SpO<sub>2</sub> values in acute medical admissions breathing air – implications for the British Thoracic Society guideline for emergency oxygen use in adult patients? [Smith, et al, Volume 83, Issue 10, Pages 1201-1205, October 2012, copyright 2012 Elsevier Ireland Ltd]. Highlights from the abstract: SpO<sub>2</sub> is routinely used to assess the well-being of patients, but it is difficult to find an evidence-based description of its normal range. The British Thoracic Society (BTS) has published guidance for oxygen administration and recommends a target SpO<sub>2</sub> of 94-98% for most adult patients. These recommendations rely on consensus opinion and small studies using arterial blood gas measurements of saturation (SaO<sub>2</sub>). Using large datasets of routinely collected vital signs from four hospitals, we analyzed the SpO<sub>2</sub> range of 37,593 acute general medical inpatients (males: 47%) observed to be breathing room air. Age at admission ranged from 16 to 105 years with a mean (SD) of 64 (21) years. 19,642 admissions (52%) were aged <70 years. SpO<sub>2</sub> ranged from 70% to 100% with a median (IQR) of 97% (95-98%). SpO<sub>2</sub> values for males and females were similar. In-hospital mortality for the study patients was 5.27% (range 4.80-6.27%). Mortality (95% CI) for patients with initial SpO<sub>2</sub> values of 97%, 96% and 95% was 3.65% (3.22-4.13); 4.47% (3.99-5.00); and 5.67% (5.03-6.38), respectively. Additional analyses of SpO<sub>2</sub> values for 37,299 medical admissions aged ≥18 years provided results that were distinctly different to those upon which the current BTS guidelines based their definition of normality. Our findings suggest that the BTS should consider changing its target saturation for actively treated patients not at risk of hypercapnic respiratory failure to 96-98%.

## CARDIOPULMONARY RESUSCITATION

The journal *Resuscitation* also published the paper, The quality of cardiopulmonary resuscitation using supraglottic airways and intraosseous devices: A simulation trial, [Reieter, et al, Volume 84, Issue 1, Pages 93-97, January 2013, copyright Elsevier Ireland Ltd]. Highlights from the abstract: [The objective of the study was] to assess whether using interventions such as laryngeal mask airways (LMA) and IO lines lead to improved resuscitation in a simulated cardiac arrest when compared to standard methods of endotracheal intubation (ETI) and central line placement. Emergency Medicine residents at a single academic center were grouped into teams of four. Each team participated in two simulated ventricular fibrillation cardiac arrests using a high fidelity simulator. Peripheral IV access was unobtainable. Only ETI supplies and a central line kit were available in one

case (control) and in the other case those supplies were replaced by an LMA and an EZ-IO drill kit (experimental). Groups were randomized to which set up they were given first. Data examined included time to airway placement, duration and success rate of airway placement, time to vascular access, time to defibrillation, and percent hands off time. Forty-four residents in 11 teams participated. Mean time to airway was shorter in the experimental group (122.8 seconds (s) vs 265.6 s,  $p = 0.001$ ). Mean duration of airway attempt was also shorter (7.6 s vs 22.7 s,  $p = 0.002$ ). Time to access was shorter in the experimental group (49.0 s vs 194.6 s,  $p = <0.001$ ). Time to defibrillation and percent hands off time did not significantly differ between the two groups. [The authors concluded that] use of an LMA and an IO device led to significantly faster establishment of an airway and vascular access in a simulated cardiac arrest. The variation in devices did not affect time to defibrillation or percent hands off time.

## FACEMASKS

BioMed Central's journal *Medical Gas Research* published the paper, Methods for evaluation of helium/oxygen delivery through non-rebreather facemasks, [Martin, et al. To view the paper, visit BioMed Central and type the title of the article.] Here is the abstract: Inhalation of low-density helium/oxygen mixtures has been used both to lower the airway resistance and work of breathing of patients with obstructive lung disease and to transport pharmaceutical aerosols to obstructed lung regions. However, recent clinical investigations have highlighted the potential for entrainment of room air to dilute helium/oxygen mixtures delivered through non-rebreather facemasks, thereby increasing the density of the inhaled gas mixture and limiting intended therapeutic effects. This article describes the development of benchtop methods using face models for evaluating delivery of helium/oxygen mixtures through facemasks. Four face models were used: a flat plate, a glass head manikin, and two face manikins normally used in life support training. A mechanical test lung and ventilator were employed to simulate spontaneous breathing during delivery of 78/22 %vol helium/oxygen through non-rebreather facemasks. Based on comparison of inhaled helium concentrations with available clinical data, one face model was selected for measurements made during delivery of 78/22 or 65/35 %vol helium/oxygen through three different masks as tidal volume varied between 500 and 750 ml, respiratory rate between 14 and 30 breaths/min, the inspiratory/expiratory ratio between 1/2 and 1/1, and the supply gas flow rate between 4 and 15 l/min. Inhaled helium concentrations were measured both with a thermal conductivity analyzer and using a novel flow resistance method. Face models borrowed from life support training provided reasonably good agreement with available clinical data. After normalizing for the concentration of helium in the supply gas, no difference was noted in the extent of room air entrainment when delivering 78/22 versus 65/35 %vol helium/oxygen. For a given mask fitted to the face in a reproducible manner, delivered helium concentrations were primarily determined by the ratio of supply gas flow rate to simulated patient minute ventilation, with the inspiratory/expiratory ratio playing a secondary role. However, the functional dependence of helium concentration on these two ratios depended on the mask design. Large differences in mask performance were identified. With continued refinement, the availability of reliable benchtop methods is expected to assist in the development and selection of patient interfaces for delivery of helium/oxygen and other medical gases.

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## RESUSCITATION SKILLS

An older article from the *Annals of Emergency Medicine* covered the topic: Ventilation skills of emergency medical technicians: A teaching challenge for emergency medicine, [Cummins et al, *Annals of Emergency Medicine* 1986 Oct;15(10):1187-92, Elsevier]. The abstract states: We assessed the ability of 64 emergency medical technicians (EMTs) to ventilate a resuscitation manikin with a bag valve mask and with a pocket face mask to determine if their skill levels met the American Heart Association standard of 12 ventilations per minute, each with a tidal volume of 800 mL or more. All ventilation attempts were made during ongoing chest compressions (60 per minute). A successful ventilation was defined as a tidal volume of 800 mL  $\pm$  40 mL. In a preliminary skills assessment, EMTs averaged 4.8 attempts with the bag valve mask and 2.9 attempts with the pocket face mask before a successful ventilation ( $P < .01$ ). In a formal skills assessment that lasted two minutes, successful ventilations per minute averaged 8.3 with the bag valve mask and 9.9 with the pocket face mask ( $P < .01$ ). EMTs passed if they averaged ten or more successful ventilations per minute; 67% passed with the bag valve mask and 77% with the pocket face mask (NS). During a ten-minute extended skill assessment the EMTs averaged 9.6 ventilations per minute with the bag valve mask and 9.5 with the pocket face mask (NS). EMTs achieved initial success and maintained continued success better with the pocket face mask, but a reasonably high percentage (67%) met an objective standard when using the bag valve mask. We propose that objective standards be used to test the skills of EMTs for any ventilatory adjunct that they are permitted to use.

## DRINKING AND RESPIRATION

The *Journal of Emergency Medicine* published the paper, Acute Alcohol Intoxication in Adolescents: Frequency of Respiratory Depression [Langhan, ML, *J Emerg Med*. 2013 Feb 26, Epub ahead of print, copyright Elsevier]. Highlights from the abstract: Adolescents and young adults are frequent users of alcohol. Younger patients may be more sensitive to the effects of alcohol than their adult counterparts, and toxicity has been known to occur at lower doses. Respiratory depression is a serious adverse effect of alcohol intoxication; however, current monitoring practices may not adequately detect respiratory depression. Our objective was to determine the frequency of hypoventilation as measured by capnography among adolescents with acute alcohol intoxication. Our secondary objective was to determine if an association exists between alcohol levels and incidence of hypoventilation. This was a prospective observational pilot study of patients 14-20 years of age with acute alcohol intoxication. Blood or breath alcohol measurements were obtained on arrival. Hourly measurements of vital signs including capnography were recorded. Sixty-five subjects were analyzed. Mean alcohol level was 185 mg/dL. Twenty-eight percent of subjects had episodes of hypoventilation. Episodes occurred in similar proportions on arrival and during the first 5 h of measurements. There was no difference in alcohol levels between subjects who did and did not hypoventilate. Oxygen desaturations occurred in 14 subjects and were associated with hypoventilation. [The study concluded:] Hypoventilation is common among adolescents who are acutely intoxicated with alcohol. It is independent of alcohol level and occurs at a steady rate during the first several hours of intoxication. Capnography should be considered as an additional monitoring device to detect these episodes and enhance patient safety.

## LOS AND HOME OXYGEN

*JAMA Pediatrics* published the paper, Decreasing Hospital Length of Stay for Bronchiolitis by Using an Observation Unit and Home Oxygen Therapy [Sandweiss, et al, *JAMA Pediatr*. 2013 Mar 11;1-7. According to the abstract, pediatric observation units (OUs) offer the opportunity to safely and efficiently care for common illnesses previously cared for in an inpatient setting. Home oxygen therapy (HOT) has been used to facilitate hospital discharge in patients with hypoxic bronchiolitis. It is unknown how implementation of a hospital-wide bronchiolitis treatment protocol promoting OU-HOT would affect hospital length of stay (LOS). The objective was to test the hypothesis that using OU-HOT for bronchiolitis would decrease LOS. DESIGN AND SETTING Participants were uncomplicated bronchiolitis patients younger than 2 years admitted during the winter seasons of 2005 through 2011. The intervention was to implement a new bronchiolitis care process encouraging use of an OU-HOT protocol. A total of 692 patients with bronchiolitis from the 2010-2011 bronchiolitis season were compared with 725 patients from the 2009-2010 season. Implementation of an OU-HOT protocol was associated with a 22.1% decrease in mean LOS (63.3 hours vs 49.3 hours). Although LOS decreased during all 6 winter seasons, linear regression and linear quantile regression analyses for the 2005-2011 LOS data demonstrated a significant acceleration in the LOS decrease for the 2010-2011 season after implementation of the OU-HOT protocol. Discharges within 24 hours increased from 20.0% to 38.4%, with no difference in ED bronchiolitis admission or ED revisit/readmission rates. After implementation of the OU-HOT protocol, the total cost per admitted case decreased by 25.4%. The authors concluded that an OU-HOT protocol for patients with bronchiolitis safely reduces hospital LOS with significant cost savings.

## PHONE IT IN

The *Journal of Telemedicine Telecare* published the paper, The implementation of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy, [Jodar-Sanchez et al, *J Telemed Telecare*, February 2013, Epub ahead of print]. The researchers conducted a pilot study of the effectiveness of home telehealth for patients with advanced chronic obstructive pulmonary disease treated with long-term oxygen therapy. Patients were randomized into a telehealth group and a control group who received usual care. Patients in the telehealth group measured their vital signs on weekdays and performed spirometry on two days per week. The data were transmitted automatically to a clinical call center. After four months of monitoring the mean number of accident and emergency department visits in the telehealth group was slightly lower than in the control group (0.29 versus 0.43) The mean number of hospital admissions was 0.38 in the telehealth group and 0.14 in the control group. During the study a total of 40 alerts were detected. The clinical triage process detected eight clinical exacerbations which were escalated by the case manager for a specialist consultation. There were clinically important differences in health-related quality of life in both groups. The mean score on the SGRQ was 10.9 versus 4.5 in the control group. The EuroQol-5D score improved by 0.036 in the telehealth group and by 0.003 in the control group. Both patients and healthcare professionals showed a high level of satisfaction with the telehealth program.

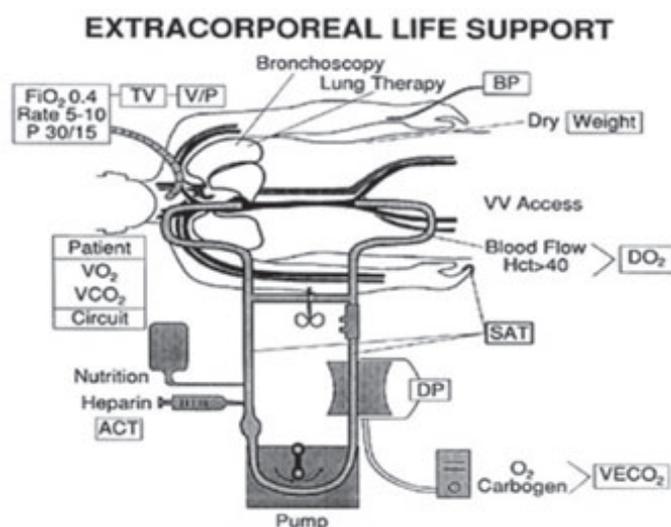
# ECLS and Supporting Critically Ill Flu Patients

Carl Sprow, RCP

ECLS (Extracorporeal Life Support) has been used in treatment and management of influenza (flu) patients with life threatening respiratory issues.<sup>1</sup> ECLS machines can be used to provide total or partial support of heart and lung function, allowing the lungs to rest and heal. In flu patients with severe respiratory compromise, ECLS system can oxygenate patient's blood outside the body, without the aid of a ventilator, further reducing any exacerbation of a ventilator acquired injury when trying to ventilate extremely compromised/injured lungs.

ECLS systems can be used in various ways and on patients from neonatal to adult populations. One of the ways it can be facilitated is to provide total support of heart and lung function during cardiac operations and is called cardiopulmonary bypass (CPB). They can also be used to provide respiratory support and this technique is called extracorporeal membrane oxygenation, also known as ECMO. ECLS devices can support circulation and gas exchange by taking over the role of the lungs function in gas exchange to support the life of the patient while the patient recovers.

Device application usually includes vascular access catheters, tubing, blood pump, an artificial lung, heat exchanger, and monitoring devices. Anticoagulation therapy also plays an important role and is done with continuous heparin infusion to avoid clotting issues but can lead to bleeding complications. Blood is removed from the patient via a tube placed in a large vein, oxygen is added and carbon dioxide is removed. Blood is returned back to the patient via another tube in another artery or vein. This process takes work off the lung and allows for rest. There are many physiological and mechanical complications that can occur while using ECLS machines and would require emergency intervention. ECLS is used on patients with severe reversible respiratory failure that have a 50% or greater chance of dying from conventional treatment.



(Zwischenberger & Bartlett, 2013)<sup>2</sup>

In one study at University Health Network's Toronto General Hospital, five influenza patients with severe respiratory issues were placed on ECLS. Their lungs were able to rest and recover with support of ECLS without a ventilator. All five patients survived and were successfully weaned from ECLS machine.

As medical technology continues to evolve and improve, we are able to provide alternative measures to influenza patients that are faced with life threatening respiratory compromise. Thanks to ECLS this can now be done without aid of a ventilator reducing possibility of further lung injury but also comes with risks and complications.

## Reference

- 1 unknown. (2013, January 21). Retrieved from Medical News Today: <http://www.medicalnewstoday.com/releases/255110.php>
- 2 Zwischenberger, J. B., & Barlett, R. H. (2013). University of Michigan Health System. Retrieved 2013, from Extracorporeal Life Support: <http://www.med.umich.edu/ecmo/about/what.htm>

Carl Sprow is Clinical Support Specialist, Hamilton Medical, Inc. This article is from Hamilton's newsletter, Intelligent Ventilation.

# Noninvasive Ventilation Immediately after Extubation Improves Weaning Outcome after Acute Respiratory Failure: a randomized controlled trial

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## Abstract

**Introduction:** Noninvasive ventilation (NIV) as a weaning facilitating strategy in predominantly chronic obstructive pulmonary disease (COPD) mechanically ventilated patients is associated with reduced ventilator associated pneumonia, total duration of mechanical ventilation, length of intensive care unit (ICU) and hospital stay and mortality. However, this benefit after planned extubation in patients with acute respiratory failure of various etiologies remains to be elucidated. The aim of this study was to determine the efficacy of NIV applied immediately after planned extubation in contrast to oxygen mask (OM) in patients with acute respiratory failure (ARF).

**Methods:** A randomized, prospective, controlled, unblinded clinical study in a single center of a 24-bed adult general ICU in a university hospital was carried out in a 12-month period. Included patients met extubation criteria with at least 72 hours of mechanical ventilation due to acute respiratory failure, after following the ICU weaning protocol. Patients were randomized immediately before elective extubation, being randomly allocated to one of the study groups: NIV or OM. We compared both groups regarding gas exchange 15 minutes, 2 hours and 24 hours after extubation, re-intubation rate after 48 hours, duration of mechanical ventilation, ICU length of stay and hospital mortality.

**Results:** Forty patients were randomized to receive NIV (20 patients) or OM (20 patients) after the following extubation criteria were met: pressure support (PSV) of 7 cmH<sub>2</sub>O, positive end expiratory pressure (PEEP) of 5 cmH<sub>2</sub>O, oxygen inspiratory fraction (FiO<sub>2</sub>) < 40%, arterial oxygen saturation (SaO<sub>2</sub>) > 90%, ratio of respiratory rate and tidal volume in liters (f/TV) < 105. Comparing the 20 patients (NIV) versus the 18 patients (OM) that finished the study forty–eight hours after extubation, the rate of re-intubation in NIV group was 5% and 39% in OM group (p=0.016). Relative risk for re-intubation was 0.13 (CI=0.017-0.946).

Absolute risk reduction for re-intubation showed a decrease of 33.9%, and analysis of the number needed to treat was 3. No difference was found in the length of ICU stay (p=0.681). Hospital mortality was 0% in NIV group and 22.2% in OM group (p= 0.041).

**Conclusions:** In this study population, NIV prevented 48 hours re-intubation if applied immediately after elective extubation in patients with more than three days of ARF when compared to OM group.

## Introduction

In critically ill adult patients, particularly patients with chronic obstructive pulmonary disease (COPD), early noninvasive ventilation weaning is associated with the decrease of mortality, ventilator associated pneumonia, length of stay in intensive care unit and hospital, total duration of mechanical ventilation and duration of invasive ventilation.<sup>1-6</sup> The effect of this benefit is not so clear in ICU mixed populations.<sup>1-6</sup>

The trials that analyzed the role of noninvasive ventilation (NIV) in weaning outcome used different weaning protocols, distinct moments of discontinuation of mechanical ventilation as well as different methods of use of noninvasive ventilation.<sup>1-6</sup>

Some authors such as Nava and colleagues used early NIV as soon as COPD patients rested their respiratory muscles, although they were not ready yet to tolerate spontaneous breathing trial.<sup>7</sup> Others, however, used NIV after COPD patients met extubation criteria.<sup>8</sup> In some studies NIV support was delivered continuously,<sup>7, 9-11</sup> while intermittently in others.<sup>12</sup> The interface used to apply NIV varied from face<sup>13</sup> to nasal mask.<sup>14</sup> The level of NIV support also differed as well as its mode of application from pressure modes<sup>13, 15-17</sup> to proportional assisted modes.<sup>14</sup> The optimal timing for transitioning patients to NIV, as well as its use in a mixed ICU population, remains to be determined.<sup>1-6</sup> We hypothesized that early application of NIV with supplemental oxygen immediately following elective or planned extubation in patients with more than three days of acute respiratory failure of various etiologies requiring mechanical ventilation would decrease the need for re-intubation compared to oxygen mask.

The objective of this randomized prospective trial was to compare the efficacy of NIV to Oxygen Mask in preventing re-intubation if NIV was used immediately following elective extubation in patients with acute respiratory failure requiring mechanical ventilation for more than 72 hours. The secondary

The authors are with the Hospital de Base de Sao Jose do Rio Preto and the University of Sao Paulo Medical School, Brazil. The authors wish to thank all the physicians, physiotherapists and nurses that took care of the patients throughout the protocol and the statisticians for the statistical analyses and Adriana Pardini for revision of the language. Reprinted from BioMed Central, Critical Care, © 2013 Ornico et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

**Table 1.** Baseline characteristics and diseases which led to acute respiratory failure of the Study Groups.

Variable	NIV (n=20)	Oxygen Mask (n=18)	p value*
Gender (M/F)	14/6	12/6	1.0
Age (years). Mean (SD)	50.79 (17.77)	48.88 (22.38)	0.77
Days of MV. Mean (SD)	9.85 (8.05)	9.5 (6.06)	0.88
APACHE II. Mean (SD)	16.90 (6.81)	15.28 (5.65)	0.43
Pneumonia, No. (%)	16 (80)	16 (88.9)	0.66
COPD, No. (%)	7 (35)	3 (16.7)	0.28
Abdominal surgery, No. (%)	5 (25)	4 (22.2)	1.0
Sepsis, No. (%)	4 (20)	2 (11.1)	0.66
Asthma, No. (%)	2 (10)	1 (5.5)	1.0
Cardiac failure, No. (%)	2 (10)	1 (5.5)	1.0

\*Significant values with significance level of 0.05. NIV, noninvasive positive pressure ventilation; APACHE II, Acute Physiology and Chronic Health Evaluation, and COPD, chronic obstructive pulmonary disease.

**Table 2.** Outcomes for the Study Groups.

Outcomes	NIV (n=20)	Oxygen Mask (n=18)	p value
Re-intubation, No. (%)	1 (5%)	7 (39%)	0.016
Re-intubation after excluding COPD, No. (%)	0 (0%) n=13	5 (33%) n=15	0.044
ICU length of stay, Mean (SD)	16.8 (11.6)	18.4 (12.2)	0.681
Hospital mortality, No. (%)	0 (0%)	4 (22.2%)	0.041

\*Significant values with significance level of 0.05. NIV, noninvasive positive pressure ventilation; COPD, chronic obstructive pulmonary disease, and ICU, intensive care unit

**Table 3.** Causes of re-intubation for the NIV and Oxygen Mask groups.

	Respiratory muscle fatigue	Atelectasis	Bronchospasm	Depressed level of consciousness
90mmHg $\ge$ SAP > 180mmHg	2 3		6	
HR > 140bpm				
Severe arrhythmia				
RR > 30 /min	1 2 3	4 5	6	
PaO <sub>2</sub> < 60mmHg or SaO <sub>2</sub> < 90%	1 2 3	4 5	6	7 1a
PaCO <sub>2</sub> > 50mmHg	1 2 3	4 5	6	7 1a
Difficulty in expectorating	1 2 3			7 1a

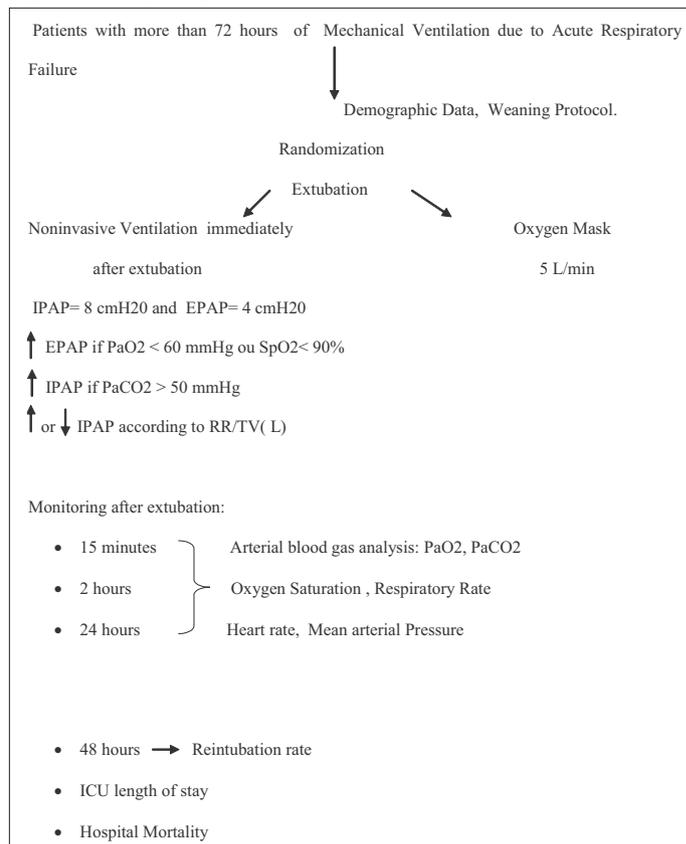
1,2,3,4,5,6,7: 7 patients in the Oxygen Mask group undergoing re-intubation. 1a: patient in the NIV group undergoing re-intubation. NIV, noninvasive ventilation; HR, heart rate; RR, respiratory rate.

objectives were to evaluate the differences between the study groups concerning Intensive Care Unit length of stay and hospital mortality.

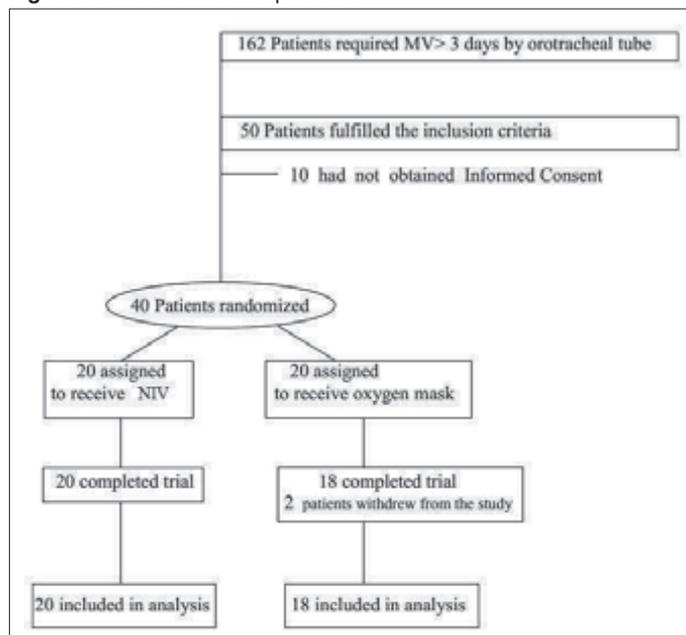
## Materials and methods

**Patients' selection, management and randomization:** The study was carried out over a 12-month period, in a single center of a 24-bed adult general ICU in a University Hospital. The study was approved by the Ethics Committee of the University of São Paulo and was registered under ISRCTN number 41524441. It was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed Consent was obtained before extubation from the closest next-of-kin for each

**Figure 1.** Study design.

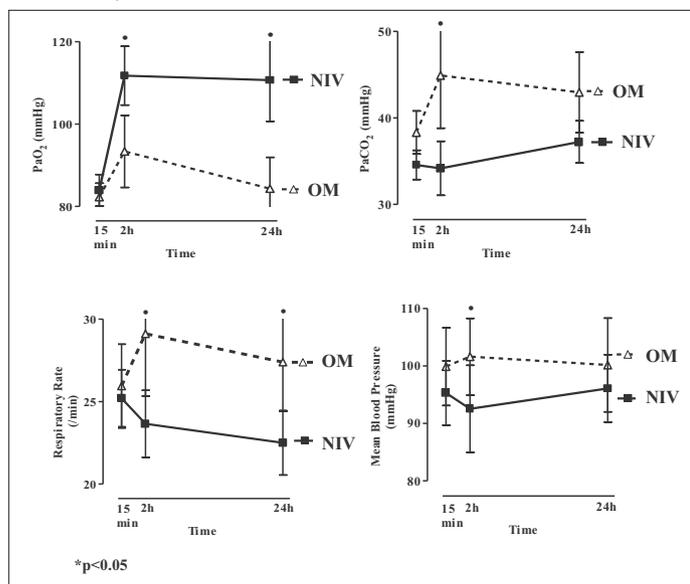


**Figure 2.** Randomization of patients.

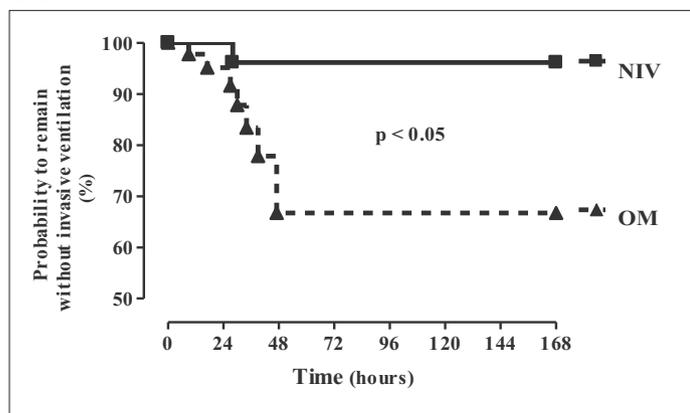


patient. Inclusion criteria: patients with acute respiratory failure (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 300 or PaCO<sub>2</sub> > 50mmHg at intubation); invasive mechanical ventilation for a period longer than 72 hours administered by orotracheal tube; weaning from invasive mechanical ventilation using ICU weaning protocol; absence of contraindications for the use of NIV, which were defined as: cardiac or respiratory arrest, severe encephalopathy (Glasgow coma scale < 10), bleeding of the upper gastrointestinal tract, hemodynamic instability or severe arrhythmia, facial surgery or

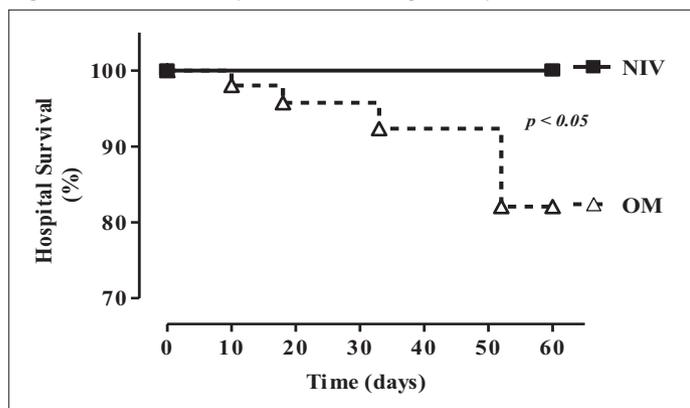
**Figure 3.** PaO<sub>2</sub>, PaCO<sub>2</sub>, RR and mean arterial pressure profile for the NIV and Oxygen Mask groups in the three different timepoints (15min, 2h and 24h).



**Figure 4.** Probability of avoiding re-intubation after 168 study hours, using the Kaplan-Meier curve with a p value obtained by the log-rank test.



**Figure 5.** Estimated hospital survival, using the Kaplan-Meier curve.



trauma or deformity, severe upper airway obstruction, inability to cooperate or protect the airways, inability to cough or clear respiratory secretions, absence of a gag reflex and severe gastric distention. Exclusion criteria: less than 18 years of age, pregnancy, and patient's refusal to participate in the study. We considered COPD patients those with any known history of underlying COPD regardless of the etiology of respiratory failure.

**Weaning protocol:** After 72 hours on invasive mechanical ventilation, patients were evaluated on a daily basis and weaning was considered when the criteria listed below were met: cardiovascular stability (hemoglobin > 8g/dl, no severe arrhythmia), hemodynamic stability (absence of vasopressors or vasopressors in doses < 5µg/Kg/min), gas exchange stability (PaO<sub>2</sub> > 60mmHg with SaO<sub>2</sub> > 90% and FiO<sub>2</sub> < 40%), pulmonary mechanics stability (control of pulmonary edema, atelectases, secretions and bronchospasm), neurological stability (Glasgow > 10), electrolytic stability (control of alkalosis, acidosis, calcium, magnesium, phosphorus, sodium, potassium), preserved cough reflex, rapid and shallow breathing rate (f/TV= ratio of respiratory rate and tidal volume in liters) < 105, absence of respiratory infection (defined as a new or progressive pulmonary infiltrate at chest X-ray, temperature < 36 C or > 37.8 C, leukocytosis (leukocytes > 12,000/ml) or leucopenia (leukocytes < 4,000/ml)).

The weaning protocol was based on a gradual reduction of pressure support ventilation mode (PSV) combined with one assist/control breath per minute of synchronized intermittent mandatory ventilation (SIMV). The adjustments of the mechanical ventilator were: PSV to obtain an expiratory tidal volume of 8ml/Kg; SIMV with a respiratory rate of 1 and a tidal volume of 8ml/Kg, FiO<sub>2</sub> < 40%, PEEP required to obtain SaO<sub>2</sub> > 90%, pressure sensitivity of 0.5cmH<sub>2</sub>O. The pressure support level was decreased by 2cmH<sub>2</sub>O every 2 hours until a PSV of 7cmH<sub>2</sub>O was reached. If f/TV > 105, PSV was increased to the previous value for a minimum period of 6 hours, after which the protocol was then resumed. In the cases where PEEP exceeded 5cmH<sub>2</sub>O, it was gradually decreased by 2 cmH<sub>2</sub>O every 6 hours until a value of 5cmH<sub>2</sub>O was reached. The patient was considered ready for extubation which was carried out in PSV of 7cmH<sub>2</sub>O, PEEP 5cmH<sub>2</sub>O, SaO<sub>2</sub> > 90%, FIO<sub>2</sub> < 40%, and f/TV < 105.

**Randomization:** A priori, we prepared blocks of 40 slips of paper each of which identified by a number (from 1 to 20) and the assigned study group (NIV or OM) written on them. These slips were folded and put in an opaque envelope. Patients were randomized immediately before elective extubation: one of the authors in the presence of other members of ICU staff drew one of the folded slips out of the opaque envelope to determine the designed study group of that patient. After that, the researchers triggered the next steps of the protocol.

**NIV group:** After randomization and still under invasive mechanical ventilation, patients assigned to NIV group were informed of the procedure they were about to undergo. After extubation, a respiratory physiotherapist adjusted a silicone nasal mask (Respironics) to the patient's face, holding it for a few minutes and then fixing it firmly and comfortably to the patient's face. The size of the mask was tailored to each patient and local treatment was used in case of pain or erythema caused by skin compression of the mask. NIV was administered by a BiPAP (Ventilatory Support System, Respironics Inc, Murrysville, PA) device model S/T-D 30 or S/T-D, in spontaneous mode for a continuous period of 24 hours. After this period, the nasal mask was replaced by a nebulization oxygen mask with a flow of 5 l/min. For all patients, the initial EPAP and delta IPAP values were 8cmH<sub>2</sub>O and 4cmH<sub>2</sub>O, respectively. Values were adjusted whenever required. In cases of hypoxemia with PaO<sub>2</sub> < 60mmHg and/or SaO<sub>2</sub> < 90%, EPAP was increased by 2cmH<sub>2</sub>O until hypoxemia improved, as well as the IPAP level, in order to maintain the delta inspiratory pressure value. IPAP was

increased or decreased according to the  $f/TV$  ratio, or in cases of hypoventilation with  $PaCO_2 > 50\text{mmHg}$ , without a prior history of  $CO_2$  retention, IPAP was increased until hypoventilation improved with minimal air leakage. All patients received oxygen supplement through a catheter connected to the nasal mask, with a flow of 5 l/min.

**Oxygen mask group:** Patients randomized to oxygen mask group received oxygen immediately after extubation through a facial mask with a flow of 5 l/min.

**Re-intubation criteria:** Re-intubation required within a period of 48 hours after extubation was considered weaning failure in any one study group. The decision for re-intubation was made by the staff physician at the ICU, in the persistent presence of one or more of the following criteria: systolic arterial pressure  $> 180\text{mmHg}$  or  $< 90\text{mmHg}$ , heart rate  $> 140\text{bpm}$ , life-threatening arrhythmia, decreased level of consciousness or intense agitation requiring sedation, respiratory rate  $> 30/\text{min}$ ,  $PaO_2 < 60\text{mmHg}$  or  $SaO_2 < 90\%$ ,  $PaCO_2 > 50\text{mmHg}$   $pH < 7.2$  or significant difficulty in eliminating respiratory secretions.

**Follow-up:** At baseline, demographic data (age and gender), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, duration of mechanical ventilation before extubation and diseases which led to acute respiratory failure were recorded for all patients. Heart rate, arterial blood pressure, respiratory rate, and hemoglobin saturation were monitored throughout the study for both groups. Three arterial blood gas analyses were carried out by radial artery puncture at 15 minutes, 2 hours and 24 hours after extubation for all patients. Patients were followed up throughout their ICU and hospital stay. The need for re-intubation was recorded as well as the length of ICU stay and hospital mortality.

**Statistical analysis:** A priori initial sample size calculation (40 patients for each group) was made aiming to show an absolute decrease in the rate of re-intubation after 48 hours of 17.85% and a relative decrease in the rate of re-intubation after 48 hours of 85% in NIV group compared to OM group. We considered the initial risk of 48 hours re-intubation rate in the oxygen mask group of 21% (a usual finding in our ICU). This reflected our assumption that the reduction of the 48 hours re-intubation ratio would decrease from 21% to 3.15%, as we informed the statistician that we expected a very high impact of noninvasive ventilation as an adjunctive weaning tool according to our clinical experience with this ICU Brazilian population. The study power was 80% and the alpha error was 5%. A first interim analysis was planned to be performed after a total of 40 patients in order to estimate the final sample size by an analyst blinded to the results and to the patients' outcomes. Student's  $t$  test was used for quantitative variables: age, days under mechanical ventilation prior to weaning, number of days in ICU and APACHE II. Repeated measures analysis of variance (ANOVA) with Bonferroni's correction was used to compare consecutive measurements of  $pH$ ,  $PaO_2$ ,  $PaCO_2$ ,  $SaO_2$ , respiratory rate, heart rate and mean arterial blood pressure. Fisher's exact test was used to compare proportions. Kaplan-Meier curve was used to estimate hospital survival and the probability that the patients breathed without ventilator assistance, comparing the two study groups by the log-rank test. Relative risk and the number needed to treat (NNT) were also calculated.  $P < 0.05$  was taken as the level of significance.

## Results

Over the 12-month study period a total of 162 patients admitted to the ICU required mechanical ventilation (orotracheal intubation) for a period greater than three days. Forty of them fulfilled the inclusion criteria and were randomized into the two groups. Twenty patients were randomized to the NIV group and underwent noninvasive ventilation using a silicone nasal mask immediately after extubation; all 20 patients in this group finished the study, while 18 of the 20 patients who were randomized to the Oxygen Mask group and underwent nebulization with an oxygen mask after extubation finished the study (two patients withdrew from the study) (Figure 1 and 2).

Analysis of demographic data, days under invasive mechanical ventilation prior to weaning, APACHE II and diseases which led to acute respiratory failure showed no statistically significant differences between groups (Table 1).

Mean  $PaCO_2$  after 15 minutes post extubation was  $34.56 \pm 3.43$  mmHg in NIV group and  $38.31 \pm 4.74$  mmHg in oxygen mask group ( $p=ns$ ). Mean  $PaO_2$  15 minutes after elective extubation was  $83.2 \pm 7.78$  mmHg in NIV group and  $82.23 \pm 6.41$  in oxygen mask group ( $p=ns$ ). Mean  $pH$  15 minutes after extubation was  $7.37 \pm 0.03$  in NIV group and  $7.38 \pm 0.03$  in the oxygen mask group. Mean respiratory rate was  $25.2 \pm 3.53$  /min in NIV group and  $25.95 \pm 4.83$  /min in oxygen mask group. Analysis of variance (ANOVA) showed a higher  $PaO_2$ , lower  $PaCO_2$ , respiratory rate and mean blood pressure in the NIV group compared to OM group along the 24 hour-period (Figure 3).

The overall re-intubation rate was 21%. Eight patients out of the 38 evaluated patients were re-intubated within 48 hours after extubation. Re-intubation rate was different in each group. One patient out of the 20 patients randomized to the NIV group was re-intubated (5%) while 7 out of the 18 patients randomized to the Oxygen Mask group were re-intubated (39%),  $p=0.016$  (Table 2 and Figure 4). This statistically significant difference was maintained even after the exclusion of patients with COPD (Table 2). The causes for re-intubation in both groups are shown in Table 3. Relative Risk for re-intubation when using NIV after extubation was 0.13 (CI=0.017-0.946), Absolute Risk Reduction (the difference in event rate between the control group and the study group) showed a decrease of 33.9%, and analysis of the Number Needed to Treat was 3.

ICU length of stay was not statistically different between the groups, with a mean of  $16.8 \pm 11.6$  days in NIV group and  $18.4 \pm 12.2$  days in Oxygen Mask group ( $p=0.681$ ) (Table 2).

Hospital mortality rate showed a statistically significant difference between groups, with no deaths during hospitalization in the NIV group and 4 deaths (22.2%) in the Oxygen Mask group ( $p < 0.04$ - Table 2 and Figure 5). It is necessary to stress that all patients that died had been re-intubated. The causes of death were pneumonia associated with sepsis in 2 patients, acute myocardial infarction in 1 patient and multiple organ dysfunction syndrome in 1 patient.

Adverse effects related to the use of NIV were observed in 2 patients and were related to the nasal mask, consisting in ulceration at the nasal area with good response to local treatment, and did not require discontinuation of NIV.

## Discussion

Recent relevant published evidence revealed that in patients with acute respiratory failure early extubation with immediate application of noninvasive ventilation has a positive impact on important outcomes, turning to advantage when compared with continuous invasive weaning, especially in COPD patients that failed in spontaneous breathing trials.<sup>1-6</sup> Its use decreases the occurrence of ventilator associated pneumonia, length of ICU and Hospital stay, total duration of mechanical ventilation, besides reducing patients mortality.<sup>1-6</sup> However, the benefit of using it in acute respiratory failure patients immediately after usual or planned extubation instead of oxygen mask in order to prevent the occurrence of respiratory failure has not been totally established. One small trial assessed noninvasive positive-pressure ventilation after extubation and found no benefit.<sup>18</sup> This study has limited generalizability because it included a high proportion of patients with self-extubations. The present study, however, showed that patients undergoing invasive mechanical ventilation for over 72 hours (our mean mechanical ventilation time was 9 days), owing to acute respiratory failure caused by different etiologies, had a lower re-intubation rate if NIV was immediately applied after extubation when compared to those undergoing conventional therapy with an oxygen mask (5% versus 39%). Our hypothesis is that the major cause for the high success rate in the NIV group was the early application of the ventilatory technique, immediately after a programmed extubation, which probably kept the upper airways open improving ventilation and oxygenation, thus preventing the overload of the respiratory muscles, the development of atelectasis, ventilation/perfusion disorders and respiratory fatigue. A critical issue related to the success of NIV in our study was the adjustment of IPAP and EPAP levels according to each patient's needs. IPAP was adjusted for ventilation adequacy, while EPAP was adjusted for the maintenance of airways and alveolar stability. These individualized adjustments to the levels of NIV support may have had a pivotal role for the avoidance of re-intubation in our population.

It is necessary to stress that NIV must be used immediately after extubation in order to avoid respiratory failure and consequent re-intubation after elective extubation. Keenan and colleagues<sup>19</sup> showed that if NIV is administered to patients that developed respiratory distress after extubation to oxygen mask, NIV will not be able to prevent re-intubation. Corroborating Keenan's results, Esteban and colleagues<sup>20</sup> showed that applying NIV to treat post extubation acute respiratory failure in non selected populations may not be effective and could even be deleterious. NIV is not indicated nowadays in cases that develop acute respiratory failure after extubation. In this situation patients need to be re-intubated and mechanically ventilated.

Four recent RCTs suggested benefit from noninvasive positive-pressure ventilation after extubation in patients who were at high risk of deterioration.<sup>8, 21-23</sup> High-risk patients were defined differently among the RCTs: 1) age greater than 65 years, cardiac failure as the cause of intubation or Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 12 at the time of extubation;<sup>21</sup> 2) more than one of the following: failure of consecutive weaning trials, chronic cardiac failure, arterial pressure of carbon dioxide greater than 45 mm Hg after extubation, more than one non-cardiac comorbidity, weak cough or stridor after extubation not requiring immediate intubation<sup>22</sup>; 3) acute exacerbation of COPD;<sup>23</sup> or 4) history of chronic respiratory disease with ventilation for more than 48 hours and

hypercapnia during the spontaneous breathing trial.<sup>24</sup> Although the four trials defined higher risk differently, they reported consistent decreases in rates of re-intubation (RR 0.42, 95% CI 0.25–0.70) and ICU mortality (RR 0.35, 95% CI 0.16–0.78), but less benefit in terms of hospital mortality (RR 0.66, 95% CI 0.42–1.04). In our study we aimed to analyze a mixed ICU population intubated and mechanically ventilated for more than 72 hours as the main risk factor. It is noteworthy that despite a lower 48 hours re-intubation rate and mean blood pressure in the NIV group compared to OM group along the 24-hour post extubation period (Figure 3) suggesting that NIV provided a better respiratory support to our patients in these critical moments after extubation.

In our study, Relative Risk Analysis showed beneficial results of the use of NIV immediately after extubation in our population. The use of NIV to avoid re-intubation in patients with acute respiratory failure was approximately 8 times when compared to oxygen mask. According to our results, the use of NIV after our weaning protocol avoided re-intubation in 1 out of every 3 patients when compared to the Oxygen Mask group, justifying its use immediately after extubation from invasive mechanical ventilation in patients with acute respiratory failure that needed more than three days of mechanical ventilation.

Another crucial issue related to our study results was the finding that hospital mortality rate was higher in the oxygen mask group. It is noteworthy that all patients who died had been re-intubated and the causes of death were pneumonia associated with sepsis in 2 patients, acute myocardial infarction in 1 patient and multiple organ dysfunction syndrome in 1 patient. This fact was previously reported in literature indicating that re-intubation is a risk factor for death in this population.<sup>24, 25</sup> Therefore all care should be taken to avoid re-intubation after elective extubation in the ICU mechanical ventilation population setting.

With reference to the use of NIV as a preventive measure to avoid re-intubation in patients on mechanical ventilation for more than 48 hours (in our study 72 hours), Chien-Ling Su and colleagues<sup>26</sup> recently analyzed 406 randomized patients assigned to oxygen mask (204 patients) or NIV (202 patients). Re-intubation rate at 72 hours was the primary outcome measure (in our study 48 hours). The authors considered extubation failure if the patients still required the use of NIV at the end of 72 hours in the NIV group or any use of NIV within the first 72 hours after extubation in the oxygen mask group (in our study the use of NIV in the oxygen group was not allowed after extubation and in case of respiratory failure our patients were re-intubated). As Chien-Ling Su and colleagues use the NIV in the oxygen mask group to treat patients with acute respiratory failure after extubation, they could decrease the re-intubation rate of their population. In our study, we used NIV during a 24-hour-period after extubation while, in Chien-Ling Su and colleagues' study, they used the NIV only for 12 hours after extubation. In our study the control group failed mainly after 24 hours post extubation (Figure 4) meaning that we could avoid respiratory failure post 24 hours extubation, whereas Chien-Ling SU could avoid re-intubation using early NIV ventilation after extubation in their control group. As the designs of the two studies were different, the results can only be interpreted taking into account the different methods used.

Recently, Vaschetto and colleagues<sup>27</sup> reported a pilot study aimed to assess the feasibility of early extubation followed

by immediate NIV compared to conventional weaning, in 20 randomized patients with resolving hypoxemic acute respiratory failure. They observed that it is possible to early extubate hypoxemic acute respiratory failure patients with no significant statistical differences in extubation failure, ICU and hospital mortality, tracheotomies, septic complications, days and rates of continuous sedation, and ICU length of stay. As most of our patients (80% in both groups) had pneumonia as the main cause of acute respiratory failure, this recent study supports our favorable results.

### Limitations

Certain limitations of this work must be recognized. We used nasal mask for the application of NIV after planned extubation. If the results with facial masks would be the same is a matter that must be tested. Our studied population was small, but we finished the study after the first interim analysis because the primary objective of the study (prevent re-intubation) was already achieved and was statistically significant ( $p=0.016$ ) and it was ethical to stop the study at that point. The problem of this early stop is that an overestimation of treatment effects could have occurred if our decision to stop the trial coincided with the random high in the treatment effect.<sup>28</sup> For that reason, further studies with a larger population must be carried out to confirm the favorable results obtained in this study and consequently expand the use of NIV to prevent re-intubation in patients that needed more than three days of invasive mechanical ventilation because of acute respiratory failure, provided NIV is applied immediately after extubation. As our study was not blinded, a potential performance bias could have influenced our outcomes because the decision to re-intubate the patients was left in the end to the discretion of the ICU attending physician, despite having reasonably objective criteria for re-intubation. For this reason, we analyzed the re-intubation rate after 168 hours or 7 days post extubation and our results were maintained the same, making the potential performance bias more remote (Figure 4).

### Conclusions

In conclusion, noninvasive ventilation compared to oxygen mask alone prevented re-intubation and decreased hospital mortality if done immediately after planned extubation in our mixed ICU patients requiring invasive mechanical ventilation for more than three days because of acute respiratory failure.

### References

- 1 Keenan SP, Sinuff T, Burns KE, Muscedere J, Kutsogiannis J, Mehta S, Cook DJ, Ayas N, Adhikari NK, Hand L, Scales DC, Rocker G, Dial S, Laupland K, Sanders K, Dodek P; Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ* 2011, 183: E195-214.
- 2 Burns KE, Adhikari NK, Keenan SP, Mead MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2010, 8:CD004127. Review.
- 3 Burns KE, Adhikari NK, Keenan SP, Mead M. Use of noninvasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. *BMJ* 2009, 338:b1574. doi: 10.1136/bmj.b1574. Review.
- 4 Antonelli M, Bello G. Noninvasive mechanical ventilation during the weaning process: facilitative, curative or preventive. *Crit Care* 2008, 12: 136.

- 5 Ferreyra G, Fanelli V, Del Sorbo L, Ranieri VM. Are guidelines for noninvasive ventilation during weaning still valid? *Minerva Anestesiologica* 2001, 77:921-6.
- 6 Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet* 2009, 374:250-9. Review.
- 7 Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, Brigada P, Fracchia C, Rubini F. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998, 128:721-8.
- 8 Ferrer M, Sellarés J, Valencia M, Carrillo A, Gonzalez G, Badia JR, Nicolas JM, Torres A. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomized controlled trial. *Lancet* 2009, 374:1082.
- 9 Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, Rodriguez-Roisin R, Torres A. Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. *Am J Respir Crit Care Med* 2003, 168:70-6.
- 10 Chen J, Qiu D, Tao D. Time for extubation and sequential noninvasive mechanical ventilation in COPD patients with exacerbated respiratory failure who received invasive ventilation. *Zhonghua Jie He He Hu Xi Za Zhi* 2001, 2:99-100.
- 11 Hill NS, Lin D, Levy M. Noninvasive positive pressure ventilation (NPPV) to facilitate extubation after acute respiratory failure: a feasibility study. *Am J Respir Crit Care Med* 2000, 161:B18.
- 12 Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. *Am J Respir Crit Care Med* 1999, 1:86-92.
- 13 Trevisan CE, Vieira SR; Research Group in Mechanical Ventilation Weaning. Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: a randomized clinical trial. *Crit Care* 2008, 12:R51.
- 14 Rabie GM, Mohamed AZ, Mohamed RN. Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD. *Chest* 2004, 126:755.
- 15 Wang C, Zhang Q, Cao Z. Pulmonary infection control window in the treatment of severe respiratory failure of chronic obstructive pulmonary diseases: a prospective, randomized controlled, multi-centre study. *Chinese Medical Journal* 2005, 118:1589-94.
- 16 Zheng R, Liu L, Yang Y. Prospective randomized controlled clinical study of sequential noninvasive following invasive mechanical ventilation in patients with acute respiratory failure induced COPD. *Chinese Journal of Emergency Medicine* 2005, 14:21-25.
- 17 Zou S, Zhou R, Chen P. Application of sequential noninvasive following invasive mechanical ventilation in COPD patients with severe respiratory failure by investigating the appearance of pulmonary-infection-control-window. *Journal of Central Southern University* 2006, 31:120-5.
- 18 Jiang JS, Kao SJ, Wang SN. Effects of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. *Respirology* 1999, 4:161-5.
- 19 Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive-pressure ventilation for postextubation respiratory distress. A randomized controlled trial. *JAMA* 2002, 287:3238-44.
- 20 Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M, Epstein SK, Hill NS, Nava S, Soares MA, *Continued on page 56...*

# Type I Arnold-Chiari Malformation with Bronchiectasis, Respiratory Failure, and Sleep Disordered Breathing: a case report

Raffaele Campisi, Nicola Ciancio, Laura Bivona, Annalisa Di Maria and Giuseppe Di Maria

## Abstract

Arnold Chiari Malformation (ACM) is defined as a condition where part of the cerebellar tissue herniates into the cervical canal toward the medulla and spinal cord resulting in a number of clinical manifestations. Type I ACM consists of variable displacement of the medulla throughout the foramen magnum into the cervical canal, with prominent cerebellar herniation.

Type I ACM is characterized by symptoms related to the compression of craniovertebral junction, including ataxia, dysphagia, nistagmus, headache, dizziness, and sleep disordered breathing. We report a case of a life-long non-smoker, 54 years old woman who presented these symptoms associated with bronchiectasis secondary to recurrent inhalation pneumonia, hypercapnic respiratory failure, and central sleep apnea (CSA).

CSA was first unsuccessfully treated with nocturnal c-PAP. The subsequent treatment with low flow oxygen led to breathing pattern stabilization with resolution of CSA and related clinical symptoms during sleep. We suggest that in patients with type I ACM the presence of pulmonary manifestations aggravating other respiratory disturbances including sleep disordered breathing (SDB) should be actively investigated. The early diagnosis is desirable in order to avoid serious and/or poorly reversible damages.

## Background

Arnold-Chiari malformation (ACM) is a complex syndrome in which the brainstem medulla, and the cerebellar tonsils and vermis herniate throughout the foramen magnum. Type I ACM is defined by the herniation of only the medulla and cerebellar tonsils whereas type II ACM is also characterized by caudal displacement of the cerebellar vermis. The main symptoms include ataxia, dizziness, chronic headache, nystagmus, twitching, oropharyngeal dysfunction, recurrent respiratory infections, paresthesia, pyramidal signs and sleep disordered breathing (SDB) encompassing a number of sleep disturbances characterized by apneas or hypopneas, intermittent hypoxemia, microarousals, and disruption of sleep continuity. All these

disturbances are related to the compression of respiratory centers and their neural pathways related to herniation. We report a case of type I ACM with recurrent aspiration-induced pneumonia, secondary bronchiectasis, respiratory failure, and central sleep apneas.

## Case report

A 54-years-old woman with type I ACM (BMI 19.2 kg/m, neck and waist circumference 34 and 65 cm respectively, Mallampati score 2), was referred to our Respiratory Unit with a history of chronic cough and purulent sputum, fever, intense dyspnea (MRC dyspnea scale 4), hoarseness, excessive daytime sleepiness (Epworth Sleepiness Scale 14), involuntary naps, snoring, nocturia and morning headaches. These respiratory symptoms had been present for more than five years. She referred six hospital admissions because of inhalation pneumonia in the last five years. Physical examination revealed normal pulse rate (66 per minute), high respiratory rate (24 per minute), normal blood pressure (115/70 mmHg) and low oxygen saturation (SpO<sub>2</sub> 90%). Cardiac auscultation was normal, whereas pulmonary auscultation revealed diffuse rales in both lungs, basal and bilateral crackles. Neurologic examination showed nistagmus, tongue twitching, dysarthria, dizziness, walking ataxia, severe dysphagia and persistent bilateral



Figure 1. Sagittal craniocervical magnetic resonance imaging section. The arrow shows cerebellar tonsils herniation through the foramen magnum until the second cervical vertebra and bulbar compression.

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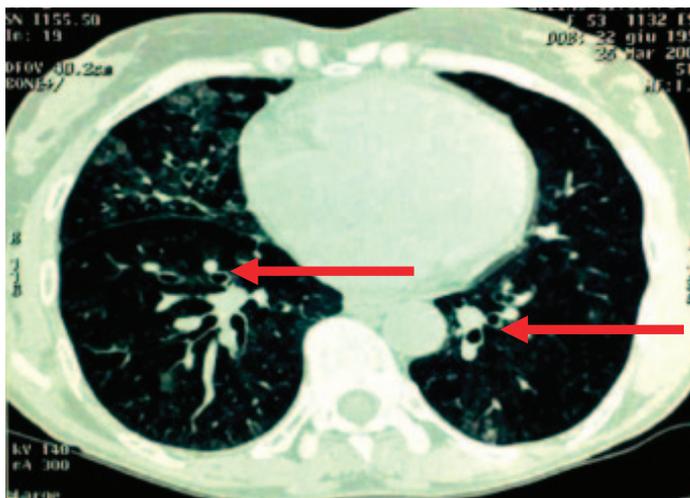


Figure 2. Bronchiectasis. The arrows show cylindrical bronchiectasis spread to both lungs appearing as “signet ring”.

abductor vocal cord paralysis. Routine blood tests gave normal results apart from high level of C-reactive protein (5.68 mg/dl), ESR (64 mm) and low serum albumin (3.3 g/dl). Cervico-medullary magnetic resonance imaging showed cerebellar tonsils herniation through the foramen magnum to the level of C2 vertebra, basilar imprint and bulbar compression [Figure 1]. Chest X-Ray showed no pulmonary consolidation whereas several cylindrical bronchiectasis of both lungs were seen on chest CT [Figure 2]. All causes for congenital bronchiectasis were excluded. The patient had no family history of cystic fibrosis,  $\alpha$ 1-antitrypsin deficiency, or other conditions that

predispose to the onset of secondary bronchiectasis such as tuberculosis or infection during childhood. Sputum smear for acid fast bacilli and Quantiferon-TB test were negative. Arterial PO<sub>2</sub>, PCO<sub>2</sub> and pH were 58, 50 mmHg, and 7.43 respectively. Pulmonary function test revealed volumes within normal limits [FVC 2,13 L (88% pred), FEV<sub>1</sub>1,67 L (93% pred), FEV<sub>1</sub>/FVC ratio 0.78. The diffusion capacity of the lung for CO (DLco): 103% pred; DLco/VA 1.47 (110% pred.). Because of excessive daytime sleepiness, heavy snoring and hypercapnic respiratory failure we performed overnight polysomnography in room air, after titration of c-PAP (9 cm H<sub>2</sub>O), and during nasal oxygen administration (FiO<sub>2</sub> 0,24%) overnight. These consisted of recording of airflow, pulse oximetry, thoracic and abdominal movements, heart rate, body position, snoring, legs positions and two-channel electroencephalogram. Apneas, hypopneas, and apnea-hypopnea index (AHI) were defined according to current criteria. Polysomnography in room air revealed an AHI of 42 events h<sup>-1</sup> with several prolonged episodes of Central Sleep Apnea (CSA) and some events of obstructive sleep apnea (OSA) and an average of arterial saturation of 89% [Figure 3]. The patient did not show any cardiovascular comorbidity (normal echocardiogram, no signs of pulmonary hypertension or cardiac arrhythmias).

After titration of c-PAP, polysomnography showed a decrease in AHI from 42 to 22 events h<sup>-1</sup> and mean of SpO<sub>2</sub> was 92%. Registration during nasal oxygen administration revealed a reduction in the number of both CSA and OSA allowing a significant improvement of AHI along with apnea duration; mean SpO<sub>2</sub> was 96% [Table 1]. Capnography was performed to evaluate changes in nocturnal hypercapnia. Average pCO<sub>2</sub> was 52 mmHg (range 44–56 mmHg). Average SpO<sub>2</sub> was 89%. During low-flow nocturnal oxygen (FiO<sub>2</sub> 0,24%) pCO<sub>2</sub> was 57 mmHg (range 53-63 mmHg); average SpO<sub>2</sub> was 96%. During wakefulness the patient returned to be hypercapnic with values similar to baseline, then worsening of average pCO<sub>2</sub> was only partial and transitory. The patient did not take any drug known to alter the sleep pattern. Administration of broad-spectrum antibiotics (piperacillin/tazobactam 4,5 g/t.i.d and Ciprofloxacin 500 mg bid) was started, and corticosteroid (prednisone 25 mg/die) was administered for 7 days. During follow up examination, the patient was clinically improved, with regression of cough, sputum, improvement in respiratory symptoms and daytime sleepiness (ESS 5), but persistent hypercapnic chronic respiratory failure.

## Discussion

This case presentation offers the opportunity to speculate about the occurrence of respiratory involvement and its mechanisms in patients with type I ACM. Sleep disordered breathing is associated with ACM and generally ascribed to two types of abnormalities: upper airway dysfunction which is associated with obstructive apneas, and abnormalities of respiratory control which is presumably involved in the pathophysiology of central sleep apneas. The latter are characterized by transient cessation of neural respiratory output during sleep resulting in poor ventilation and impaired gas exchange. The transient cessation of respiratory drive could be due to: firstly, an outright defect in respiratory drive; secondly, a transient instability in an otherwise intact respiratory control system; and thirdly, a transient active inhibition of respiratory motor drive. In addition, patients may be either hypercapnic or non-hypercapnic. The hypercapnic group, which includes patients with central hypoventilation and a number of neurological syndromes, is consistent with the first pathophysiological mechanism. The non-hypercapnic group

**Table 1 Polysomnographic data at baseline, during C-PAP breathing, and during continuous oxygen administration**

	Polysomnographical data		
	Baseline	C-PAP	FiO <sub>2</sub> 24%
<b>Polysomnography</b>			
Total Sleep Time	7 h 03 m	7 h 40 m	7 h 30 m
Sleep onset latency	18,8 m	21,3 m	18,8 m
% Sleep efficiency	89	90	92
% Slow Wave Sleep	27	31	33
% REM	19	22	25
<b>Respiratory Events</b>			
AHI	42	22	1
AC	125	63	3
AO	1	9	1
AM	9	0	0
HI	186	77	1
CH	175	72	3
OH	11	5	0
O <sub>2</sub> saturation	89%	92%	96%
ODI	43	15,7	3,0
cT90	30%	21%	0%
Nadir SaO <sub>2</sub>	82	84	90

AHI Apnoea/hypopnoea index, AC Central apnea, AO Obstructive apnoea, AM Mixed apnoea, HI Hypopnoea; CH Central Hypopnoea, OH Obstructive Hypopnoea, ODI Oxygen Desaturation Index, cT90 percentage of sleep time spent with SaO<sub>2</sub> below the threshold of 90%; SaO<sub>2</sub>: arterial saturation; REM Rapid Eye Movements.

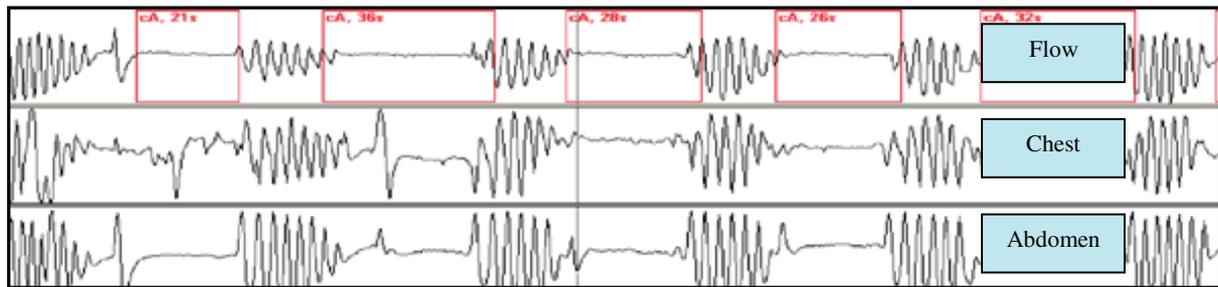


Figure 3. Central sleep apnoeas. Flow, chest and abdomen pattern during central sleep apnoeas.

includes patients with idiopathic hyperventilation and periodic breathing. Pathophysiologically this group is consistent with the second or third mechanism. These patients typically have a low or normal awake  $pCO_2$ . In OSA, pharyngeal anatomy, upper airway muscles responsiveness during sleep, arousal threshold, and loop gain may all contribute to the occurrence of apnea presence and severity of central apnoeas. During sleep reflex muscles activation is reduced and if the airway anatomy is quite deficient will likely lead to substantial or complete airflow obstruction, yielding a hypopnea or apnea. The patient had the hypercapnic form of CSA the risk of apnea resulted from both obstructive (short neck, limited mobility of soft palate and tongue) and central causes. Central causes may include: 1) compromised vascular supply to the brainstem due to compression; 2) insensitivity of peripheral chemo-receptors, due to brainstem involvement; 3) direct compression of the respiratory center. In our case both central and obstructive apnoeas was confirmed with polysomnography. Nasal c-PAP (9  $cmH_2O$ ), after proper titration, was partially effective in improving the AHI and apnea duration, but limited compliance to the treatment. Polysomnography was repeated during low flow oxygen administration resulting in a significant reduction in both number and duration of CSA and an increase in  $SpO_2$  (average apnea duration in baseline condition 16.5 seconds; after low flow oxygen administration 11.2 sec). The use of supplemental low flow oxygen, as mentioned in another case report of a patient with primary alveolar hypoventilation, chronic hypercapnia and CSA, led to a decrease in number and duration of central apnoeas. The improvement produced by oxygen may have been due to the fact that the patient had no demonstrable ventilatory response to hypoxia during wakefulness, and therefore may have developed hypoxic brainstem depression during sleep. The

findings suggest that oxygen therapy during sleep may be beneficial in patients with primary alveolar hypoventilation and CSA leading to significant improvement of SDB and all related symptoms. Oxygen administration during sleep has been associated with reproducible reduction of AHI [Table 1] Type I ACM, whether alone or in combination with syringomyelia, can cause a great number of progressive disorders such as dysphagia, alveolar hypoventilation, inhalation pneumonia, and respiratory failure. In our patient recurrent aspirations with consequent inhalation pneumonia occurred. The most important mechanism of recurrent aspiration pneumonia was dysphagia. The alterations underlying dysphagia are stretch injury to the lower cranial nerves caused by caudal displacement of the medulla or compression of the swallowing centers in the brainstem. Probably the pressure determined by the cerebellar tonsils on the hypoglossal nuclei and other swallowing centers located in the medulla is tough to be the leading cause of the dysphagia. Recurrent aspirations result in several respiratory infections which may lead both to post-inflammatory bronchiectasis and

lung parenchymal damage, causing chronic respiratory failure (CRF). Respiratory failure as the early manifestation in type I ACM is uncommon and, generally, is the result of postoperative conditions. Cylindrical bronchiectasis, as documented in Figure 2, have become a source of repeated infections with recurrent exacerbations of CRF, chronic cough, intense dyspnea and fever treated with antibiotics and often requiring hospitalization. Respiratory failure probably has been caused not only by neuromuscular disorders affecting the diaphragm due to compression of neural centers in the brainstem, but also resulted from swallowing disturbances and dysphagia further complicated by recurrent aspiration pneumonia.

### Conclusions

This case report suggests that a neurologic cause can always be considered for recurrent aspiration pneumonia and progressive dysphagia, even in absence of prominent signs and symptoms. The high prevalence of sleep apnea syndrome in patients with neurological disorders indicates that respiratory disturbances during sleep should be systematically screened even in ACM patients, in order to prevent nocturnal respiratory failure and all the risks associated with nocturnal intermittent hypoxia. In summary, central sleep apnea can be the typical manifestation of ACM and may be a life-threatening condition. The severity of CSA may explain the reported increased incidence of death during sleep in ACM patients. Using a low flow oxygen during sleep, even in hypercapnic patients, avoids mechanical ventilation that is often not well tolerated. Oxygen administration allows to solve CSA and all related cerebrovascular risks associated with nocturnal respiratory failure and sleep fragmentation, improving quality of life. Oxygen therapy can generate potentially detrimental effects. The most relevant of these is the worsening of hypercapnia, which is mediated by mechanisms such as hypoventilation and ventilation-perfusion redistribution. Particularly sleep itself generates ventilatory alterations that include an increase in airway resistance and decreased sensitivity of respiratory centers. Arterial blood gases samples should be periodically taken at awakening to assess  $pCO_2$  in order to prevent hypoventilation from the oxygen therapy. The availability of further clinical studies for the treatment of CSA with low flow oxygen in hypercapnic patients is desirable to avoid serious and irreversible damage.

# Severe Lower Respiratory Tract Infection in Infants and Toddlers from a Non-affluent Population: viral etiology and co-detection as risk factors

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## Abstract

**Background:** Lower respiratory tract infection (LRTI) is a major cause of pediatric morbidity and mortality, especially among non-affluent communities. In this study we determine the impact of respiratory viruses and how viral co-detections/infections can affect clinical LRTI severity in children in a hospital setting.

**Methods:** Patients younger than 3 years of age admitted to a tertiary hospital in Brazil during the months of high prevalence of respiratory viruses had samples collected from nasopharyngeal aspiration. These samples were tested for 13 different respiratory viruses through real-time PCR (rt-PCR). Patients were followed during hospitalization, and clinical data and population characteristics were collected during that period and at discharge to evaluate severity markers, especially length of hospital stay and oxygen use. Univariate regression analyses identified potential risk factors and multivariate logistic regressions were used to determine the impact of specific viral detections as well as viral co-detections in relation to clinical outcomes.

**Results:** We analyzed 260 episodes of LRTI with a viral detection rate of 85% (n = 222). Co-detection was observed in 65% of all virus-positive episodes. The most prevalent virus was Respiratory Syncytial Virus (RSV) (54%), followed by Human Metapneumovirus (hMPV) (32%) and Human Rhinovirus (HRV) (21%). In the multivariate models, infants with co-detection of HRV + RSV stayed 4.5 extra days (p = 0.004), when compared to infants without the co-detection. The same trends were observed for the outcome of days of supplemental oxygen use.

**Conclusions:** Although RSV remains as the main cause of LRTI in infants our study indicates an increase in the length of hospital stay and oxygen use in infants with HRV detected by RT-PCR compared to those without HRV. Moreover, one can speculate that when HRV is detected simultaneously with RSV there is an additive effect that may be reflected in more severe clinical outcome. Also, our study identified a significant number of children infected by recently identified viruses, such as hMPV and Human Bocavirus (HBov), and this is a novel finding for poor communities from developing countries.

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## Background

Lower respiratory tract infections (LRTI) represent an important public health burden in the first years of life accounting for approximately one fifth of all deaths in children below five years of age, especially in developing countries.<sup>1</sup> The specific role of newly identified viruses on LRTIs, like Human Metapneumovirus (hMPV), has been studied in recent years.<sup>2</sup> However, its impact among non-affluent populations has been scarcely evaluated. In such locales, infants with respiratory syncytial virus (RSV)-associated LRTIs present a three times greater risk of a fatal event, when compared to their peers in developed countries.<sup>3</sup>

Although RSV is well recognized as the main agent associated with severe LRTIs, recent data indicate that other viruses may play a significant role in these clinical outcomes. Human rhinovirus (HRV) seems to be of particular interest, as the most prevalent virus in respiratory illnesses even in the first years of life,<sup>4,5</sup> being associated with severe acute bronchiolitis, especially among children of atopic parents.<sup>6</sup> Moreover, a recent study showed that, in a population of preterm infants, HRV was the most prevalent agent associated with severe bronchiolitis.<sup>7</sup> Also of interest is the fact that wheeze-related HRV infection in the first year of life is associated with an increased risk for developing asthma later in life,<sup>8</sup> and that this effect was greater than the observed in relation to RSV.<sup>9</sup>

The impact on severity of early life respiratory infections may be also affected by viral co-detections diagnosed through sensitive PCR analyses. Some studies have shown a positive association between viral co-detection and worse clinical outcomes,<sup>10,11</sup> while others have failed to show results in the same direction.<sup>12-14</sup>

**Table 1 Characteristics and outcomes of the population included in the study (260 children)**

Sex, female, n (%)	103 (40)
Age, months, median (range)	5 (1-35)
Age, <6 months, n (%)	128 (49)
Maternal smoking during pregnancy, n (%)	74 (29)
Prematurity, n (%)	62 (24)
Family history of asthma*, n (%)	149 (58)
LOS <sup>+</sup> , days, median (range)	4 (2-8)
Use of oxygen, days, median (range)	3 (1-6)

<sup>+</sup> LOS: length of hospital stay; \* for parents and/or siblings.

**Table 2 Viral detection by RT-PCR, among 260 children**

Overall prevalence of viruses	n (%)
No vírus detected	38 (14.1)
RSV	139 (53.5)
hMPV	84 (32.3)
HRV	54 (20.8)
HBov	27 (10.4)
Influenza (A or B)	33 (12.7)
Para-influenza (1 or 2)	17 (6.5)
Adenovirus	17 (6.5)
Coronavirus	3 (1.2)
Co-detections	n (%)
RSV + HRV	22 (8.5)
RSV + HMPV	37 (14.2)
RSV + Others*	26 (10.0)
HRV + Others**	29 (11.2)
HMPV + Others***	16 (6.1)
HMPV + Others***	16 (6.1)

RSV: Respiratory syncytial virus; HMPV: Human metapneumovirus; HRV: Human rhinovirus.

\* Bocavirus + influenza A or B.

\*\* HMPV + influenza A or B.

\*\*\* Bocavirus + influenza A or B.

The aims of our study were to determine the current impact of newly identified viruses on the severity of LRTI in infants seen in the emergency room and pediatric wards from a tertiary hospital in a developing country, and how specific viruses alone or in co-detections increased the degree of clinical severity of disease.

## Methods

**Subjects and study design:** Infants and toddlers younger than three years of age, with a diagnosis of LRTI, admitted to the emergency room (ER) or pediatric wards of a tertiary hospital in Porto Alegre, southern Brazil, were recruited for this study, during the months of greatest prevalence for acute pediatric respiratory viral illnesses (i.e., from April to November) in 2007.<sup>4,15</sup> The great majority of patients seen in this particular setting come from low-income families, with health coverage provided by the Brazilian free-access public health system.

LRTI was defined by the presence of signs and symptoms of an acute respiratory infection (cough, nasal discharge, oropharyngeal hyperemia, with or without fever), and lower respiratory signs (tachypnea, retractions, prolonged expiratory time, or crackles/wheezing on auscultation). Chest radiographs were taken only at medical assistant discretion, to avoid unnecessary X-ray exposure, and thus were not used for

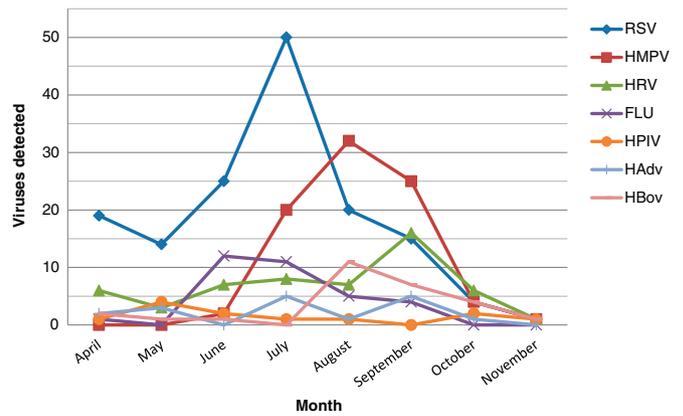


Figure 1. Monthly numbers of samples positive for the different viruses from the subjects studied.

diagnostic purposes. Children who were admitted in the ER with signs and symptoms of a LRTI for at least 6 hours were considered eligible, once symptoms had started within the previous 5 days. Patients with other co-morbidities such as neuromuscular diseases, previous cardiopulmonary disorders, immunodeficiencies, or important congenital anomalies were excluded. We also excluded patients with a hospitalization due to LRTI in the previous 30 days. Bacterial pneumonia was excluded by clinical presentation and chest X-rays findings.

Within the first 24 hours of hospitalization, medical information was collected from parents or guardians through a standardized questionnaire. Data regarding clinical conditions at admission, vital signs, and signs of respiratory distress were obtained from the medical charts. Information on use of medications, clinical course of the disease until discharge, use of supplemental oxygen, and length of hospital stay were prospectively collected. These two latter variables were used as the main clinical outcomes, serving as surrogates for clinical severity. Supplemental oxygen was withdrawn when pulse oximetry was equal or greater than 94% in room air for at least 6 hours, as this is the standard clinical procedure in the hospital. Sample size was estimated based on few previous similar studies, since data analyzing the association between viral co-detection and our main outcomes was scarce at the time this project was planned.<sup>16-18</sup>

**Nasopharyngeal sample collection:** Nasopharyngeal aspiration with a standardized technique using vacuum and a sterile collector were performed in all children within the first 48 hours of admission. Samples were immediately split into aliquots, including one in TRIzolW, and stored at  $-80^{\circ}\text{C}$ , until shipment to the Laboratory of Viral Pathogenesis, at the University of São Paulo School of Medicine, Ribeirão Preto.

**Table 3 Univariate analyses of risk factors for length of hospital stay and days with supplemental oxygen (n = 260)**

	Length of hospital stay			Days with supplemental oxygen		
	$\beta^*$	(95% CI)	p	$\beta^*$	(95% CI)	p
Sex, female	0.4	(-0.9 - 1.7)	0.553	0.5	(-0.6 - 1.7)	0.372
Age, $\leq 6$ months	3.8	(2.7 - 5)	<0.001	3.8	(2.8 - 4.9)	<0.001
Prematurity	0.4	(-1.0 - 1.9)	0.570	0.4	(-1.0 - 1.7)	0.605
Maternal smoking during pregnancy	1.2	(-0.2 - 2.6)	0.106	1.3	(-0.02 - 2.7)	0.054
Family Hx asthma	2.4	(1.2 - 3.6)	<0.001	2.4	(1.3 - 3.5)	<0.001

Hx: history; \* number of extra days, compared to negative counterparts.

**Table 4 Multivariate analysis for length of hospital stay (dependent variable), and HRV adjusting other risk factors**

	Yes		No		$\beta^*$	95% CI	P
	Mean	(95% CI)	Mean	(95% CI)			
HRV	7.7	(6.1 - 9.3)	5.5	(4.7 - 6.2)	2.2	(0.5 - 3.9)	0.011
Sex (female)	6.8	(5.6 - 8.0)	6.3	(5.4 - 7.3)	0.4	(-0.6 - 1.5)	0.419
Age $\leq 6$ months	8.2	(7.0 - 9.3)	5.0	(3.9 - 6.0)	3.2	(2.0 - 4.3)	<0.001
Family Hx of asthma	7.2	(6.2 - 8.2)	6.0	(4.8 - 7.1)	1.2	(0.1 - 2.3)	0.035
Prematurity	6.7	(5.4 - 7.9)	6.5	(5.5 - 7.4)	-0.2	(-1.4 - 1.0)	0.749
Maternal smoking	6.8	(5.6 - 8.2)	6.3	(5.3 - 7.2)	0.6	(-0.6 - 1.8)	0.354

Hx: history; \* number of extra days in hospital, compared to negative counterparts.

**Viral detection by individual real-time RT-PCR:** To isolate RNA from nasal aspirates, 250  $\mu$ L were extracted according to the manufacturer's protocol (Invitrogen, Carlsbad, CA, USA). DNA was extracted from a sample of 200  $\mu$ L of nasal aspirate using the Wizard Genomic DNAW purification kit, following manufacturer's instructions (Promega, Madison, WI, USA). The detection of viruses was done by Real Time PCR, using the Taqman SystemW (Applied Biosystems, NJ, USA), with specific primers and probes in a thermal cycler (7300 Real Time PCR systemW - Applied Biosystems). Real Time PCR reactions for cellular gene ( $\beta$ -actin) were also performed for internal quality control.

For viruses with a RNA genome (i.e., HRV, Influenza Virus-A [FLUAV], human parainfluenza virus [HPIV], RSV, hMPV and human coronavirus [HCoV]), the transcription into cDNA was done with reverse transcriptase (high capacity cDNA reverse transcription kitW, Applied Biosystems), using 1  $\mu$ g from the extracted RNA, according to the manufacturers' protocol. The qPCR assays were performed using 3  $\mu$ L of the DNA extraction or cDNA (approximately 150 ng), 0.33 pmoles for primers, 0.17 pmoles for probes and 7.5  $\mu$ L of master mix of TaqManW (Applied Biosystems). Amplifications were performed with 45 cycles of denaturation at 95°C for 15 seconds and annealing-extension at 60°C for one minute, except for hMPV, when annealing was done at 55°C for 30 seconds, and extension at 60°C for one minute.

Statistical analysis: Demographics were summarized as mean or median and range according to their distribution. Characteristics among groups were compared, accordingly, using two-sample t-test, Mann-Whitney, Chi-square or Fisher's exact test.

Generalized linear models (Tweedie model with Identity link function) were used to analyze the relationships between

main outcomes (length of stay in the hospital and time in use of supplemental oxygen) and the predictor variables (virus detection [yes/no], sex, age, prematurity (i.e. <37 weeks of gestation), maternal smoking during pregnancy, family asthma). All variables with a significance of  $p < 0.15$  were considered in the univariate models and those with significance of  $p < 0.05$  in the multivariate analysis. All analyses were performed using SPSS v.18 (SPSS Inc, Chicago, IL).

This study was approved by the local Institutional Ethics Committees (06/03467 - Pontificia Universidade Católica do Rio Grande do Sul and 4856/2004 - Universidade de São Paulo). Parents or legal guardians read and signed an informed consent approved for this study.

## Results

Two hundred and sixty patients were enrolled in the study. Characteristics of the patients recruited are presented in Table 1. In the whole sample there were more boys than girls, almost half of children were younger than six months, 24% of all children were born premature, 29% had been exposed to tobacco during gestation, and more than a half had a family history of asthma (parents or siblings). Overall, median hospital length was 6 days and median supplemental oxygen requirement was 5 days.

The presence of viruses was detected by PCR in 222 (85%) of all LRTI episodes. Co-detection was present in 146/260 (56%). The frequencies of viral detection and co-detection are shown in Table 2. The most common single infection was related to RSV (54%), followed by hMPV (32%), and HRV (21%).

During the surveyed time RSV has shown an incidence peak in the beginning of the cold season (i.e. from April to November) in the southern hemisphere, followed in late winter by peaks of hMPV, HRV, and HBoV (Figure 1). Other viruses such as HPIV

**Table 5 Multivariate analysis for length of hospital stay (dependent variable) and HRV + RSV (co-detection), adjusting for other risk factors**

	Yes		No		$\beta^*$	95% CI	P
	Mean	(95% CI)	Mean	(95% CI)			
RSV + HRV	10.0	(7.0 - 13.0)	5.5	(4.8 - 6.3)	4.5	(1.4 - 7.5)	0.004
Age $\leq 6$ months	9.4	(7.7 - 11.1)	6.1	(4.6 - 7.7)	3.3	(2.2 - 4.5)	<0.001
Sex (female)	7.9	(6.2 - 9.6)	7.6	(6.0 - 9.2)	0.3	(-0.7 - 1.4)	0.517
Family Hx of asthma	8.3	(6.7 - 9.9)	7.2	(5.5 - 8.9)	1.1	(0.04 - 2.2)	0.043
Prematurity	7.8	(6.1 - 9.5)	7.7	(6.1 - 9.4)	-0.04	(-1.2 - 1.2)	0.952
Maternal smoking	8.1	(6.3 - 9.9)	7.4	(5.9 - 8.9)	0.7	(-0.5 - 2.0)	0.243

Hx: History; \* number of extra days in hospital, compared to negative counterparts.

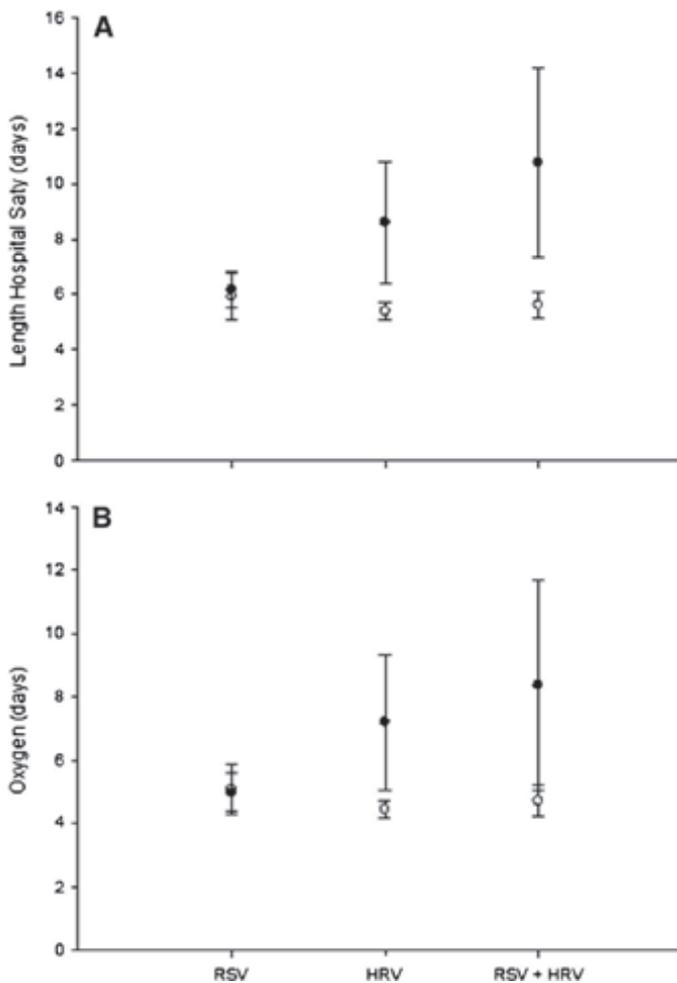


Figure 2. Comparison of RSV, HRV and RSV plus HRV in regards to: (A) length of hospital stay and (B) days of supplemental oxygen use. Black circles: group of infants  $\leq 6$  months of age; white circles: group of infants  $> 6$  months of age. The groups of HRV and RSV + HRV were significantly different ( $p < 0.05$ ), when compared by age. Values expressed as mean  $\pm$  SD of days.

and Human Adenovirus (HAdv) showed low but constant rates throughout the season.

In the univariate analyses, length of hospital stay and need of supplemental oxygen were significantly associated with age ( $\leq 6$  months), maternal smoking during pregnancy and with family history of asthma (parents and/or siblings) (Table 3). Infants younger than 6 months of age stayed in hospital 3.8 days longer than older infants ( $p < 0.001$ ), and those with a family history of asthma stayed 2.4 days longer than those without a family history of asthma ( $p < 0.001$ ). Also, infants 6 months of age or younger needed supplemental oxygen for an extra 3.8 days, when compared to older infants/children. A similar finding was observed for children with a family history of asthma, who required 2.4 extra days of oxygen compared to those without the family history of asthma (Table 3). Other risk factors, such as breastfeeding, indoor smoking, current parental smoking, siblings, and overcrowding were not significantly associated with neither of the main outcomes.

Infants with positive PCR for HRV alone as well as those co-detected with RSV and HRV also had significantly longer hospital stays (3.2 days,  $p = 0.001$ ; and 5.5 days,  $p = 0.002$ , respectively) than those with other detected viruses. Extended time in use of

supplemental oxygen was also associated with HRV (2.8 days,  $p = 0.002$ ) and RSV (3.7 days,  $p = 0.013$ ), but also with Influenza virus A or B (2.2 days,  $p = 0.042$ ), when compared to those with other viruses in single or in co-detection.

Infants with HRV-LRTIs stayed an extra 2.2 days in hospital ( $p = 0.011$ ), for a total of 7.7 (95% CI: 6.1-9.3) days when compared to those with other infections, after adjusting for potential confounding variables (Table 4). Table 5 shows that infants with combined HRV and RSV positive PCR in the same samples stayed 4.5 extra days ( $p = 0.004$ ) than those without HRV and RSV in these adjusted models (that included sex, age  $\leq 6$  versus  $> 6$  months, prematurity, family history of asthma and maternal smoking during pregnancy), (95% CI: 7.0-13.0) days. Time in use of supplemental oxygen followed the same association trends. Infants with proven RSV infections needed 4.75 (95% CI: 3.97-5.53) extra days of oxygen, while those with HRV used supplemental oxygen for 1.4 extra days, and those with RSV and HRV co-detection for 2.2 days, when compared to infants presenting positive PCRs for other viruses alone or in combinations. Figure 2 illustrates the association between HRV and RSV + HRV co-detection with increased length of hospital stay and oxygen use, and this effect is especially significant for infants younger than 6 months of age. Influenza viruses were not associated with longer use of supplemental oxygen when controlling for the demographic variables.

## Discussion

Our results suggest that infants with severe LRTI and positive PCR for HRV, alone or in co-detection with RSV, stayed hospitalized longer periods and utilized more supplemental oxygen, when compared to children infected by other viruses, including those with RSV- alone. Our data also reinforce previous findings that identified RSV as the major agent associated with severe LRTIs among children in a hospital setting, in populations of low socio-economic status, where other environmental and social variables potentially play a role.<sup>16,17</sup> Infants younger than six months and those with a family history of asthma/recurrent wheeze are also at greater risk for disease severity.

RSV was the most frequently detected virus, accounting for a high burden of LRTIs in our population. Although it is not possible to establish an unequivocal correlation between LRTIs and upper airway viral detection, the finding of RSV in over 50% of hospitalized children in our study strongly suggests that its impact is still indeed very high in this region, regardless of the presence of newly identified viruses. These results are in accordance with recently published studies in Brazil, which also identified RSV as the main agent responsible for severe LRTI, especially in a hospital setting. Nascimento and coworkers have shown an overall viral detection rate of 93% from nasopharyngeal samples in a small group of children below 2 years of age, and reported RSV as the most prevalent virus (63.6%).<sup>19</sup> Another study aiming to investigate the role of HBoV and hMPV in LRTIs in southern Brazil also showed similar results (at least one positive virus in 90% of the samples and RSV positive in 49.3%).<sup>20</sup> The high detection rate of RSV in children with LRTI in a hospital setting such as ours is consistent with most studies worldwide and the burden due to viral respiratory disease seems as high in these locales as they are in more developed countries. A recent analysis of children admitted into the hospital due to acute bronchiolitis in Texas, USA, has shown a steady increase in admissions over a 5-year period and this has been credited mostly to RSV.<sup>21</sup> This increasing role for severe viral LRTIs,

observed also in other studies, is probably explained by a series of complex environmental and social changes that seem to affect how viruses spread in communities.

Some studies have reported different clinical outcomes for specific viruses causing LRTIs, especially in the presence of co-detections, such as with RSV and HBoV,<sup>22,23</sup> while others did not reproduce such findings<sup>17,24,25</sup> and these associations remain unclear. A lack of association between an overall finding of any viral co-detection and LRTI severity was reported in studies performed in non-affluent countries,<sup>2,12,26</sup> as well as in developed countries.<sup>13,14</sup> In our study, patients detected with HRV alone and RSV + HRV presented increased length of hospitalization and increased time of supplemental oxygen use. Papadopoulos et al. has shown a five-fold increase in clinical severity in infants with acute bronchiolitis due to HRV, compared to those infected only with RSV. Compared to those with positive RSV samples without HRV co-detection, infants with HRV were older, had lower birth weights and were hospitalized earlier.<sup>16</sup> Some explanations for apparently contradictory findings in a myriad of studies could be attributed to the lack of uniform criteria for subject inclusion and standardized statistical analysis.<sup>14</sup> Other plausible explanations are the natural variation in HRV prevalence in different seasons and possible variations in the prevalence of type C HRV. This agent is associated with more severe disease and was already described as a major cause of LRTI in infants from non-affluent countries.<sup>27,28</sup> Unfortunately, in our study, we were not able to determine the prevalence of HRV subtypes, and this stands as an interesting subject for further research.

The association of HRV (alone or with RSV) with LRTI severity and atopy has not been widely studied. The relationship between persistent wheezing at 3 years and at 6 years versus relevant HRV infection in early life is well established,<sup>9,29</sup> but there are few studies looking at these relationships in the first year of life. A recent study suggests that the relationship between HRV in early life LRTI and subsequent recurrent wheeze/asthma is dependent on allergic sensitization, which seems to precede the viral insult in a causal model.<sup>30</sup> This association we have found between HRV with increased severity (using the surrogates of length of hospital stay and days in supplemental oxygen) is a major finding. Hence, the association between HRV infection, increased severity and atopy remains to be better clarified.

It has already been shown that HRV is able to reduce cell proliferation and decreases the self-repair capacity of bronchial epithelial cells.<sup>31</sup> Therefore, our data may suggest that in certain subsets of patients the burden of HRV in acute LRTI should be considered distinct from that of other viruses. Another plausible explanation for our findings could be the possibility of HRV persistence in the airways leading to an “over detection” of the virus, simultaneously with those infected only by RSV.<sup>32</sup> In our study this hypothesis seems improbable since we detected a clear worsening in the clinical markers in patients with RSV that were also detected with HRV.

Another interesting finding of our study was the high prevalence of newly described viruses. hMPV was detected in almost one third of all episodes, but did not seem to affect the main outcomes studied here, in the way RSV and HRV have done. While the recognition of the impact of human hMPV is increasing, its prevalence is still probably underestimated in clinical practice, since laboratory testing has become widely available only in recent years.<sup>18,24,33</sup> HBoV was also detected

in a large number of nasal samples and it was very frequently associated (co-detected) with other agents. In our study, only 2/27 patients with HBoV had this virus detected as single agent. The overall HBoV detection rate was higher in our data compared to previous studies,<sup>34,35</sup> and this may be explained again by natural seasonal variations. It is also interesting to notice the seasonal pattern of both hMPV and HBoV, which present their peak prevalence rates in late winter, right after the RSV peak, which occurs earlier in winter.

The main limitation of our study is the lack of surveillance in consecutive years, which could have biased results in case of an outbreak of one specific virus in a given year. Our eight months of viral surveillance could potentially have failed to detect any atypical outbreak, which did not seem likely to have occurred. Also, reliable tests capable of ruling out bacterial co-detection were not available at the time of the study. This could have underestimated the burden of bacteria in our sample and the co-detection of viruses and bacteria remains an interesting issue for further studies.

## Conclusion

In our study, RSV was the most prevalent viral agent in hospitalized patients with LRTI and the co-detection of HRV in patients with RSV infection increased hospital stay and days in use of supplemental oxygen. Interestingly, even in developing countries, the role of recently discovered viruses needs to be further studied in order to identify novel risk factors of susceptibility/severity, and new treatment targets for these agents. We also highlight the role of HRV as an important risk factor for severe LRTI, particularly when simultaneously associated with RSV, which strongly suggests that co-detection may also mean co-infection, since the combination of the two agents seem to affect clinical outcomes. Longitudinal studies with control groups are necessary to confirm these results in populations at greater risk for severe respiratory disease.

## References

- 1 Global action plan for prevention and control of pneumonia (GAPP). [http://www.who.int/maternal\\_child\\_adolescent/documents/9789241596336/en/](http://www.who.int/maternal_child_adolescent/documents/9789241596336/en/).
- 2 Freymuth F, Vabret A, Cuvillon-Nimal D, Simon S, Dina J, Legrand L, Gouarin S, Petitjean J, Eckart P, Brouard J: Comparison of multiplex PCR assays and conventional techniques for the diagnostic of respiratory virus infections in children admitted to hospital with an acute respiratory illness. *J Med Virol* 2006, 78(11):1498–1504.
- 3 Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, O'Brien KL, Roca A, Wright PF, Bruce N, et al: Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010, 375(9725):1545–1555.
- 4 Pitrez PM, Stein RT, Stuermer L, Macedo IS, Schmitt VM, Jones MH, Arruda E: [Rhinovirus and acute bronchiolitis in young infants]. *J Pediatr (Rio J)* 2005, 81(5):417–420.
- 5 van der Zalm MM, Uiterwaal CS, Wilbrink B, de Jong BM, Verheij TJ, Kimpen JL, van der Ent CK: Respiratory pathogens in respiratory tract illnesses during the first year of life: a birth cohort study. *Pediatr Infect Dis J* 2009, 28(6):472–476.
- 6 Miller EK, Williams JV, Gebretsadik T, Carroll KN, Dupont WD, Mohamed YA, Morin LL, Heil L, Minton PA, Woodward K, et al: Host and viral factors associated with severity of human rhinovirus-associated infant respiratory tract illness. *J Allergy Clin Immunol* 2011, 127(4):883–891.

- 7 Miller EK, Bugna J, Libster R, Shepherd BE, Scalzo PM, Acosta PL, Hijano D, Reynoso N, Batalle JP, Coviello S, et al: Human rhinoviruses in severe respiratory disease in very low birth weight infants. *Pediatrics* 2012, 129(1):e60–e67.
- 8 Jackson DJ, Johnston SL: The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010, 125(6):1178–1187. quiz 1188–1179.
- 9 Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee WM, Shult PA, Reisdorf E, et al: Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008, 178(7):667–672.
- 10 Calvo C, Garcia-Garcia ML, Blanco C, Vazquez MC, Frias ME, Perez-Brena P, Casas I: Multiple simultaneous viral infections in infants with acute respiratory tract infections in Spain. *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology* 2008, 42(3):268–272.
- 11 Richard N, Komurian-Pradel F, Javouhey E, Perret M, Rajoharison A, Bagnaud A, Billaud G, Vernet G, Lina B, Floret D, et al: The impact of dual viral infection in infants admitted to a pediatric intensive care unit associated with severe bronchiolitis. *Pediatr Infect Dis J* 2008, 27(3):213–217.
- 12 De Paulis M, Gilio AE, Ferraro AA, Ferronato AE, do Sacramento PR, Botosso VF, Oliveira DB, Marinheiro JC, Harsi CM, Durigon EL, et al: Severity of viral coinfection in hospitalized infants with respiratory syncytial virus infection. *J Pediatr (Rio J)* 2011, 87(4):307–313.
- 13 Marguet C, Lubrano M, Gueudin M, Le Roux P, Deschildre A, Forget C, Couderc L, Siret D, Donnou MD, Bubenheim M, et al: In very young infants severity of acute bronchiolitis depends on carried viruses. *PLoS One* 2009, 4(2):e4596.
- 14 Suryadevara M, Cummings E, Bonville CA, Bartholoma N, Riddell S, Kiska D, Rosenberg HF, Domachowske JB: Viral etiology of acute febrile respiratory illnesses in hospitalized children younger than 24 months. *Clin Pediatr* 2011, 50(6):513–517.
- 15 Thomazelli LM, Vieira S, Leal AL, Sousa TS, Oliveira DB, Golono MA, Gillio AE, Stwien KE, Erdman DD, Durigon EL: Surveillance of eight respiratory viruses in clinical samples of pediatric patients in southeast Brazil. *J Pediatr (Rio J)* 2007, 83(5):422–428.
- 16 Papadopoulos NG, Moustaki M, Tsolia M, Bossios A, Astra E, Prezerakou A, Gourgiotis D, Kafetzis D: Association of rhinovirus infection with increased disease severity in acute bronchiolitis. *Am J Respir Crit Care Med* 2002, 165(9):1285–1289.
- 17 Wilkesmann A, Schildgen O, Eis-Hubinger AM, Geikowski T, Glatzel T, Lentze MJ, Bode U, Simon A: Human metapneumovirus infections cause similar symptoms and clinical severity as respiratory syncytial virus infections. *Eur J Pediatr* 2006, 165(7):467–475.
- 18 Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, Wright PF, Crowe JE Jr: Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004, 350(5):443–450.
- 19 Nascimento MS, Souza AV, Ferreira AV, Rodrigues JC, Abramovici S, Silva Filho LV: High rate of viral identification and coinfections in infants with acute bronchiolitis. *Clinics (Sao Paulo)* 2010, 65(11):1133–1137.
- 20 Pilger DA, Cantarelli VV, Amantea SL, Leistner-Segal S: Detection of human bocavirus and human metapneumovirus by real-time PCR from patients with respiratory symptoms in Southern Brazil. *Memorias do Instituto Oswaldo Cruz* 2011, 106(1):56–60.
- 21 Garcia CG, Bhone R, Soriano-Fallas A, Trost M, Chason R, Ramilo O, Mejias A: Risk Factors in Children Hospitalized With RSV Bronchiolitis Versus Non- RSV Bronchiolitis. *Pediatrics* 2010, 126(6):e1453–e1460.
- 22 Midulla F, Scagnolari C, Bonci E, Pierangeli A, Antonelli G, De Angelis D, Berardi R, Moretti C: Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. *Arch Dis Child* 2010, 95(1):35–41.
- 23 Moriyama Y, Hamada H, Okada M, Tsuchiya N, Maru H, Shirato Y, Maeda Y, Hirose Y, Yoshida M, Omura Y, et al: Distinctive clinical features of human bocavirus in children younger than 2 years. *Eur J Pediatr* 2010, 169(9):1087–1092.
- 24 Zhang SX, Tellier R, Zafar R, Cheung R, Adachi D, Richardson SE: Comparison of human metapneumovirus infection with respiratory syncytial virus infection in children. *Pediatr Infect Dis J* 2009, 28(11):1022–1024.
- 25 Bezerra PG, Britto MC, Correia JB, Duarte Mdo C, Fonceca AM, Rose K, Hopkins MJ, Cuevas LE, McNamara PS: Viral and atypical bacterial detection in acute respiratory infection in children under five years. *PLoS One* 2011, 6(4):e18928.
- 26 Venter M, Lassauniere R, Kresfelder TL, Westerberg Y, Visser A: Contribution of common and recently described respiratory viruses to annual hospitalizations in children in South Africa. *J Med Virol* 2011, 83(8):1458–1468.
- 27 Fuji N, Suzuki A, Lupisan S, Sombrero L, Galang H, Kamigaki T, Tamaki R, Saito M, Aniceto R, Olveda R, et al: Detection of human rhinovirus C viral genome in blood among children with severe respiratory infections in the Philippines. *PLoS One* 2011, 6(11):e27247.
- 28 Linsuwanon P, Payungporn S, Samransamruajkit R, Posuwan N, Makkoch J, Theanboonlers A, Poovorawan Y: High prevalence of human rhinovirus C infection in Thai children with acute lower respiratory tract disease. *J Infect* 2009, 59(2):115–121.
- 29 Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, Kirk CJ, Reisdorf E, Roberg KA, Anderson EL, et al: Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005, 116(3):571–577.
- 30 Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, Lee WM, Gern JE, Lemanske RF Jr: Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. *Am J Respir Crit Care Med* 2012, 185(3):281–285.
- 31 Xatzipsalti M, Psarros F, Konstantinou G, Gaga M, Gourgiotis D, Saxon- Papageorgiou P, Papadopoulos NG: Modulation of the epithelial inflammatory response to rhinovirus in an atopic environment. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology* 2008, 38(3):466–472.
- 32 Mahony JB: Detection of respiratory viruses by molecular methods. *Clin Microbiol Rev* 2008, 21(4):716–747.
- 33 van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, Osterhaus AD: A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001, 7(6):719–724.
- 34 Arnold JC, Singh KK, Spector SA, Sawyer MH: Undiagnosed respiratory viruses in children. *Pediatrics* 2008, 121(3):e631–e637.
- 35 Zheng LS, Yuan XH, Xie ZP, Jin Y, Gao HC, Song JR, Zhang RF, Xu ZQ, Hou YD, Duan ZJ: Human bocavirus infection in young children with acute respiratory tract infection in Lanzhou, China. *J Med Virol* 2010, 82(2):282–288.

# Functional Exercise Capacity and Health-related Quality of Life in People with Asbestos Related Pleural Disease: an observational study

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## Abstract

**Background:** Functional exercise capacity in people with asbestos related pleural disease (ARPD) is unknown and there are no data on health-related quality of life (HRQoL). The primary aims were to determine whether functional exercise capacity and HRQoL were reduced in people with ARPD. The secondary aim was to determine whether functional exercise capacity was related to peak exercise capacity, HRQoL, physical activity or respiratory function.

**Methods:** In participants with ARPD, exercise capacity was measured by the six-minute walk test (6MWT) and incremental cycle test (ICT); HRQoL by the St George's Respiratory Questionnaire and physical activity by an activity monitor worn for one week. Participants also underwent lung function testing.

**Results:** 25 males completed the study with a mean (SD) age of 71 (6) years, FVC 82 (19)% predicted, FEV1/FVC 66 (11)%, TLC 80 (19)% predicted and DLCO 59 (13)% predicted. Participants had reduced exercise capacity demonstrated by six-minute walk distance (6MWD) of 76 (11)% predicted and peak work rate of 71 (21)% predicted. HRQoL was also reduced. The 6MWD correlated with peak work rate ( $r=0.58$ ,  $p=0.002$ ), St George's Respiratory Questionnaire Total score ( $r=-0.57$ ,  $p=0.003$ ), metabolic equivalents from the activity monitor ( $r=0.45$ ,  $p<0.05$ ), and FVC % predicted ( $r=0.52$ ,  $p<0.01$ ).

**Conclusions:** People with ARPD have reduced exercise capacity and HRQoL. The 6MWT may be a useful surrogate measure of peak exercise capacity and physical activity levels in the absence of cardiopulmonary exercise testing and activity monitors.

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## Background

Asbestos related pleural disease (ARPD) is a worldwide problem with non-malignant pleural disease a common manifestation of asbestos exposure. Despite tighter regulations in the use of asbestos in many developed countries, the legacy of asbestos exposure remains and the incidence of asbestos-related pleural abnormalities continues to rise.

Asbestos related pleural disease may result in pleural fibrosis.<sup>1</sup> Despite being recognized as a separate entity to pulmonary fibrosis,<sup>2</sup> ARPD remains poorly investigated and understood. The ensuing symptoms, such as shortness of breath on exertion<sup>3,4</sup> are similar to other chronic respiratory diseases and may cause considerable functional impairment to the individual. Previous studies have demonstrated abnormal responses or reductions in peak exercise capacity during cardiopulmonary exercise testing<sup>5-7</sup> in people with ARPD. However, no studies have investigated the effects of ARPD on functional exercise capacity.

The six-minute walk test (6MWT) is a measure of functional

**Table 1 Demographic data, pulmonary function and smoking history**

	n=25 mean (SD)
Age, yr	71 (6)
Height, cm	174 (5)
Weight, kg	84 (12)
BMI, kg/m <sup>2</sup>	28 (3)
FVC, % pred	82 (19)
FEV <sub>1</sub> , % pred	74 (20)
FEV <sub>1</sub> /FVC %	66 (11)
TLC, % pred	80 (19)
FRC, % pred	80 (23)
RV, % pred	78 (29)
D <sub>L</sub> CO, % pred	59 (13)
KCO, % pred	84 (18)
Smoking, pack year	12 (15)
Never smoked (n)	6

*n* = number; *SD* = standard deviation; *yr* = year; *cm* = centimetre; *kg* = kilogram; *BMI* = body mass index; *m* = metre; *FVC* = forced vital capacity; % pred = percentage of predicted value; *FEV<sub>1</sub>* = forced expiratory volume in one second; *TLC* = total lung capacity; *FRC* = functional residual capacity; *RV* = residual volume; *D<sub>L</sub>CO* = diffusing capacity for carbon monoxide; *KCO* = carbon monoxide transfer coefficient.

**Table 2 Exercise test results for the 6MWT and the ICT, health-related quality of life and physical activity data**

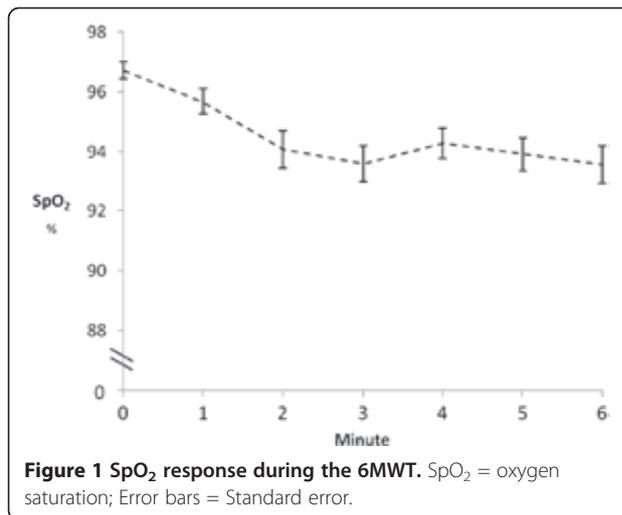
	mean (SD)
<b>6MWT</b>	<b>n=25</b>
6MWD, m	486 (68)
6MWD, % pred	76 (11)
Resting SpO <sub>2</sub> , %	97 (1)
Desaturation, %	4 (3)
Peak PR, % pred*	67 (11)
Dyspnoea at test end	2 (2)
RPE at test end	1 (2)
<b>ICT</b>	<b>n=25</b>
Work rate <sub>peak</sub> , W	114 (36)
Work rate <sub>peak</sub> , % pred	71 (21)
VO <sub>2</sub> peak, % pred	83 (22)
VE, L/min	54 (14)
VE/MVV	63 (16)
Resting SpO <sub>2</sub> , %	99 (1)
Desaturation, %	1 (2)
PR, % pred	82 (13)
Dyspnoea at peak	4 (2)
RPE at peak	5 (2)
<b>HRQoL</b>	<b>n=25</b>
SGRQ Symptoms	29 (21)
SGRQ Activity	34 (22)
SGRQ Impacts	15 (14)
SGRQ Total	23 (15)
<b>Physical activity</b>	<b>n=23</b>
Average daily steps	9072 (3186)
Average daily METs	1.3 (0.2)
Average daily EE, cal	2630 (459)

SD = standard deviation; 6MWT = six-minute walk test; n = number; 6MWD = six-minute walk distance; m = metre; % pred = percentage of predicted value; SpO<sub>2</sub> = oxygen saturation; PR = pulse rate; RPE = rate of perceived exertion; ICT = incremental cycle test; W = watts; VO<sub>2</sub>peak % pred = percent of predicted normal maximal oxygen uptake; VE = minute ventilation; MVV = maximal voluntary ventilation; HRQoL = health-related quality of life; SGRQ = St George's Respiratory Questionnaire; METs = metabolic equivalent; EE = energy expenditure; cal = calorie.  
\* Predicted PR = 220 - age.

exercise capacity widely used in the assessment of lung diseases including chronic obstructive pulmonary disease (COPD).<sup>8</sup> Evidence is growing for the value of the 6MWT in evaluating functional exercise capacity in interstitial lung diseases<sup>9</sup> yet functional exercise capacity in people with ARPD is unknown.

The effects of ARPD on health-related quality of life (HRQoL) have not previously been investigated. Chronic respiratory diseases are frequently associated with decrements in HRQoL.<sup>10</sup> Furthermore, there are no data on the effects of ARPD on levels of physical activity. Levels of physical activity in other lung diseases, such as COPD, have been linked to health outcomes and HRQoL.<sup>11,12</sup>

The primary aims of this study were to determine whether functional exercise capacity and HRQoL were reduced in people with ARPD. The secondary aim was to determine whether



**Figure 1** SpO<sub>2</sub> response during the 6MWT. SpO<sub>2</sub> = oxygen saturation; Error bars = Standard error.

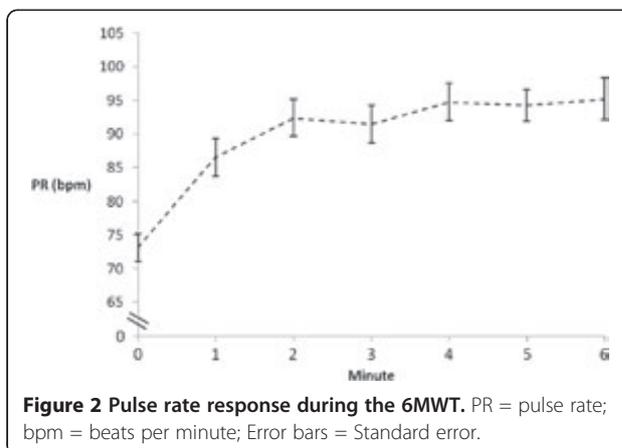
functional exercise capacity was related to peak exercise capacity, HRQoL, physical activity or respiratory function.

### Methods

**Subjects:** This observational study was conducted at Royal Prince Alfred Hospital, Sydney, Australia from November 2008 – August 2010. Participants were recruited through the Workers' Compensation Dust Diseases Board (DDB) of New South Wales, respiratory physicians, support groups, workers' unions and newsletters for returned servicemen.

People were eligible to participate if they had a diagnosis of ARPD, defined as asbestos-related diffuse pleural thickening and/ or rounded atelectasis. Diagnosis had been established by the participant's respiratory physician or the DDB Medical Authority, a panel of three respiratory physicians with specialist knowledge in occupational lung disease. The diagnostic process at the DDB has previously been described, and includes radiological investigation, lung function testing, clinical examination by a thoracic physician and a lifetime occupational history.<sup>13</sup> Computerized tomography (CT) scans had been conducted on all participants prior to study commencement.

People were excluded from the study if they had mesothelioma; discrete parietal pleural plaques as their only manifestation of dust exposure; cardiovascular, neurological or orthopedic conditions limiting exercise performance; were on long term oxygen therapy; could not understand English; or had participated in pulmonary rehabilitation within the last 12 months.



**Figure 2** Pulse rate response during the 6MWT. PR = pulse rate; bpm = beats per minute; Error bars = Standard error.

**Table 3 Mean difference in end exercise PR, dyspnoea and RPE between ICT and 6MWT**

Variable	ICT mean (SD)	6MWT mean (SD)	Mean difference (95%CI)	p
PR, b/min	122 (19)	100 (15)	21 (14 to 28)	<0.001
Dyspnoea, score	4 (2)	2 (2)	3 (2 to 4)	<0.001
RPE, score	5 (2)	1 (2)	4 (3 to 5)	<0.001

ICT = incremental cycle test; 6MWT = six-minute walk test; SD = standard deviation; CI = confidence interval; PR = pulse rate; b/min = beats per minute; RPE = rate of perceived exertion.

**Pulmonary function tests:** Participants performed pulmonary function tests of spirometry, lung volumes (body plethysmography) and single breath diffusing capacity for carbon monoxide (DLCO) (SensorMedics, Yorba Linda, CA). Tests were performed according to American Thoracic Society (ATS) guidelines and results expressed as a percentage of predicted values.<sup>14-16</sup> Maximal voluntary ventilation (MVV) was calculated as forced expiratory volume in one second (FEV1) multiplied by 40.<sup>17</sup> Forced vital capacity (FVC) and DLCO were the pulmonary function values used in the correlation analyses.

**Exercise testing:** Participants performed two 6MWTs (6MWT 1 and 6MWT 2) according to ATS guidelines<sup>18</sup> on a 32-metre oval track with tests separated by a minimum of 30 minutes. Throughout both tests standardized instructions and encouragement were given. Each minute pulse rate (PR) and oxygen saturation (SpO<sub>2</sub>) were measured (Radical<sup>™</sup>, Masimo Corporation, Irvine, CA) and dyspnea and rate of perceived exertion (RPE) scores ranging from 0–10 (0 was “nothing at all” and 10 was “maximal”) were recorded.<sup>19,20</sup> The better 6MWT was used for analysis.

On a second day of testing, participants performed a symptom-limited incremental cycle test (ICT) to peak work capacity on an electromagnetically-braked cycle ergometer (Lode BV, Groningen, The Netherlands). Following two minutes of rest and one minute of unloaded cycling, work rate was increased every minute by a predetermined amount, from 5 to 20 W.min<sup>-1</sup> according to the participant’s self-reported exercise capacity and disease severity so that the test was approximately 10 minutes duration.<sup>21</sup> Breath-by-breath values for oxygen uptake (VO<sub>2</sub>) and carbon dioxide output (VCO<sub>2</sub>) were obtained (Vmax Encore, SensorMedics, Yorba Linda, CA). Volume and gas calibration were performed prior to each test. Pulse rate and SpO<sub>2</sub> were simultaneously measured and dyspnoea and RPE scores were recorded each minute and at peak work rate. The test was ceased when the participant reached symptom-limited maximum. Results of the 6MWT and ICT were compared to predicted normal values.<sup>22,23</sup>

**Health-related quality of life (HRQoL):** Participants completed the St George’s Respiratory Questionnaire (SGRQ).<sup>24</sup> A priori, the “Activity” domain and “Total” score from the SGRQ were identified to examine against measures of exercise capacity.

**Physical activity:** Participants wore an activity monitor (SenseWear Pro3 Armband, BodyMedia, Pittsburgh, PA) for one-week when not attending exercise testing. Participants were instructed to wear the armband continuously, removing it only when showering or swimming. The activity monitor, worn on the right triceps, incorporated a biaxial accelerometer and sensors for skin temperature, heat flux, and galvanic skin resistance. Mean data on steps per day, the daily metabolic equivalents (METs) and energy expenditure were recorded. A minimum compliance of three days of wear with a daily compliance level

of 85% was specified for increased measurement accuracy.<sup>25</sup> If this level of compliance was not achieved, the data or day was excluded from analysis.

**Statistical analysis:** Statistical analysis was performed on PASW-Windows (release 18.0; PASW, Chicago, IL). Data are expressed as mean (SD) or (95% CI). A paired-sample t test was used to compare the distance walked in 6MWT 1 and 6MWT 2, and to compare dyspnea, PR and RPE achieved in the better 6MWT with those from the ICT. Relationships between variables were examined using Pearson’s correlation coefficients. The level of significance was set at a p-value of <0.05.

## Results

**Subjects:** Twenty-eight male participants were assessed with 25 included in the study. The reasons for non-inclusion of three participants were pain affecting exercise performance (one), neurological impairment (one) and a significant degree of emphysema (one). Mean anthropometric data and pulmonary function are shown in Table 1.

**Exercise capacity:** Participants demonstrated reduced functional exercise capacity measured by the 6MWT when compared to predicted values<sup>22</sup> (Table 2). Participants also demonstrated reduced peak work capacity. The subjective reasons for ceasing the ICT were dyspnoea in eight participants, leg fatigue in ten participants and combined dyspnoea and leg fatigue in seven participants.

**Health-related quality of life:** Participants demonstrated reduced levels of HRQoL across all domains of the SGRQ. Mean data are shown in Table 2.

**Repeatability of the six-minute walk test:** There was a significant mean difference between 6MWT 1 and 6MWT 2 of 13

**Table 4 Relationships between 6MWD or peak work rate and HRQoL scores, pulmonary function tests and measures of physical activity (r-values)**

Variable	ARPD n=25	
	6MWD	Peak work rate
FVC, % pred	0.52 <sup>†</sup>	0.59 <sup>†</sup>
D <sub>L</sub> CO, % pred	0.50 <sup>‡</sup>	0.64 <sup>*</sup>
Daily steps	0.38	0.24
Daily METs	0.45 <sup>‡</sup>	0.22
Daily energy expenditure	0.06	0.25
SGRQ Total	-0.57 <sup>†</sup>	-0.71 <sup>*</sup>
SGRQ Activity	-0.50 <sup>‡</sup>	-0.70 <sup>*</sup>

\*p <0.001, †p <0.01, ‡p <0.05.

ARPD = asbestos related pleural disease; n = number; 6MWD = six-minute walk distance; FVC = forced vital capacity; % pred = percentage of predicted value; D<sub>L</sub>CO = diffusing capacity for carbon monoxide; METs = metabolic equivalent; SGRQ = St George’s Respiratory Questionnaire.

metres (95% CI: 6 to 21) ( $p < 0.001$ ) with 80% of participants walking further on 6MWT 2.

**Responses during the better 6MWT:** In the better 6MWT, 44% of participants desaturated by  $\geq 4\%$ . There was a significantly greater desaturation during the 6MWT compared to the ICT, mean difference 3% (95% CI: 1 to 4), ( $p < 0.001$ ). The PR, RPE and dyspnea responses at the end of the 6MWT were significantly lower than at the end of the ICT (Table 3). The minute-by-minute SpO<sub>2</sub> and PR responses during the 6MWT are shown in Figures 1 and 2.

**Relationships between functional and peak exercise capacity:** There were significant positive correlations between 6MWD and peak work rate,  $r = 0.58$  ( $p = 0.002$ ) and between 6MWD and VO<sub>2</sub> peak (ml/kg/min),  $r = 0.53$  ( $p = 0.006$ ).

**Physical activity:** The activity monitor data was unavailable for two participants who did not wear it for the minimum three days due to skin irritation. Among remaining participants, the activity monitor was worn for a mean (SD) of 6 (1) days with a mean compliance of 98 (1)%. Physical activity data are presented in Table 2.

**Relationships of exercise capacity to lung function, physical activity and health-related quality of life:** The 6MWD was significantly correlated with pulmonary function, physical activity and HRQoL (Table 4).

## Discussion

This study examined the effects of ARPD on functional exercise capacity and HRQoL. The main findings were people with ARPD had reduced functional exercise capacity and HRQoL, despite only having pleural involvement. In addition, this study showed significant relationships of functional exercise capacity to peak exercise capacity, physical activity and HRQoL in people with ARPD. The relationships demonstrated that a lower 6MWD was significantly associated with a lower peak work rate, level of physical activity and HRQoL. Such findings have not been previously demonstrated.

Functional exercise capacity and peak exercise capacity were reduced compared to predicted values. At peak exercise, the limiting symptom was leg fatigue in 40% of participants and dyspnoea in 32% of participants. Leg fatigue at exercise levels below predicted peak may indicate peripheral deconditioning<sup>26</sup> whereas dyspnoea as the limiting symptom may be attributable to decreased chest wall compliance caused by diffuse pleural thickening.<sup>5</sup> These findings differ from a study in people with idiopathic pulmonary fibrosis (IPF), which reported that 35% of participants stopped exercise due to leg fatigue and 65% due to dyspnea.<sup>27</sup> This difference is likely due to greater disease severity in the IPF group compared to the people with ARPD, but also may be attributable to the slightly older age of our participants. The higher prevalence of leg fatigue may be associated with skeletal muscle changes attributable to aging,<sup>28</sup> resulting in greater peripheral deconditioning and earlier onset of leg fatigue.

Health-related quality of life was reduced in people with ARPD as measured by the SGRQ domains. Despite these reductions, people with ARPD had higher levels of HRQoL than reported in people with IPF<sup>29</sup> and COPD.<sup>30</sup> To our knowledge, this is the first study to demonstrate that people with ARPD experience reductions in HRQoL.

In people with ARPD we have demonstrated a moderate relationship between 6MWD and peak work rate, although weaker than relationships in COPD ( $r = 0.63$ ,  $p < 0.002$ ;  $r = 0.75$ ,  $p < 0.001$ ).<sup>31,32</sup> We have also demonstrated a moderate relationship between 6MWD and VO<sub>2</sub>peak (ml/kg/min), although weaker than in end-stage lung diseases ( $r = 0.73$ ,  $p < 0.001$ ).<sup>33</sup> This is likely due to the lesser disease severity in our participants. Despite this, the relationship between 6MWD and peak exercise capacity suggests that the 6MWT may be a useful surrogate measure of peak exercise capacity in people with ARPD when cardiopulmonary exercise testing is unavailable.

The 6MWT correlated moderately with the SGRQ Total score and the SGRQ Activity domain score, similar to relationships reported in COPD and interstitial lung disease.<sup>24,29</sup> This suggests the impact of ARPD on HRQoL may be reflected by the SGRQ, a questionnaire originally designed for people with COPD.

Physical activity differs from exercise capacity. Higher levels of daily physical activity have health benefits for people with COPD<sup>34</sup> or coronary artery disease.<sup>35</sup> Conversely, reduced physical activity is related to increased morbidity and mortality in COPD.<sup>11</sup> In this study, the 6MWD correlated more strongly with daily METs than did peak work rate, demonstrating the 6MWD may better reflect daily physical activity than a peak exercise test. This is likely the consequence of daily activities being performed at sub-maximal levels of intensity, rather than maximal levels of intensity.<sup>18</sup> In the absence of activity monitors in the clinical setting, the 6MWT may be a useful surrogate measure of physical activity.

There was a significant increase in distance walked between the first and second 6MWT of 13 metres or 3%, a smaller increase than reported in COPD<sup>36</sup> and interstitial lung disease.<sup>9</sup> In COPD, two 6MWTs are recommended to obtain an accurate measure of functional exercise capacity. The small increase in distance walked in the second 6MWT in people with ARPD questions whether repeat testing is clinically important in this population. However, functional exercise capacity may be underestimated if a second test is not performed.

Participants demonstrated a greater arterial oxyhaemoglobin desaturation during the 6MWT compared to the ICT, similar to people with COPD, and related to the larger exercising muscle mass utilized during the 6MWT.<sup>31</sup> We have demonstrated a peak cycle test is not required to examine arterial oxyhaemoglobin desaturation in people with ARPD and the 6MWT may provide valuable and unique information on oxygen desaturation during exercise.

The development of ARPD is often characterized by a long latency period from exposure to dust to development of disease.<sup>37</sup> As a result, the mean age of participants was 71 years. With increasing age, the FEV<sub>1</sub>/FVC ratio is known to decrease and the FEV<sub>1</sub>/FVC ratio in our participants was within the range of predicted normal values for people of this age.<sup>14</sup>

This study has some limitations. No data were collected on the metabolic and ventilatory responses to the 6MWT so no direct comparisons can be made for these outcomes with the ICT. People on long term oxygen therapy were excluded so the findings of this study cannot be extrapolated to such patients. We did not exclude people if they had a smoking history as this would be unrepresentative of the patient population. Finally,

we did not have a group of healthy aged-matched controls upon which a statistical comparison could be made, however data were compared to previously published predicted values for functional and peak exercise capacity.

## Conclusions

This is the first investigation of the effect of ARPD on functional exercise capacity, demonstrating that this population has reduced functional exercise capacity measured by the 6MWT. This study has also established that people with ARPD have reduced HRQoL. Furthermore, we have shown the 6MWD correlated with peak exercise capacity, HRQoL and physical activity. The 6MWT would be a simple test to perform and integrate into clinical practice to determine functional exercise capacity in people with ARPD and may be a useful surrogate measure of peak exercise capacity and physical activity in the absence of cardiopulmonary exercise testing and activity monitors. With few treatment options available for people with ARPD, research is required to address whether the impairments of reduced exercise capacity and HRQoL are amenable to pulmonary rehabilitation.

## References

- 1 Becklake MR, Bagatin E, Neder JA: Asbestos-related diseases of the lungs and pleura: uses, trends and management over the last century.[erratum appears in *Int J Tuberc Lung Dis*. 2008 Jul;12(7):824]. *Int J Tuberc Lung Dis* 2007, 11(4):356–369.
- 2 Selikoff IJ: The occurrence of pleural calcification among asbestos insulation workers. *Ann N Y Acad Sci* 1965, 132(1):351–367.
- 3 McGavin CR, Sheers G: Diffuse pleural thickening in asbestos workers: disability and lung function abnormalities. *Thorax* 1984, 39(8):604–607.
- 4 Yates DH, Browne K, Stidolph PN, Neville E: Asbestos-related bilateral diffuse pleural thickening: natural history of radiographic and lung function abnormalities. *Am J Respir Crit Care Med* 1996, 153(1):301–306.
- 5 Picado C, Laporta D, Grassino A, Cosio M, Thibodeau M, Becklake MR: Mechanisms affecting exercise performance in subjects with asbestos-related pleural fibrosis. *Lung* 1987, 165(1):45–57.
- 6 Miller A, Bhuptani A, Sloane MF, Brown LK, Teirstein AS: Cardiorespiratory responses to incremental exercise in patients with asbestos-related pleural thickening and normal or slightly abnormal lung function. *Chest* 1993, 103(4):1045–1050.
- 7 Shih JF, Wilson JS, Broderick A, Watt JL, Galvin JR, Merchant JA, Schwartz DA: Asbestos-induced pleural fibrosis and impaired exercise physiology. *Chest* 1994, 105(5):1370–1376.
- 8 Stevens D, Elpern E, Sharma K, Szidon P, Ankin M, Kesten S: Comparison of hallway and treadmill six-minute walk tests. *Am J Respir Crit Care Med* 1999, 160(5 Pt 1):1540–1543.
- 9 Eaton T, Young P, Milne D, Wells AU: Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med* 2005, 171(10):1150–1157.
- 10 Ferrer M, Alonso J, Morera J, Marrades RM, Khalaf A, Aguar MC, Plaza V, Prieto L, Anto JM: Chronic obstructive pulmonary disease stage and health-related quality of life. The quality of life of chronic obstructive pulmonary disease study group. *Ann Intern Med* 1997, 127(12):1072–1079.
- 11 Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM: Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006, 61(9):772–778.
- 12 McGlone S, Venn A, Walters EH, Wood-Baker R: Physical activity, spirometry and quality-of-life in chronic obstructive pulmonary disease. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2006, 3(2):83–88.
- 13 Park EK, Hannaford-Turner KM, Hyland RA, Johnson AR, Yates DH: Asbestos-related occupational lung diseases in NSW, Australia and potential exposure of the general population. *Ind Health* 2008, 46(6):535–540.
- 14 Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999, 159(1):179–187.
- 15 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, european community for steel and coal. Official statement of the european respiratory society. *Eur Respir J Suppl* 1993, 16:5–40.
- 16 Crapo RO, Morris AH: Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981, 123(2):185–189.
- 17 Campbell SC: A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *J Occup Med* 1982, 24(7):531–533.
- 18 American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002, 166(1):111–117.
- 19 Burdon JG, Juniper EF, Killian KJ, Hargreave FE, Campbell EJ: The perception of breathlessness in asthma. *Am Rev Respir Dis* 1982, 126(5):825–828.
- 20 Borg GA: Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982, 14(5):377–381.
- 21 Roca J, Whipp BJ: Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS task force on standardization of clinical exercise testing. European respiratory society. *Eur Respir J* 1997, 10(11):2662–2689.
- 22 Jenkins S, Cecins N, Camarri B, Williams C, Thompson P, Eastwood P: Regression equations to predict 6-minute walk distance in middle-aged and elderly adults. *Physiother* 2009, 25(7):516–522.
- 23 Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N: Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985, 131(5):700–708.
- 24 Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. *Am Rev Respir Dis* 1992, 145(6):1321–1327.
- 25 Watz H, Waschki B, Meyer T, Magnussen H: Physical activity in patients with COPD. *Eur Respir J* 2009, 33(2):262–272.
- 26 Gosselink R, Troosters T, Decramer M: Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996, 153(3):976–980.
- 27 Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, Arizono S: Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest* 2005, 127(6):2028–2033.
- 28 Payton OD, Poland JL: Aging process. Implications for clinical practice. *Phys Ther* 1983, 63(1):41–48.
- 29 Chang JA, Curtis JR, Patrick DL, Raghu G: Assessment of health-related quality of life in patients with interstitial lung

- disease. *Chest* 1999, 116(5):1175–1182.
- 30 Spruit MA, Watkins ML, Edwards LD, Vestbo J, Calverley PM, Pinto-Plata V, Celli BR, Tal-Singer R, Wouters EF: Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort. *Respir Med* 2010, 104(6):849–857.
  - 31 Luxton N, Alison JA, Wu J, Mackey MG: Relationship between field walking tests and incremental cycle ergometry in COPD. *Respirology* 2008, 13(6):856–862.
  - 32 Hill K, Jenkins SC, Cecins N, Philippe DL, Hillman DR, Eastwood PR: Estimating maximum work rate during incremental cycle ergometry testing from six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2008, 89(9):1782–1787.
  - 33 Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L: The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. *Chest* 1995, 108(2):452–459.
  - 34 Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM: Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. *Am J Respir Crit Care Med* 2007, 175(5):458–463.
  - 35 Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, et al: Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity). *Circulation* 2003, 107(24):3109–3116.
  - 36 Sciruba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, Wise RA: Six-minute walk distance in chronic obstructive pulmonary disease: reproducibility and effect of walking course layout and length. *Am J Respir Crit Care Med* 2003, 167(11):1522–1527.
  - 37 American Thoracic Society: Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med* 2004, 170(6):691–715.
- Noninvasive Ventilation...continued from page 41*
- D'Empaire G, Alia, I, Anzueto A. Noninvasive positive pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004, 350: 2452-2460.
  - 21 Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med* 2006, 173:164-70.
  - 22 Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, Beltrame F, Navalesi P. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med* 2005, 33:2465-70.
  - 23 Luo H, Cheng P, Zhou R. Sequential BiPAP following invasive mechanical ventilation in COPD patients with hypercapnic respiratory failure. *Hunan Yi Ke Da Xue Xue Bao* 2001, 26:563-5.
  - 24 Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on outcome of mechanical ventilation. *Am J Respir Crit Care Med* 1997, 112:186-92.
  - 25 Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998, 158:489-93.
  - 26 Su CL, Chiang LL, Yang SH, Lin HI, Cheng KC, Huang YC, Wu CP. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter, randomized, controlled trial. *Respir Care*. 2012, 57: 204-10.
  - 27 Vaschetto R, Turucz E, Dellapiazza F, Guido S, Colombo D, Cammarota G, Della Corte F, Antonelli M, Navalesi P. Noninvasive ventilation after early extubation in patients recovering from hypoxemic acute respiratory failure: a single-centre feasibility study. *Intensive Care Med*. 2012, 38: 1599-606.
  - 28 Briel M, Bassler D, Wang AT, Guyatt GH, Montori VM. The dangers of stopping a trial too early. *J Bone Joint Surg Am*. 2012, 94: 56-60.



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