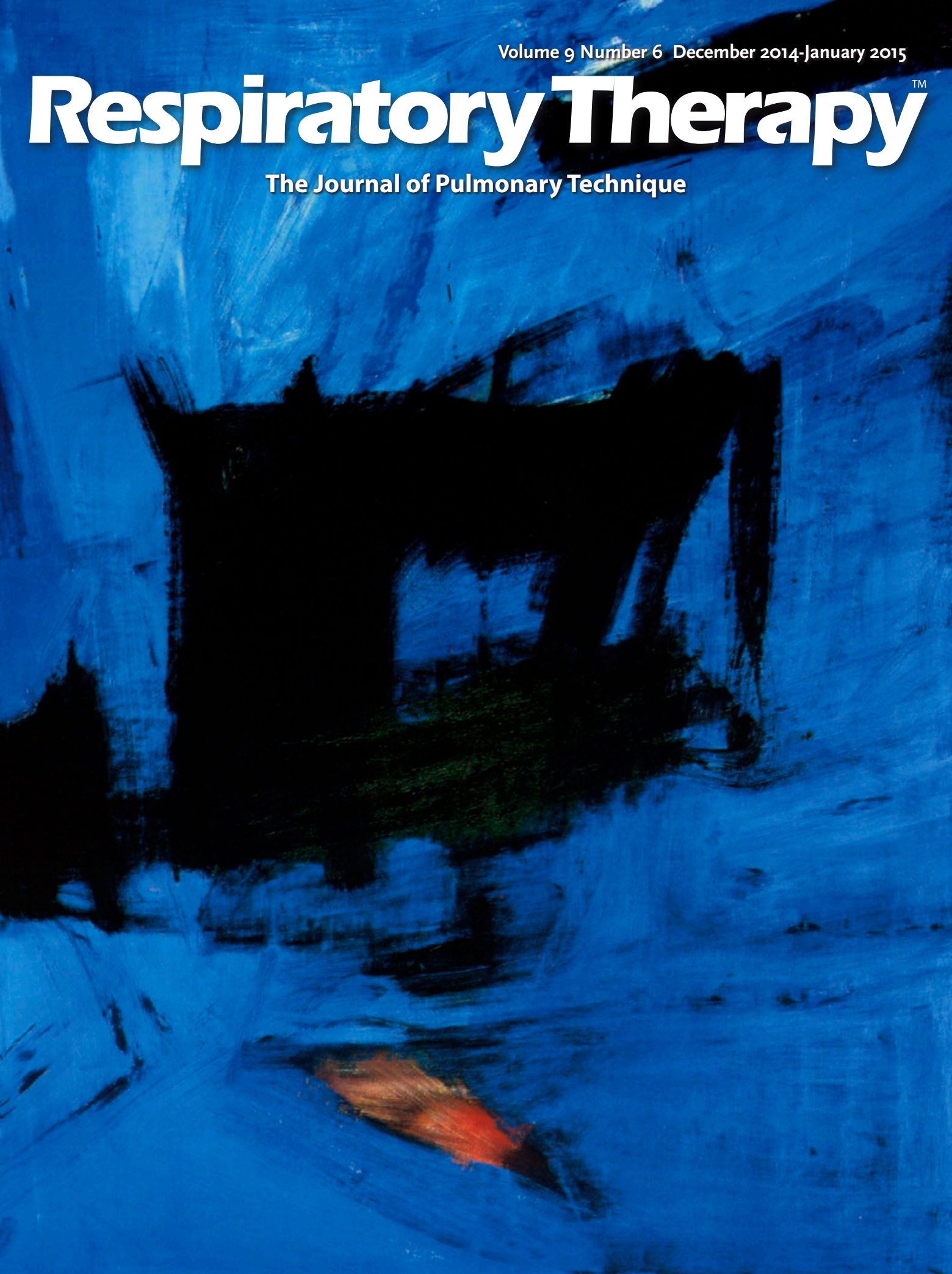


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The Journal of Pulmonary Technique





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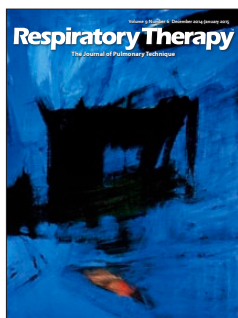


Table of Contents

DEPARTMENTS

- 7 Testing Percussive Nebulizer Flow
- 10 News
- 22 AARC Executive Previews
- 29 Interview

ARTICLES

- 30 Alarm Management and Patient Safety
- 32 Improving Endotracheal Tube Flows
- 36 Biphase Cuirass Ventilation Success Stories
- 40 Understanding Aerosol Delivery System Efficiency
- 42 Benefits of Helium-Oxygen Therapy
- 44 NIOV: A Breath of Fresh Air
- 45 Non-Pharmacological Management of COPD
- 53 Benefits of Physical Activity on Patients with COPD
- 60 Nitric Oxide Impacts on COPD

Editorial

What Counts

Paul Mathews, PhD, RRT, FCCM, FCCP, FAARC

Respiratory Care, like all health professions, exists to provide skilled, knowledgeable and compassionate care to patients and by extension to the families and others who are involved in the patient's life. Over the course of time our field has evolved from the mostly-on-the-job trained oxygen orderly of the 1940's and 1950's to today's Respiratory Therapists mostly holding college degrees at the Associates and more commonly now at the Bachelors and Masters degree level.

As our education and clinical expertise improved they did so with concurrent expansion of and improvements in both knowledge and technologic bases. Since the mid to late 1960's there has been a constant undercurrent of discontent as the desired education expectations for practitioners have increased. Those who argue that educational status is not "important" often site the OJT who is an outstanding caregiver. What they fail to reveal is the number of those OJT's meeting that criteria. No one will argue the point that some OJT's are, in fact, good or even superior caregivers. But the fact is those people are phasing out of the work force due to retirement or the effects of aging. Who will replace them? It will likely be RTs with Associates or Bachelors degrees.

From the days of the OJT (on the job trained for you youngsters) to the development in the 1960's of one, and then 2-year programs offering certificates of completion and Associate degrees, and now with the current growth in the number of 4-year Bachelor degree programs and Masters programs our educational system has matured and grown stronger in relation to those of nursing. Nursing education has run the gamut from the hospital-based programs to 2-year AS programs (ASN), BS (BSN) programs to graduate level Masters (MSN). Nursing has developed Doctoral Level programs (both clinical (Doctor of Nursing Practice—DNP and Academic PhD and EdD).

However, many of our fellow allied health professions have outstripped our accomplishments in this area. OT and PT have BS entry levels, Masters Degree programs and both academic (PhD) and Clinical Doctorate Programs (DOT and DPT). Many BS level RT programs are available both traditional on campuses and additionally many programs at this level are available as online programs. Additionally, Masters level programs of both types are also available.

When asked about these programs a large number of currently practicing RTs say that these programs are too expensive or too far away, or are too time consuming for them to become involved. Another commonly heard comment is that "I am a good RT, I know my stuff, I don't need to increase my educational level."

I would suggest that it is your duty as a health professional to be a lifelong learner. It is not enough to be a good (at least by self assessment) therapist. The 'good therapist' today runs the risk of being the one who just 'gets along' tomorrow. Lifelong learning is what professionals do. Why? Especially in the health care professions our clients (patients) depend on us to not only know how to "do" something, but also to know and understand why we are doing that procedure, what the expected effects are, what potential hazards are attached to the procedure and how the procedure reacts in light of the patient's disease process.

It is clear that the practice of Respiratory Care is becoming larger in both scope of
Continued on page 8...

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Can A Nebulizer Be Used To Deliver High Frequency High Flow Nasal Cannula ((Hf)₂Nc) Ventilation?

Mitchell Goldstein, Carter Tong, T Allen Merritt, Elba Fayard, Michael Terry, Michael Tiras, Ricardo Peverini

Introduction

The Vortran PercussiveNEB (P-NEB) is a compact, single patient, multiple use, disposable high frequency intrapulmonary percussive nebulizer intended for the clearance of endobronchial secretions in adult patients. According to the specification, "During exhalation the pneumatic capacitor and pulmonary modulator cycle to deliver high frequency (typically 11-30 Hz) pressure bursts to provide an effective intrapulmonary percussion treatment." According to the product user guide, "the high frequency pressure bursts are identical to those delivered by a high frequency ventilator." However, there are few studies to support whether this device could actually be used to provide high frequency ventilation. We demonstrated the potential for HFV using this device (Snowbird 2013), but noted that the PEEP levels produced might not support its use in situations where more pressure was required.

Objective

We asked if the P-NEB produced adequate flow to use as a (HF)₂NC device.

Methods

Wall flow was connected to the P-NEB according to specification. The P-NEB mouthpiece (outlet) was connected via an adapter in parallel with a Fleisch pneumotachograph connected to a Validyne Flow and Pressure transducers. Flow to the P-NEB was varied from 35 LPM to 50 LPM while the nebulizer pressure bias control was through 10 turns from minimal to maximal pressure. The exit port of the pneumotachograph was occluded to simulate a low compliance model in exhalation. Data was sampled at 1 kHz using Easy Sense for the IBM PC (Validyne). Pressure and Flow scalars were analyzed in Matlab R2012b (8.0.0.783) (The Mathworks, Inc.) using the Signal Processing Toolbox 6.18. Data was analyzed and plotted using Statistica 10 (StatSoft, Inc. (2011). STATISTICA (data analysis software system), version 10. www.statsoft.com).

Results

As shown below for the 50 LPM setting, successive changes in the bias flow (twists) produced log based pressure gradient increases in peak pressure ventilation. Concomitantly, increased twists produced an exponential fall in frequency with an increase in mean airway pressure. Up rise time (U_{riseT}) and down rise time (D_{riseT}) were characteristically different between flows.

The rate of rise of the waveform (U_{rate}) and the rate of fall of the waveform (D_{rate}) were similar across the two flows studied (see graphics).

Discussion

Although the measured range of mean airway pressure delivered is below where most high frequency ventilation occurs (see graphic), there may be application of this technology to nasal ventilation, especially during transport, given the small size of the device. At the same time, the higher than usual requisite flow rates may limit the usefulness of this technology in transport. A dampening effect is evident at the higher settings with respect to the peak pressures. This may be related to an internal dumping mechanism within the device to prevent excessive pressure delivery, although an improved test lung compliance may change the propagation at the higher end of the curve.

The frequency range measured extends below the manufacturer specification, which may in fact enhance the usefulness of the device. Although similar changes were noted with pressure and flow at entrainment of 35 LPM (below stated minimum flow), there were situations where a number of settings appeared flow starved.

Even at the higher end (50 LPM), there may not be enough flow entrainment for larger pediatric or adult patients. The amount of flow required may be a limitation to the perceived usefulness of the device.

Although the nebulization component of the P-Neb was not studied in this model, there may be alterations in parameters based on the simultaneous entrainment of water vapor. This can result in deeper or more thorough gas mixing and rapid CO₂ clearance. Turbulence from these entrained instantaneous high flow rates and pulsations may be responsible for augmented diffusion. Deep airway pulsation as well as an asynchronous filling of lung units may establish what is commonly known as the Pendeluft effect, with rapid emptying and equilibration of CO₂ across these areas of the lung where closely associated alveolar unit have unequal time constants. Direct bulk flow, Taylor dispersion, Pendeluft, Asymmetric velocity profiles, Cardiac mixing, and Molecular diffusion have been suggested as mechanisms which may be responsible for rapid CO₂ removal on high frequency ventilation and may also be applicable in this model. Optimal (HF)₂NC produced by the P-NEB may produce these same effects especially if optimal magnitude and amplitude matching is used, resulting in

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improved lung volume recruitment, improved oxygenation, and lower pCO₂ observed when supplemented by the infant's own spontaneous respiratory drive.

Pillow et al¹ has termed these frequencies as noise. Measurements of terminal airway resistance² in collapsed canine lungs during slow volume recruitment of terminal airways have been found to be governed by power-law distribution arising from vibratory changes associated with threshold phenomena propagating down a branching structure such as the airways.³ Application of variable respiratory rates and tidal volumes in porcine oleic acid model of lung injury has demonstrated improved oxygenation and compliance.⁴ Fetal lambs ventilated using a high frequency CPAP device had higher pH, paO₂, reduced alveolar protein, decreased paCO₂, and improved ventilation homogeneity.⁵

The P-NEB provides a vibratory component to the pressure waveforms superimposed on the desired mean CPAP setting set by the user that varies depending on gas flow, twists setting and compliance of the respiratory system. These vibratory pressure fluctuations, when superimposed on the infant's spontaneous respiratory rate may promote airway opening and lung volume recruitment resulting in improved gas exchange. In fact, there are discrete frequencies and mean airway pressures that appear to be associated with increased twists. This may improve gas exchange over continuous flow CPAP and produce a clinically significant reduction in paCO₂ in infants with Respiratory Distress Syndrome.

Similar to High Frequency Ventilation, application of a vibratory CPAP may be protective. The (HF)2NC produced by the P-NEB in the presence of non-homogenous lung expansion may recruit alveoli without marked pressure waveforms generation thereby protecting the lungs.⁶

Editorial...continued from page 4

practice (what we can do legally) and technologically (what "tools" we use to do those things). Both of these characteristics demand a work force that is not only multi-skilled, but one that is adept at learning and applying these new technologies.

The US Bureau of Labor Statistics (BLS) has predicted that between 2010 and 2020 the rate of growth for Respiratory Therapist jobs will increase by 28% or 31,200 jobs; double the average growth rate of all jobs. It makes sense that this increase in positions will require specialists and supervisor positions as has happened in past jobs growth surges. Employers, HR professional and RT department managers will likely do two things; hire (promote) from within the organization and try to select the persons with the most experience and education—those most likely to adapt, lead and learn efficiently and effectively.

The health care system and the patients who use that system demand and deserve the best, most knowledgeable caregivers. Most state licensure acts require that practitioners engage in Continuing Education (CE). Additionally, the National Board for Respiratory Care (NBRC) also has CE requirements in order to maintain NBRC Certification and Registration. Many of the State Licensing Boards accept college credits as meeting the CE requirements (see the licensing regulations/requirements for your state for specific information). For a listing of state requirements see the following web site (<http://bit.ly/1xLehjJ>).

Conclusion

1. The P-Neb produces a clinically meaningful vibration that may reduce CPAP failure.
2. Clinical studies continue to define the benefits of vibration in terms of reductions in paCO₂ and improvement in paO₂ when used as an alternative to continuous flow CPAP.
3. Although the undiscovered P-NEB may have value in providing high frequency ventilation in certain applications, it may not be powerful enough in all circumstances.
4. The ability to generate an oscillating flow signature may be useful in neonatal (HF)2NC.

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The costs of CE can, in part, be used to offset the cost of formal higher education. This results in at least a partial Buy One Get One (my granddaughter says that I should just type BOGO) situation. Many employers have tuition reimbursement policies to further offset costs. Going "back to school" should not be intimidating—the odds are good that many of your online and on campus fellow students are at least as old as you and were at least as hesitant to start taking classes again. Time and effort requirements will naturally vary but experience tells us that it gets easier and less time consuming over time—in fact you may even come to enjoy it.

The following quote provides some direction and a fore thinking philosophy for all health care professionals.

"What counts in life is not the mere fact that we have lived. It is what difference we have made in the lives of others that will determine the significance of the life we lead." — Nelson Mandela, 1953.

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News

■ December 2014-January 2015

Transport Ventilation for Neonates

Hamilton Medical has introduced a new item for the “most fragile patients” with the release of the HAMILTON-T1 with neonatal option — a high-end transport ventilator. Although not yet available in the US, during transport the HAMILTON-T1 delivers the same performance as a fully featured NICU ventilator at the bedside. Hamilton Medical says it supports tidal volumes of just 2 ml, and allows for effective, safe, and lung-protective ventilation for even the smallest preemies. The neonatal flow sensor accurately measures pressure, volume, and flow proximal to the patient. This guarantees the required sensitivity and response time, and prevents dead space ventilation. Therefore, the patient is better synchronized and the work of breathing (WOB) is reduced. The new neonatal expiratory valve can balance even the smallest differences in pressure and offers the neonate the possibility to breathe spontaneously in each phase of a controlled breathing cycle. In addition to all modern neonatal ventilation modes, the HAMILTON-T1 offers a new generation of nCPAP. In the new nCPAP-PC (pressure control) mode, you only define the desired CPAP target value for your patient and the ventilator automatically and continuously adapts the required flow to the patient's condition and possible leaks. Thanks to the demand flow technology, your patient will receive only as much flow as is necessary to obtain the set CPAP target. This reduces WOB, reduces the need for user interventions and ensures optimal leak compensation. You will also require less oxygen for transport and noise caused by the ventilator decreases distinctively. For mobility, the built-in high-performance turbine makes it independent of compressed air, gas cylinders or compressors. This saves weight and space and even noninvasively ventilated neonates can be transported over long distances. The combination of a built-in and an optional hot-swappable

battery provides a battery operation of more than 9 hours. This can be extended indefinitely with additional hot-swappable batteries.

FDA Approved

3B Medical, Inc. announced FDA 510(k) clearance of the BPAP 25A, adding this new member to their already innovative PAP therapy line-up. The BPAP 25A is full featured Auto Bi-level device, offering the latest features that help patients achieve better compliance and the Provider improve its bottom line. The BPAP 25A will come standard with advanced features like RESlex Exhalation Relief, a full range of Pressure Support, advanced clinical settings, and will integrate with 3B's innovative management system, iCodeConnect.

Duaklir Genuair Gets Positive Buzz

Almirall S.A. (ALM) announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) had issued a positive opinion for the regulatory approval of Duaklir Genuair (aclidinium bromide/formoterol fumarate) in all EU member states as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). Acclidinium bromide/formoterol fumarate is a fixed dose combination of two approved long-acting bronchodilators. Acclidinium bromide is a novel anticholinergic or long acting muscarinic antagonist (LAMA). Formoterol fumarate is a long-acting beta-agonist (LABA). As part of its assessment, CHMP reviewed efficacy and safety data of aclidinium bromide/formoterol fumarate BID from more than 2,000 patients. The clinical program included 11 clinical studies conducted in 29 countries worldwide. In the EU, the European Commission generally follows the recommendations of the CHMP (EMA) and delivers its final decision within three months after the CHMP recommendation. The decision



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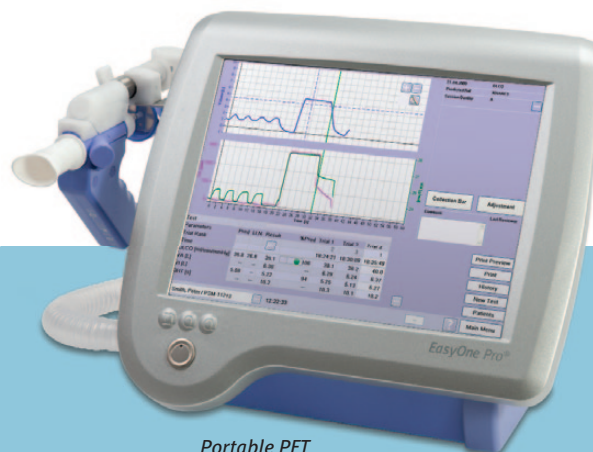
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will be applicable to all 28 EU member states plus Iceland and Norway. Acclidinium bromide/formoterol fumarate will be marketed in Europe by Almirall under the trade name Duaklir Genuair and Brimica Genuair.

Antimicrobials Prescribed Excessively

Nearly 60% of acute respiratory tract infection visits resulted in antimicrobial

prescriptions overall compared with an expected prescribing rate of 27.4%.

That's according to Matthew P. Kronman, MD, MSCE, of the University of Washington in Seattle, and colleagues, who conducted a meta-analysis of articles published between 2000 and 2012 on the microbial etiology of acute otitis media, sinusitis, bronchitis, upper respiratory infection and pharyngitis among previously healthy children.

They concluded that future interventions are needed to reduce ongoing unnecessary antimicrobial prescribing rates for these common childhood infections. Researchers used data from the National Ambulatory Medical Care Survey to determine national estimates for antimicrobial prescribing for acute respiratory tract infections.

Analysis included 12 studies on AOM, 34 articles on sinusitis, 15 articles on bronchitis and upper respiratory infections, and 11 articles on pharyngitis. Bacteria were isolated during 64.7% of AOM episodes.

Of these, *Streptococcus pneumoniae* was isolated in 44.1%, *Haemophilus influenzae* in 36.3%, *Moraxella catarrhalis* in 7.5% and *Streptococcus pyogenes* in 5.5%. Thirty-five percent of bacterial isolates from acute otitis media episodes required second-line therapy. Acute respiratory tract infections had an

average annual rate of 525 per 1,000 population and accounted for 27% of all ambulatory clinic visits to pediatricians and general or family practitioners. Sinusitis visits increased by 0.05% per year and upper respiratory infection visits decreased by 0.2% per year during the study period. Annual antimicrobial prescribing rate ranged from 51.5% to 61.6% among acute respiratory tract infection visits between 2000 and 2010. Average

annual antimicrobial prescribing rates were 88.8% for sinusitis, 85.9% for AOM, 71.5% for bronchitis, 56.9% for pharyngitis and 24.4% for upper respiratory infection. Researchers estimated 11.4 million preventable antimicrobial prescriptions for acute respiratory tract infections occurred each year. An average of 59% of acute respiratory tract infection visits received first-line therapy. Individually, 75.6% of upper respiratory infection visits received first-line therapy, 58.5% of pharyngitis visits, 55% of sinusitis visits, 46.2% of AOM visits and 28.5% of bronchitis visits.

BD Gobbles up CareFusion

BD and CareFusion announced a definitive agreement under which BD will acquire CareFusion for \$58.00 per share in cash and stock, or a total of \$12.2 billion, to create a global leader in medication management and patient safety solutions. The agreement has been unanimously approved by the Boards of both companies. The

combination of the two companies' complementary product portfolios will offer integrated medication management solutions and smart devices, from drug preparation in the pharmacy, to dispensing on the hospital floor, administration to the patient, and subsequent monitoring. The combination is hope to



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improve quality of patient care and reduce healthcare costs by addressing unmet needs in hospitals, hospital pharmacies and alternate sites of care to increase efficiencies, reduce medication administration errors and improve patient and healthcare worker safety.

EU to Breathe Easier

Breathe Technologies, a developer and manufacturer of innovative medical technologies for patients with respiratory insufficiency diseases and neuromuscular diseases, announced that it received CE Certification for its Non-Invasive Open Ventilation (NIOV) System, enabling the company to market and sell the device in the European Union. In addition, the NIOV System has been recognized by the European Respiratory Society with its Product of Outstanding Interest (POINT) Award for 2014. The Breathe NIOV System is the first and only wearable ventilation system for people with respiratory insufficiency to receive a CE Mark. The Breathe NIOV System provides augmented tidal volume, which reduces the work of breathing for people with respiratory insufficiency caused by chronic obstructive pulmonary disease (COPD), including Alpha-1 Antitrypsin Deficiency.

Air Cleared on Use of Mist

The FDA has approved a mist formulation of a medication aimed at chronic obstructive pulmonary disease (COPD), the drug's maker said. The tiotropium bromide inhalation spray—dubbed Spiriva Respimat—is indicated for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, Boehringer Ingelheim of Ingelheim, Germany, said in a statement. The mist formulation is expected to be commercially available in January, the company said. A dry powder version of tiotropium bromide (Spiriva HandiHaler) was already indicated to reduce exacerbations of COPD, but the mist version—which is dosed differently as well—had run into repeated concerns about the risk of mortality and cardiovascular events. Tiotropium is a long-acting anticholinergic agent that acts as a bronchodilator. The dry powder version has well-known side effects related to the anticholinergic effects, including dry mouth, constipation, and urinary retention. The most common side effects associated with the mist are sore throat, cough, dry mouth, and sinus infection, the company statement said. The HandiHaler uses a propellant, while the Respimat system delivers a liquid mist from a spring-loaded actuator.

Sedation Protocols Get New Application to Help

CareFusion announced the availability of a new capability on the CareFusion Respiratory Knowledge Portal to help clinicians improve patient care for ventilated patients. Appropriate use of sedatives in critically ill patients helps improve tolerance associated with invasive interventions, like mechanical ventilation, and also helps to decrease physiologic stress and improve patient care. However, maintaining deep sedation in critically ill patients is associated with increased duration of mechanical ventilation, increased ICU length of stay and increased brain dysfunction. The new Sedation Analytics application combines data from CareFusion mechanical ventilators and the company's Alaris System infusion pumps to identify variability from the ICU sedation protocol at the hospital. A key strategy for sedation optimization is the use of daily spontaneous awakening trials (SATs), also known as sedation vacations, which are planned interruptions to continuous sedative infusions. Spontaneous breathing trials, which happen during a sedation vacation, help clinicians

determine if the patient is ready to be weaned from the ventilator. The Sedation Analytics application can measure compliance with the hospital's protocols for sedation vacations and spontaneous breathing trials, and can detect increases in sedation over a specified limit. On average in the United States, a ventilated patient in an ICU bed for one day costs hospitals \$2,296. After the fourth day, the average daily cost of care for the ventilated patient goes up to \$3,917. In a typical 400-bed hospital with 40 critical care ventilators, these daily costs can add up to more than \$18 million per year. A 10 percent reduction in ventilator time for 15 percent of the most difficult-to-wean patients could result in an estimated \$700,000 in savings per year with significant potential for additional savings in the remaining 85 percent of patients. The CareFusion Respiratory Knowledge Portal is an analytics and reporting tool that enables hospitals to measure clinical and process variability in mechanical

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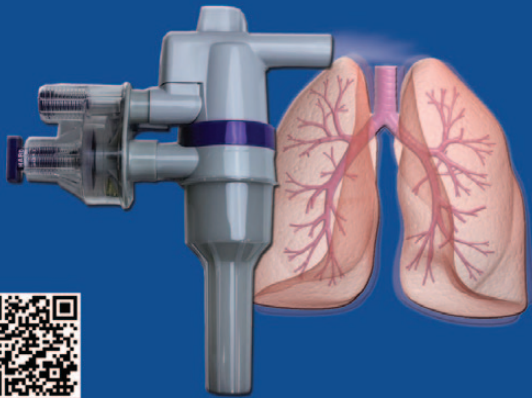



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ventilation by providing actionable information to help hospitals improve patient care. In addition to the new Sedation Analytics application, reporting capabilities include ventilator weaning analytics, lung protective strategies analytics, alarm policy compliance analytics and ventilator associated event surveillance.

Outcomes Improved

The Robarts Research Institute (Western University, London, ON) released a study demonstrating that, after 3 weeks of daily use, the Aerobika device provides statistically significant outcomes in patients with Chronic Obstructive Pulmonary Disease (COPD) and Bronchiectasis. The study evaluated patients' on Pulmonary Function Test, Six Minute Walk Test, the St. George's Respiratory Questionnaire (SGRQ), the Patient Evaluation Questionnaire (PEQ) and Hyperpolarized Helium-3 Magnetic Resonance Lung Imaging (3He MRI). Patients' improvements included increased mucus clearance, decreased cough frequency and breathlessness, and enhanced exercise tolerance. Additionally, the study revealed that patients reported an overall improvement in quality of life, without any adverse events reported while using the device. The Aerobika Oscillating Positive Expiratory Pressure (OPEP) device is a drug-free, easy to use, hand-held device with a proprietary pressure-oscillation dynamic that provides intermittent resistance and creates positive pressure and oscillations simultaneously, which mobilizes and assists mucociliary clearance to the upper airways where it can be coughed out.

Carescape Added to the Ventilator Landscape

GE Healthcare put its new innovations in Intensive Care

Medicine on display at the European Society of Intensive Care Medicine (ESICM) annual congress in Barcelona. Its new CARESCAPE R860 is an intuitive Critical Care ventilator, which uses advanced lung protection tools and an innovative user interface, to help improve patient care. About 24 percent of all patients mechanically ventilated will develop Ventilator Induced Lung Injury for reasons other than acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). GE supports scientific belief that a lung protection strategy can help ensure the different zones of lungs receive the treatment they need, thus potentially reducing these adverse events. The CARESCAPE R860 simplifies the use of advanced tools to tailor treatment for each patient by measuring patients' lung volume and potential lung recruitability, the ability of the lung alveoli to open, and titrating the appropriate positive end-expiratory pressure (PEEP) to allow better oxygenation. GE Healthcare is also sponsoring Life Priority, the public arm of European Society of Intensive Care Medicine (ESICM), to help raise awareness of the importance of Intensive Care medicine. This sponsorship involves support of its Wheels of Life truck, equipped as an ICU, which travels to strategic sites around Europe and offers free training in resuscitation to the general public and clinicians.

Mepolizumab Earns Good Press

GSK is highlighting results published in the New England Journal of Medicine (NEJM) and presented at the European Respiratory Society (ERS) congress, providing further data from the two pivotal Phase III asthma studies of mepolizumab, an investigational IL-5 antagonist monoclonal antibody:

- MENSEA – Mepolizumab as adjunctive therapy in patients with Severe Asthma

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• **SIRIUS – The SteroId ReductIon with MepolizUmab Study**
The objective of these studies was to evaluate the impact of mepolizumab on a number of key endpoints. Both studies met their primary endpoints, with patients receiving mepolizumab achieving a statistically significant reduction in the frequency of clinically significant asthma exacerbations compared to placebo in MENSA, and a statistically significant reduction of daily oral corticosteroid (OCS) dose during weeks 20-24 compared to the dose determined during the optimisation phase in SIRIUS. Treatment with mepolizumab also enabled patients in the studies to experience improved quality of life and improved asthma control as set out further below. Mepolizumab is not currently approved anywhere in the world. GSK is progressing towards global filings of mepolizumab for severe eosinophilic asthma by the end of 2014.

FDA has Finger on Pulse Oximetry

Nonin Medical, Inc., the inventor of finger pulse oximetry and a leader in noninvasive medical monitoring, announced that the Food and Drug Administration (FDA) has cleared the Nonin Model 3231 OEM/eHealth finger pulse oximeter for use in the United States. The finger pulse oximeter plugs into a telemedicine hub or kiosk through a USB connector and measures oxygen saturation and pulse rate in pediatric to adult patients. The Model 3231 received EU certification last year. The Model 3231 features accuracy advantages, including Nonin's clinically proven PureSAT Pulse Oximetry (SpO2) technology, which utilizes intelligent pulse-by-pulse filtering to provide precise oximetry measurements—even in the presence of motion, dark skin tones, low perfusion, rapid SpO2 changes and other challenging conditions. PureSAT automatically adjusts to each patient's condition to provide fast and reliable readings that clinicians can act on. Exclusive Nonin CorrectCheck technology, which provides feedback via a digital display if the patient's finger is not placed correctly in the device. CorrectCheck is helpful since improper finger placement may lead to incorrect readings. SmartPoint capture, an algorithm developed by Nonin that automatically determines when a high quality measurement is ready to be stored. This helps to ensure that each reading transmitted by the Model 3231 is accurate.

Combination Drug Therapy Best for Older Adults

New research says combination drug therapy aimed at opening the airways and reducing inflammation appears to be the best treatment for older adults with chronic obstructive pulmonary disease (COPD), especially those with asthma. COPD patients who received a combination of long-acting beta agonists and inhaled corticosteroids were less likely to die or require hospitalization because of their breathing disorder, compared to people receiving only one of the two medications, Canadian researchers report. The study findings were published in the *Journal of the American Medical Association*. The findings go against the official guidelines for treating COPD, but actually support what most chest physicians are doing in the clinic, said lead author Dr Andrea Gershon, a scientist with the Sunnybrook Health Sciences Center and the Institute for Clinical Evaluative Sciences in Toronto. Current treatment guidelines call for COPD patients to first receive a long-acting beta agonist, which relaxes the muscles of the airways and widens them, resulting in easier breathing. If that doesn't work, physicians then can add an inhaled corticosteroid, which reduces inflammation. Further, researchers found that the combination therapy did not compound a person's risk of side effects from either drug, most notably osteoporosis and pneumonia.

ResMed Introduces Astral Devices

ResMed has introduced the Astral 100 and Astral 150 devices in the United States. The Astral platform is ResMed's new generation of portable, lightweight, and user-friendly life support ventilators. ResMed's new Astral life support ventilators offer unparalleled mobility and ease of use for patients suffering from neuromuscular disease, chronic obstructive pulmonary disease (COPD), and other adult and childhood respiratory disorders. The U.S. launch comes on the heels of Astral's successful introduction to European and select Asia-Pacific markets earlier this year. Astral 100 and Astral 150 life support ventilators give freedom back to patients: they offer the best battery-to-weight ratio on the market with an eight-hour internal battery and a weight of only 7 lbs. Two optional eight-hour external batteries provide a total run-time of 24 hours. With this expanded mobility, chronically ill adult and pediatric patients who would otherwise be hospitalized can be safely treated away from the hospital for a more enriched life. Less time in the hospital can also mean reduced cost of care. The Astral 150 life support ventilator received the prestigious Red Dot Product Design Award for 2014. Red Dot is the world's largest design competition.

Roche Buys InterMune

Roche Holding announced it's buying U.S. biotech company InterMune for \$8.3 billion cash. The deal will give the Swiss pharmaceutical giant access to InterMune's innovative therapies in pulmonology and fibrotic diseases, expanding its respiratory treatments portfolio. InterMune's portfolio has "medical differentiation that fits very well with our pulmonary portfolio," Roche CEO Severin Schwan told CNBC. InterMune's standout treatment, pirfenidone, is expected to launch in the U.S. this year. The medicine treats idiopathic pulmonary fibrosis (IPF), which causes progressive scarring of the lungs leading to loss of function.

Study says Lung Flute Sounds Sweet

Patients with chronic obstructive pulmonary disease (COPD) report improved symptoms and health status when they use a hand-held respiratory device called the Lung Flute, according to a new study by the University at Buffalo. Usually caused by smoking, COPD, which includes chronic bronchitis and emphysema, is the third leading cause of death in the U.S. The Lung Flute, manufactured by Medical Acoustics, (Buffalo), uses sound waves to break up mucus in the lungs. The device allows patients to clear lung mucus simply by blowing into the hand-held respiratory device, which produces a low frequency acoustic wave. Published on Sept. 23 in *Clinical and Translational Medicine*, the 26-week study demonstrates that patients using the Lung Flute experience less difficulty breathing and less coughing and sputum production than a control group, which saw no change in COPD symptoms. The device is approved by the Food and Drug Administration (FDA) to treat COPD and other lung diseases characterized by retained secretions and congestion. It also is approved by FDA to obtain deep lung sputum samples for "laboratory analysis and pathologic examination."

Company Eyes Cancer Test

Veracyte, a molecular diagnostics company, announced an agreement to acquire Allegro Diagnostics Corp., a company that develops genomic tests for a preoperative diagnosis of lung-cancer, a decision that could allow it to enter the pulmonology market by 2015, with the launch of a new lung cancer test. Allegro's lung cancer test helps to assess which patients with

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lung nodules who have had a non-diagnostic bronchoscopy result have low risk to develop cancer and, therefore, can be monitored with CT scans instead of other invasive procedures. Allegro's lung cancer test, taken on cytology samples obtained from bronchoscopy, is able to detect molecular changes and the presence of malignancy in the respiratory airways that are correlated with disease. Veracyte's decision to acquire Allegro will allow the first to fulfill the plans of fastening its entrance on the pulmonology market, suggested Bonnie H. Anderson, president and chief executive officer through the company's released information, adding that Allegro test will enable the company not only to "improve care for patients with lung nodules," but also "to resolve diagnostic ambiguity preoperatively." This can be a way of avoiding more invasive procedures and also of reducing healthcare costs, Anderson explained.

AARC EXECUTIVE PREVIEWS

Covidien

Booth 442

What products will you be presenting at AARC?

Puritan Bennett 980 ventilator and the Nellcor Portable SpO₂ Patient Monitoring System.

Are there any new products you wish to emphasize?

Covidien is excited to share our latest solutions for enhancing patient care and safety at the American Association for Respiratory Care (AARC) Congress 2014. Covidien's featured innovations include the Puritan Bennett 980 ventilator and the Nellcor Portable SpO₂ Patient Monitoring System.

Puritan Bennett 980 ventilator: The new acute care ventilator from Covidien—designed to be simple, safe and smart—helps enable patients to breathe more naturally† through some of the most innovative breath technology available. For clinicians, one of the most critical goals is to get patients off mechanical ventilation as soon as possible. The Puritan Bennett 980 ventilator can help with a range of software capabilities, including Proportional Assist* Ventilation Plus (PAV*+) and Leak Sync software. Proportional Assist* Ventilation Plus (PAV*+) has been shown to help reduce asynchrony,¹⁻³ which studies have shown may reduce days on mechanical ventilation.⁴⁻⁶ The Puritan Bennett 980 ventilator system is designed for patients ranging from neonatal to adult. Patients on mechanical ventilation are often sedated to ease agitation and help them tolerate breath support and other medical interventions.⁷ The Puritan Bennett 980 ventilator features advanced synchrony tools that help clinicians set the ventilator to adapt to their patients' unique needs and help provide the appropriate level of support throughout the breath. The ventilator conducts hundreds of calculations every 5 milliseconds to stay in tune with patients' demands, helping to ensure that patients receive the flow and volume they want—when they want it—from breath to breath.

Nellcor Portable SpO₂ Patient Monitoring System: Part of a comprehensive Covidien respiratory function monitoring portfolio, this convenient, handheld patient monitor is simple to use and ideal for fast, accurate, motion-tolerant monitoring of pulse rate and blood oxygenation (SpO₂). The Nellcor Portable SpO₂ Patient Monitoring System's compact design and ability

to perform in challenging conditions make it an ideal tool for multiple critical clinical screenings including: Six Minute Walk Test, Critical Congenital Heart Disease Screening and Car Seat Challenge Test. The lightweight system is user-friendly and features a home care mode that expands the utility of the monitor beyond the hospital to home-use environments. With a simplified user interface, patients can clearly view their vital sign readings, and the settings cannot be easily altered by the patient, so clinicians can feel confident prescribing the home-use of this monitor. The system also features a sleep study mode that enables dimming the LCD display and silencing alarms to prevent disrupting patients' sleep. The monitoring system includes a vivid three-inch color LCD screen, as well as connectivity to analytics tools and patient management systems. It is compatible with the entire line of Nellcor sensors with OxiMax technology and offers a robust monitoring feature set including SpO₂, pulse rate, Nellcor SatSeconds alarm management, pleth waveform, blip bar and tabular trend information. The monitor incorporates Nellcor digital signal processing technology to deliver accurate, reliable SpO₂ and pulse rate values even during challenging conditions, such as patient motion, noise, signal interference and low perfusion, all of which can interfere with assessing a patient's respiratory status. †Compared to conventional volume control mechanical ventilation. * Proportional Assist and PAV are registered trademarks of The University of Manitoba, Canada. Used under license. **References** 1. Xirouchaki N, Kondili E, Vaporidi K, et al. Proportional assist ventilation with load-adjustable gain factors in critically ill patients: comparison with pressure support. *Intensive Care Med.* 2008;34(11):2026-2034. 2. Xirouchaki N, Kondili E, Klimathanaki M, Georgopoulos D. Is proportional-assist ventilation with load-adjustable gain factors a user-friendly mode? *Intensive Care Med.* 2009;35(9):1599-1603. 3. Costa R, Spinazzola G, Cipriani F, et al. A physiologic comparison of proportional assist ventilation with load-adjustable gain factors (PAV+) versus pressure support ventilation (PSV). *Intensive Care Med.* 2011;37(9):1494-1500. 4. 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. 5. 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. 6. Epstein SK. Optimizing patient-ventilator synchrony. *Semin Respir Crit Care Med.* 2001;22(2):137-152. 7. Siegel MD. Management of agitation in the intensive care unit. *Clin Chest Med.* 2003;24(4):713-725.

Draeger

Booth #606 and satellite booth outside academic hall

What products will you be presenting at AARC?

Adult Ventilation: Savina 300, Evita Infinity V500, Carina, Oxylog 3000plus; Neonatal Ventilation: Babylog VN500; Neonatal Transport: Globe-trotter GT5400 (New product announcement at show); Neonatal warming & resuscitation: Resuscitaire with AutoBreath; Monitoring: Infinity Acute Care System; Architectural products: GeminaDuo wall mount system; Accessories/Service: Disposable circuits, Filters/HME, disposable expiratory valves, and oxygen delivery devices; Elite Service Package Education: ICON, A Breath Ahead online portal for Respiratory Care.

Are there any new products you wish to emphasize?

The new Globe-Trotter GT5400 Neonatal incubator transport

system is the only product that has been certified according to international safety standards for land and air transport. The system includes essential functions such as thermoregulation, ventilation, intravenous infusion pumps and monitors.

Discuss educational/training materials you'll be offering.

Draeger will have A Breath Ahead, our interactive portal for the Respiratory Care community online at the booth. Visitors to our booth can view and interact with the site to learn about webinars, video interviews, articles and case studies presented by key opinion leaders. They will also learn how they can earn complimentary continuing respiratory care education (CRCE) credits. www.draeger.com/abreathahead Neonatal Care Today is an educational conference designed exclusively for respiratory therapists and nurses caring for sick newborns. The 2015 conference agenda will be discussed and information handed out for our Columbus, OH event on April 10 and Boston on May 29. ICON representatives will be available at our booth to discuss their clinician support services and technologies to enhance patient care and safety. www.intensivecareonline.com.

Electromed

Booth 346

What products will you be presenting at AARC?

Electromed will present the SmartVest Airway Clearance System at AARC congress 2014. The SmartVest System uses high frequency chest wall oscillation (HFCWO), a proven clinical therapy prescribed for people with airway clearance needs. Clinical research shows HFCWO to be highly effective at clearing airways of excess mucus and helping reduce infections and hospitalizations that can result when impaired airway clearance is inadequately treated. The SmartVest System consists of an inflatable garment connected to a programmable air pulse generator. During therapy, the SmartVest garment inflates and deflates rapidly, administering high-speed "hugs" to the upper body. Gentle yet powerful "mini coughs" loosen, thin and propel mucus toward major airways, where it can be more readily coughed up or suctioned away.

Are there any new products you wish to emphasize?

Electromed recently introduced the next generation SmartVest System, model SQL. The SmartVest SQL was designed to stand apart from the competition with features that our patients and clinicians requested to improve therapy adherence. The SmartVest SQL was designed 25% smaller, 5dB quieter and 25% lighter than previous versions. In addition to being significantly smaller, quieter, and lighter, some of the features include a single-hose design for greater freedom of motion, patented Soft Start technology to better acclimate the patient to therapy and a programmable ramp option.

Why should AARC participants visit your display?

Participants will learn firsthand what makes the SmartVest System a preferred choice for HFCWO therapy through hands-on demonstration of the innovative SmartVest SQL System. In today's healthcare environment, there is a comprehensive focus to reduce hospital readmission penalties associated with the Affordable Care Act. Solutions like the SmartVest System help patients with impaired airway clearance improve bronchial drainage, reducing the likelihood of future lung infections and other health risks and complications. Electromed is the only HFCWO device company to earn Home Care Accreditation from

The Joint Commission, a symbol of quality and commitment to meeting performance standards for in-home patient therapy and service. We look forward to seeing you in Las Vegas!

Impact Instrumentation, Inc.

Booth 415

What products will you be presenting?

Impact Instrumentation, Inc. is a US-based manufacturer of world-class Portable Critical Care Ventilators, Portable and On-Board Aspirators, Specialty Mounting Systems and test equipment. The 731 Series of ventilators include Eagle II for hospital and MRI use, EMV+ for military and mass casualty use and the AEV for non-invasive mask CPAP ventilation. These vents are rugged, weigh less than 10 lbs., offer AC, SIMV (EMV+ and Eagle II only) and CPAP/BiPAP modes with automatic leak compensation, a simple intuitive user interface, reduced O2 consumption, a battery run time of 10+ hrs, built-in rapid charger and SpO2 and can be used on patients as small as 5 kg. The Eagle II ventilator is an ideal solution for intra-hospital transports as well as ER and ICU bedside ventilation. The Eagle II MRI ventilator can be used in MRI suites with magnets as large as 3 Tesla and can be placed as close as 2 meters (6.6 feet) to the magnet's bore opening. Available 12-foot patient circuits are designed to optimize performance in the MRI suite. Workhorse ventilators that have been on the market and serving the medical, transport, military and mass casualty community for many years include the 754 Eagle and the 73X ventilators.

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Why should AARC participants visit your display?

Impact has grown from a start-up company occupying a small office 38 years ago with 2 founding members to 3 large manufacturing facilities and over 160 employees in West Caldwell, New Jersey. Impact has had many significant product introductions over the years completely focused on the medical industry. Impact re-invests millions of dollars into research and development each year and has a commitment to continuous improvement in manufacturing and new product development. R & D is the largest investment for Impact. Impact offers both on-line and in person technical and clinical training for its products. Respiratory therapists employed by Impact as well as paramedics and nurses are principally responsible for on-site training at the customer's facility at no charge. On-line training is supported by video, Power Point and competency presentations. Impact's products can be found in hospitals, ambulances, stockpiles, ships and aircraft, fire and rescue services, and over 20 military services world-wide including the US, Israel, Singapore and Australia. Future ventilation products will continue to focus on ease-of-use, communication capabilities, built-in advanced technologies and clinical functional capabilities.

MGC Diagnostics

Booth 258

What products will you be presenting at AARC?

MGC Diagnostics will feature recent product developments and technology advancements, including systems for pulmonary function testing: Platinum Elite Plethysmograph and Ultima Series with Real Time Diffusion (RTD) MultiGas Technology which deliver clinically significant graphic data and immediate results; gas exchange systems: Ultima Series CPX and CardiO2 with integrated ECG and the CCM Express Indirect Calorimeter. Our latest version of BreezeSuite software incorporates the latest HIPAA-HITECH Security Safeguards to protect your patient's Identifiable Health Information and features BreezeSuite Web Review for test interpretation anywhere, anytime. We will also be showcasing the CPFS/D USB full function spirometer and ResMonPro FOT (Forced Oscillation Technique) which help to determine the degree of obstruction, expiratory flow limitation, heterogeneity, and bronchial reversibility with no forced maneuvers.

Are there any new products you wish to emphasize?

MGC Diagnostics will be displaying our latest technology and invite you to stop by our booth for a personal presentation on our newest innovative products which include the Sleep Virtual product line of sleep diagnostics acquisition devices.

Discuss educational/training materials you'll be offering.

Managing the MGC Diagnostics exhibit will be our best in class clinical, sales and support staff available to answer not only your product questions, but provide expert consultation for your clinical application and cardiorespiratory business needs.

What speakers or papers will you be featuring?

We will be hosting Gregg Ruppel, MD, RRT, RPFT, FAARC in our booth on December 10 from 10am-3pm. Gregg Ruppel is an Adjunct Professor in Pulmonary, Critical Care and Sleep Medicine. Gregg will be available to answer clinical questions regarding cardiopulmonary testing, applications and various diagnostics topics.

Why should AARC participants visit your display?

MGC Diagnostics delivers diagnostic solutions for detection, classification and management of cardiorespiratory patients worldwide. This singular focus guides our strategy and defines our commitment to customers, employees and shareholders. These attributes make us uniquely qualified to solve today's challenges and uncover solutions for tomorrow's opportunities.

Mercury Medical

Booth 716

What products will you be presenting at AARC?

The new endOclear catheter for cleaning ET tubes will be in the spotlight this year. Otherwise referred to as a "mucus shaver," its advantages are unsurpassed in the industry: reduces risk of infection, reduces patient's work of breathing, reduces the number of days on a ventilator as well as the length of stay in the ICU, all contributing to significantly reducing the overall total healthcare costs.

What other products will you be presenting?

Coupled with Flow-SafeII, Mercury Medical will be showing the brand new Flow-Safe II EZ CPAP & Nebulizer system with unparalleled advantages. Flow-Safe II EZ represents a major leap in product innovation and is the second runner up for the European Respiratory Society's Product of Outstanding Interest Award for 2013. Taking emergency care to a whole new level, Flow-Safe II EZ is the ONLY ONE disposable CPAP system on the market that delivers consistent CPAP pressure while providing an integrated nebulizer using only one oxygen source. Additionally, it has an on/off switch that controls the nebulizer only, not the CPAP pressure. CPAP pressure is still controlled by the flow meter. Compared with other systems that require two sources, Flow-Safe II EZ consumes less oxygen. Three mask sizes are available: large adult, small adult and child. Also being displayed is the next evolution of Neo-Tee with in-line adjustable PIP controller and override button for PIP pressures needed above 40 cm H₂O. It also incorporates the next generation of manometers with larger, easier to view numbers, particularly in dim NICU lighting conditions. It's the industry's first and ONLY ONE disposable Infant T-Piece Resuscitator with Built-In Pressure Relief and Color-Coded Manometer on the Tee. Mercury is the ONLY ONE company with three types of resuscitation systems: CPR, Hyperinflation and a T-Piece. Mercury will also be announcing a new Hyperinflation bag, NuFIO2. NuFIO2 incorporates an Adjustable Pressure Limiter (APL) and color-coded manometer for quickly identifying airway pressure. A variety of configurations will be available with and without expansion tubing—which will be applicable for transport and MRI. An exciting new addition to the adult CPR/ CPR-2 bag line will be a manometer integrated with timing light that blinks every 6 seconds (10 breaths a minute) indicating time to squeeze the bag to prevent stacking of breaths; and the manometer is critical to monitor pressure and prevent chances of aspiration. Economical, high-quality disposable CPR bags in a variety of configurations will also be exhibited along with the colormetric CO₂ line, including Neo-StatCO₂<Kg, the ONLY ONE CO₂ detector specifically designed for tiny babies with an expanded patient weight range of 0.25kg to 6kgs. The air-Qsp (Self-Pressurizing) complements the family of Masked Laryngeal Airways. The air-Qsp design is the ONLY ONE Masked Laryngeal Airway that prevents potential for overinflation. When delivering PPV, the increased airway pressure increases the pressure

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Odds of
Survival to
Discharge
Doubled¹

2x

Good Neuro
Outcomes
Doubled²

2x

Depth

Depth
2.3
in

Rate

Rate
101
cpm

Release

Release

¹ Bobrow BJ, et al. *Ann Emerg Med*. 2013 Jul;62(1):47–56.e1. Epub 2013 Mar 7.

² Davis, DP. A New Algorithm for CPR Training. Medcom Trainex CEU program. 2012.

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within the cuff creating a good seal, (consistently over 20 cm H₂O). Increase in cuff seal pressure occurs at the exact time you need it...during the upstroke of ventilation. Key advantages: Simpler, no inflation line or pilot balloon-eliminates the extra step of inflation and guesswork of adding air to the mask cuff; eliminates mask cuff over inflation; the removable color coded connector allows intubation through it using standard ET tubes. Mercury Medical will also be showing a new gauge design (0 -60 cm H₂O) for the ONLY ONE disposable NIFometer on the market.

Are there any new products that you wish to emphasize?

Mercury's new products mentioned previously (endOclear, Flow-Safe II EZ, Neo-Tee with in-line controller and override button, NuFIO₂ hyperinflation, Manometer with integrated timing light, Neo-StatCO₂<Kg, air-Qsp and NIFometer) all improve patient outcomes at an economical cost.

Discuss what educational/training materials you'll be offering.

Full product training will be provided at the booth by Mercury Medical Product Specialists. We will provide product information brochures, DVD's, wall charts/posters with specifications and offer free samples. The samples will be provided by fully trained sales representatives who will provide comprehensive product in-servicing at the attendees facilities.

What speakers or papers will your company be featuring?

Founder and Chief Medical Officer for endOclear, Brad Eugene Vazales, MD will be giving presentations at the Mercury booth on how endOclear cleans ET tubes. Please visit the Mercury booth for scheduled times.

Why should AARC participants visit your display?

Mercury is a leading manufacturer of respiratory products and is highlighting several key industry first disposable products that save money for the hospital and health facility and improve patient outcomes at the same time. Mercury is the ONLY ONE company that has introduced the product types mentioned previously: endOclear, Flow-Safe IIEZ, Neo-Tee with in-line controller and override button, NuFIO₂, Manometer with integrated timing light, Neo-StatCO₂<Kg, air-Qsp and NIFometer. It will be critically important for clinicians and their C- level team to learn about how endOclear has documented and "reproduced" savings with the McLaren hospital system and projects savings between \$7-8 million per year with their Process Improvement strategy to reduce ventilator days. Additionally, due to the changing NRP guidelines, it will be important for clinicians like RT Directors and NICU nurses to visit our display as they are actively looking for neonatal resuscitation devices that meet these NRP guideline requirements. For instance, the Neo-Tee offers more consistent inspiratory and expiratory pressure than other devices. It is affordable for use at every NICU, L&D and ED bedside. One of the latest requirements is that every NICU stock "size one" laryngeal mask for rescue airways. air-Q is the infant rescue airway solution for meeting this requirement. Furthermore, NRP recommends using a colormetric CO₂ on the supraglottic airway connector to ensure proper placement with rapid color change. Mercury provides the ONLY ONE disposable CO₂ detector solution for premature infants below 1 kg with the Neo-StatCO₂. Clinicians should visit our display to get a first-hand view of our products and advantages.

Michigan Instruments

Booth 254

What products will you be presenting at AARC?

We will be presenting our full line of lung simulation equipment, including the Training & Test Lung, the Breath Simulation Module, the PneuView3 software and all related accessories.

Are there any new products you wish to emphasize?

Our PneuView3 software, which was released in July of this year, will be featured in our booth. The PneuView3 software application calculates and displays real time, numerous respiratory parameters and waveforms. Data can also be exported for later review. While most training and test lungs on the market are built to perform a handful of simulations and are not fully to scale, the newly designed Michigan Lung and PneuView3 Software provide users with a further comprehensive simulation to improve respiratory products, calibrate ventilators, and ultimately deliver better care and treatments to patients. The combination of the new software application and improved product design brings significantly improved user capabilities and applications.

Discuss educational/training materials you will be offering.

The Training & Test Lung has been a staple of many classrooms since its release in the 1970s. The updated software (PneuView3, released in July of this year) has adapted this device to modern respiratory care practices. Anyone currently using a test lung of any kind should definitely stop by our booth to see how the PV3 System can revolutionize respiratory simulation in their department.

What speakers or papers will you be featuring?

Michigan Instruments will be staffing booth 254 with members of the PneuView3 development team. Each and every one of them is an expert on the PV3 software and modern respiratory simulation.

Why should AARC participants visit your display?

We have new lung simulators! Guests should stop by our booth to see cutting-edge simulation technology at work in their industry.

NDD Medical

Booth 232

What products will you be presenting at AARC?

We are very excited to be showcasing our entire line of products at AARC. Our EasyOne Plus spirometer is the #1 selling portable spirometer in the US. It is easy to use and powered by 2 AA batteries. The Easy on-PC spirometer uses the power of a PC, laptop or tablet to perform spirometry. It offers challenge testing, pediatric incentives and real time curves. The EasyOne Pro and EasyOne Pro LAB are the next generation in portable pulmonary function testing. Both devices leverage ndd's leading edge Ultrasonic TrueFlow technology, eliminating the problems associated with traditional methods of flow measurement. The Pro performs DLCO testing, spirometry and full lung volumes in just 20 minutes where the Pro LAB takes those capabilities one step further by performing multiple-breath nitrogen washout to

obtain complete lung volumes, FRC and LCI measurements with ease, accuracy and reliability. To learn more, visit www.nddmed.com.

Discuss educational/training materials you'll be offering.

As a market leader in spirometry we are always striving to educate our customers towards improving lung health and also prevention through early lung function testing. Through our social media outlets we provide educational pieces on lung disease, tips on spirometry testing, latest news in respiratory and much more. Follow us on Twitter at twitter.com/nddMedical for updates. We also offer visual training through our YouTube channel. This great resource is for both new and existing customers. Viewers will learn how to prep and perform tests while also learning technical tidbits that will help provide the best possible care when utilizing our equipment. More information can be found at youtube.com/nddmed.

What speakers or papers will you be featuring?

On Wednesday, we will have a surprise pulmonary expert at the booth (#232). He will be available to answer any questions the participants have in regards to lung function.

Why should AARC participants visit your display?

ndd's booth will be filled with prizes, a surprise guest and lung function testing! Respiratory Therapists will have the chance to participate in a free live demonstration of the product of their choice. They will learn how to diagnose and treat lung disease earlier and with greater precision. It also gives them the chance to meet and speak with all the members of the ndd team.

NJR

Booth N/A

What products will you be presenting at AARC?

The No-Bite V, suction catheter introducer. BEST PRACTICE SOLUTION when nasal suctioning is contraindicated. Every RT is familiar with nasopharyngeal or nasotracheal suctioning and the many problems associated with inserting a suction catheter up a patient's nose. To name a few: bleeding, pain and trauma, coiling of suction catheter, MRSA colonization's in nares, and the list goes on... So basically with the No-Bite V, you can avoid all these problems by avoiding the nose altogether! It makes suctioning easy for not only the caregiver but also the patient.

Are there any new products you wish to emphasize?

The No-Bite V is newer but we already have a growing number of Top Hospital References! It has been out on the market for about 2.5 years and we have been very, very busy! It is now becoming popular worldwide. The RT community has been very excited about adding the No-Bite V to their toolbox.

Discuss educational/training materials you'll be offering.

At our booth we will be offering No-Bite V in-servicing on mannequin heads, everybody is welcome to practice the techniques in a return demonstration. Also, we always offer a free online No-Bite V training with an opportunity to earn 0.5 CERP credits on our website www.NJRMedical.com. Once you finish the online course, you can print out your certificate.

What speakers or papers will you be featuring?

We will have the inventor of the No-Bite V at our booth and assisting the in-servicing. Also we will have case studies

documenting the success of the No-Bite V in both the ICU environment as well as the Hospice and Palliative Care setting.

Why should AARC participants visit your display?

The No-Bite V suction catheter introducer makes RT's lives easier and that is why every RT needs to learn this product at our booth. It's not only easier for the RT, but also the patient.

Passy-Muir, Inc.

Booth 513

What new products will you be presenting at AARC?

Passy-Muir Inc. will be providing a new handout for the Ventilator Application of the Passy-Muir Valve which highlights important steps for ventilator application with volume control ventilation. Also available are the Patient Education Handouts which are tear off sheets for use at the bedside illustrating head and neck anatomy with tracheostomy placement and airflow with and without the Passy-Muir Valve. This handout also lists important clinical information and instructions about the Passy-Muir Valve including how the valve works, clinical benefits, application and troubleshooting, care and cleaning.

What new products will you be featuring that are of current importance?

The Pocket T.O.M. is a more portable pocket-sized version of our popular Tracheostomy T.O.M. Tracheostomy Teaching and Observation Model. The Pocket T.O.M. displays the same cutaway view of the upper aero-digestive tract and anatomy with tracheostomy, and can be easily taken to the bedside for patient education. It is great for spontaneous staff teaching as well. The Pocket T.O.M. includes model, cuffed tracheostomy tube, syringe, 3 Passy-Muir Valves, and simulated nasogastric tubing. It can be easily cleaned between patients.

Discuss educational/training materials you'll be promoting at the convention.

At AARC, the Ventilator Instructional Tracheostomy Observation (VITO) mannequin will be featured to demonstrate the ventilator application of the Passy-Muir Valve. This simulated ventilator demonstration will aid clinicians in understanding the important aspects of ventilator application and why early rehabilitation with the Passy-Muir Valve can result in a faster weaning process, a shorter length of stay and reduced costs. At Passy-Muir, Inc. education and clinical support for professionals and patients has always been of utmost importance. Our newest FREE web-based continuing education opportunities will be featured, along with the, pocket-sized quick reference guide.

What speakers or papers will your company be featuring?

Clinical specialist, Linda Dean, RRT will be presenting "What's In That Stoma? Demystifying Tracheostomy Tubes, Stents, Buttons, etc."

Why should AARC participants visit your display?

The Passy-Muir Tracheostomy and Ventilator Swallowing and Speaking Valve is the only closed position valve that restores more normal physiology, thus offering numerous clinical benefits beyond communication. A visit to the Passy-Muir, Inc. booth will provide the respiratory professional with contemporary evidence based research and education to improve care and reduce costs associated with tracheostomized and mechanically ventilated

patients. Respiratory care professionals are key players in helping to safely and effectively progress these patients to more cost effective levels of care. Clinicians will learn how early use of the Passy-Muir Valve can accelerate this process, thus reducing costs and improving quality of life. Our expert Clinical Specialists will answer questions and help provide the knowledge needed to advance outcomes of the tracheostomized patient.

Respiralogics

Booth 145

What products will you be presenting?

Respiralogics is a provider of innovative products for NICU, PICU, Adult Critical Care and special care units. We are dedicated to providing patients and health care providers exceptional products. Respiralogics will present the Babi.Plus Bubble CPAP System, Baby Line of nCPAP products, the Danny Ties trach ties and the Sil.Flex Stoma Pads and TC Pads.

What new products will you be presenting?

The complementary Baby Line of products for delivery of Bubble CPAP. Respiralogics' new baby line represents a major leap forward in the delivery and maintenance of nCPAP and non-invasive ventilation for infants in the NICU and PICU by providing comfortable, secure and skin-friendly fixation.

Baby Cap and Circuit Bumpers for the baby who Just Wants A Soft, Comfortable Cap. Baby Cap holds the nasal prongs and circuit in place with the Circuit Bumpers, providing optimal fixation for infants receiving nCPAP and NIV therapy.

Baby Nose Bumper and Mustache for the baby who Just Wants To Have A Pretty Nose after therapy is complete. The skin-friendly Baby Nose Bumper "mustache" is made of RespiraGel, Respiralogics' new hydrocolloid- based adhesive. Baby Nose Bumper gently holds the nasal interface to the mustache-area, providing a secure grip and gentle cushion for the nares.

Baby Chin Strap for the baby who Just Can't Keep Their Mouth Closed. Baby Chin Strap is a single patient use device intended to help keep small patients' mouths closed during delivery of nasal CPAP and NIV. Baby Chin Strap provides support with a soft, skin-friendly strap placed under the chin and secured to the Baby Cap with hook and loop tabs. Baby Chin Strap is a comfortable solution for mouth leaks.

What new products will you be featuring that are of current importance?

Bubble CPAP, a breathing assistance system, is showing promising results in decreasing the incidence of chronic lung disease among premature infants. CPAP is a breathing system commonly used in the NICU to deliver heated and humidified airflow and pressure to an infant's lungs via short nasal prongs in the nose that assists in keeping the infant's lungs open at end exhalation while allowing them to spontaneously breathe. Adding bubbles to the CPAP is proving to be of benefit in effectively treating these infants and allowing them to breathe on their own. The Babi.Plus Bubble nCPAP System was designed to provide a simple method for delivery of Bubble CPAP that will allow for focus on the infant and not the devices. The patent pending design delivers accuracy and stability throughout the course of therapy.

Danny Ties: Danny Ties are unique tracheostomy tube holders with a softer and more comfortable fit around the neck for patients of all ages. The patient with a tracheostomy needs to have a tube holder that securely holds the artificial airway in place to prevent accidental decannulation. As important, the tube holder needs to provide a soft, comfortable fit about the neck while minimizing skin irritation under the collar. Danny Ties are made of soft, absorbent cotton that lays smooth at the edges of the collar, minimize skin irritation and reduce skin breakdown under the collar. The patent pending design of the Danny Ties evenly distributes the quilted collar around the neck to minimize pressure points on the skin.

Sil.Flex Stoma Pads and TC Pads: The Sil.Flex TC Pad and Sil. Flex Stoma Pad are designed to cushion the area between the flange and the stoma site reducing movement and pressure at the site from the time of the procedure. The contoured surface of the Sil.Flex Pads provides a stable, comfortable interface between the flange and the patient's neck. Early use of the Sil.Flex Pads may assist in reducing irritation and tissue breakdown at the stoma site as well stabilize the tracheostomy tube. Use of the Sil. Flex Pads may decrease the air leak around the stoma site during trach weaning or during speech therapy by improving the seal between the pad the stoma.

Discuss educational/training materials you'll be promoting.

The strong clinical background of our staff and strategic partners serve you well in presentation of new concepts for delivery of patient care, exploration of your requirements to meet clinical needs and assistance with justification through the value analysis process. Most important, we are there to provide ongoing support for your team.

Stop by for a demonstration of Bubble CPAP to see how easy it is to implement a Bubble CPAP program in your NICU. Take the time to see our unique solutions and products that provide patients a better quality of life and clinician's new tools to deliver effective care, implement quality initiatives and improve patient outcomes.

Vortran Medical Technology

Booth 565

What products will you be presenting?

We will be showing our VAR (VORTRAN Automatic Resuscitator) PercussiveNEB, IPPB device, and our Airway Pressure Monitor.

What new products will you be presenting?

We are working on a new model of the VAR and should have one to show!

Why should AARC participants visit your display?

We always have studies and training videos available at our booth! And to see the world's only fully disposable ventilator!

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Daniel Davis, MD, Professor of Clinical Emergency Medicine, UC San Diego Medical Center.

Respiratory Therapy: Why have resuscitation outcomes basically stayed the same (not improved) over the years?

Daniel Davis: I believe the explanations are different for each of the past several decades. We actually experienced improvements in survival from out-of-hospital cardiac arrest from the 1980's to the 1990's with the advent of widespread AED use among first responding agencies. Those improvements disappeared during the 2000's as we began to emphasize ALS interventions (intubation, medications, rhythm analysis) that distracted from and interfered with basic chest compressions. The story of the last 10 years has come from new technology that has exposed our relatively poor resuscitation performance in and out of the hospital. This includes low-quality chest compressions, frequent interruptions, and widespread intra- and post-arrest hyperventilation. I believe we will see improvements over the next 10 years as we put it all together.

RT: What changes in resuscitation did you see as challenges for improving outcomes?

DD: Rather than identifying any changes in resuscitation, I would suggest that it was the lack of change that was the primary challenge in improving outcomes. Instead of a major breakthrough in our understanding of cardiac arrest, it has been the recognition that we simply need to optimize adherence with existing guidelines and recommendations. This has required a refocusing of attention on basic chest compressions. In addition, there appears to be a collective pessimism—even apathy—regarding cardiac arrest, which must be overcome before providers can be engaged to do the right thing.

RT: We heard about your ART program, what are the core principles of your program?

DD: ART would be best described as a system of care in that the program integrates multiple components of an institution, whether that is a hospital, an EMS agency, or a geographic network of prehospital and inpatient institutions. Training is adaptive in that it is customized to the institution, provider type, and practice environment. In its ideal form, ART relies heavily on performance improvement data to inform changes to the program, whether those changes involve modifications to training, new programs, optimization of treatment guidelines, or acquisition of new equipment. Ultimately, ART is outcomes driven, allowing an institution to do whatever is necessary to

decrease arrest incidence, improve survival, and better inform patients and family regarding end-of-life issues.

RT: What does the data show after implementation of your training program?

DD: The success of art in both reducing arrest incidence and improving survival has been uncannily consistent across multiple environments. We have seven years of data from UCSD, with a doubling of survival and a decrease in arrest incidence by 50%. Almost identical data have been provided by the va hospital in San Diego. Our air medical units have doubled survival and decreased arrests in the context of airway management, with improved intubation success and a decrease in peri-intubation desaturations. The most recent data from ground EMS agencies also document a doubling of survival and a dramatic improvement in CPR quality in less than a year following ART implementation.

RT: Does technology contribute to your program and improving outcomes?

DD: Technology plays an important role throughout the ART program. Performance improvement metrics incorporate data from defibrillators and other monitoring devices to better document resuscitation performance. Training uses advanced technology to provide resuscitation performance feedback and to allow providers to practice using the equipment that would be incorporated into actual clinical practice. Finally, technology is utilized to improve resuscitation outcomes and provide real-time feedback.

RT: What are the financial considerations for training and improving outcomes?

DD: ART allows such flexibility in determining institutional needs for training, that the cost of the program has been consistently less than traditional platforms. The real economic advantages of ART, however, come with the improved clinical outcomes. Whether you calculate the actual cost of unanticipated arrests, medicolegal costs, pay-for-performance/value-based purchasing metrics, or marketing advantages, there are real dollars behind reductions in preventable deaths. That is where the true value lies for integrated programs like ART.

Input on questions was provided by Gary Hochstetler of Zoll Medical. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

Alarm Management and Patient Safety: How Less is More

Erich Faust

An estimated 85 percent to 99 percent of alarms in health care facilities don't require clinical intervention. Because of this high percentage of insignificant alerts, clinicians often develop "alarm fatigue," which can result in their tuning out these notifications and missing the alarms that truly signal a patient's critical medical crisis.

Device manufacturers are making strides to create smarter alarm management systems by focusing on reducing clinically insignificant alarms while still detecting and reporting intervention-required alarms. But there is more work that needs to be done.

The Issue

A great deal of hospital-based patient care is delivered with the help of technology. Electrocardiograms (ECGs), continuous oxygen saturation monitors, and smart pumps use alarms to alert clinical staff of a current or impending issue. However, the many devices used on a single patient can produce hundreds of alarms daily.¹ As a result an entire hospital unit can be taken over by the constant ringing of thousands or even tens of thousands of daily alarms.²

Because many of these alarms are "false" and do not require care giver intervention, clinicians' response may be dulled to the numerous alarms—both the false alarms as well as potentially critical ones. Intelligent alarm management strategies need to be created and implemented to reduce the number of nuisance alarms while simultaneously identifying alarm conditions that require an intervention.

Smart Alarm Management

There are many factors that can trigger clinically-insignificant alarms. Some of the reasons include alarm thresholds set "too tight," default alarms not adjusted to individual patient needs, and sensors that are not correctly applied.^{1,3} Improving the accuracy of monitors can greatly reduce clinically insignificant alarms. Last, ensuring that all clinicians have a thorough, working knowledge of the use of patient-monitoring technology will improve the accuracy of monitors and reduce the likelihood that transient events will sound alarms.

Today, device manufacturers are creating technology to help prevent false alarms, such as Nellcor SatSeconds clinician-

controlled alarm management. The product differentiates between serious oxygen desaturations and minor transient events by taking into account both the depth and duration of a patient's desaturation. As a result, clinicians can evaluate brief desaturation events in context with their depth and shallow desaturations in context with their duration. This means that instead of having an alarm sound every time a patient's saturation value crosses the threshold, an alarm sounds only when a desaturation event is clinically significant to the patient's condition, based on settings designed by the clinician.⁴

Smart Capnography alarm management technology in the Covidien Smart Alarm for Respiratory Analysis algorithm (SARA) also recognizes and reduces clinically insignificant respiratory alarms, while accurately reflecting the patient's condition. This helps preserve clinician vigilance for significant alarms.

Clinical studies comparing SARA technology with existing alarm algorithms have shown that this technology creates alarms for all significant events recognized by the existing algorithm, provides a clearer indication of patient-ventilatory status changes and simultaneously lowers total alarms.^{5,6}

The reduction in alarms does not affect the accuracy of the output provided by SARA technology. In fact, SARA technology provides a more precise indication of patient ventilatory status changes, while responding to only clinically significant events.

In general, the smallest unstable respiratory pattern, such as snoring or periods of pain, can lead to alarms going off and disturbing a patient's sleep. A more selective and safe alarm system, like SARA, leads to fewer nighttime interruptions and improves patient compliance.

This evolution in alarm management will ease the alarm overload that leads to alarm fatigue, ultimately increasing clinical efficiency and improving patient safety.

Summary

Alarm fatigue is a serious issue that affects both caregivers and patients throughout the health care system. The need is evident for more intelligent alarm-management systems that reduce clinically insignificant alarms while simultaneously identifying alarm conditions that require an intervention. Device manufacturers have a responsibility to design patient monitoring solutions that can ease the burden of the thousands or even
Continued on page 34...

Erich Faust is the Director Respiratory Function, US, Patient Monitoring, Covidien.



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1. Wong, M et al. First National Survey of Patient Controlled Analgesia Practices. Physician-Patient Alliance for Health and Safety, 2013.

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Clearing the Way for Better Patient Outcomes

Chris Campbell

If you've ever grabbed a hose that's been sitting in the shed all winter for that first watering of the garden in spring, you know all too well how long it takes for the water to make its way past all the gunk stuck inside. The hose gurgles and rumbles, and the water comes out in fits and spurts before finally forming a smooth stream.

It's annoying getting it to flow properly.

Now imagine a patient attached to an endotracheal tube (ETT). The ETT wants to flow, but it's clogged with all sorts of biofilm and mucus debris clinging to the sides of it.

It's not annoying—it's damaging to a patient's body.

That's because this build-up increases four areas dangerous to a patient's health:

1. the risk of infection;
2. the work the patient has to do to breathe;
3. the number of days on a ventilator;
4. and the length of stay in an ICU.

What's needed is something that will clear that ETT quickly and efficiently.

According to researchers, the problem is that a common method used to clean ETTs—known as closed suction—just isn't effective enough in removing the residual biofilm and secretions from the tube walls.

A study by experts at Massachusetts General Hospital (1) had this to say: "Evidence suggests that, even if periodically repeated during MV, standard suctioning is not efficient enough in order to preserve the ETTs original lumen size, and then its nominal function. Abrupt occlusion is rare, but can be life-threatening, potentially requiring emergent airway restoration. Endotracheal tube exchange may be required to ventilate and oxygenate the patient, a high-risk procedure in an emergency ICU setting. On the contrary, partial occlusion due to secretion accumulation is ubiquitous and recklessly snubbed, with an average estimated loss of intra-luminal ETT volume between 9% and 15% (4,5). The occlusion percentage increases the resistance to airflow within the ETT, thereby imposing additional work of breathing to critically ill patients. Moreover, pathogens-laden secretions stationed within the

tube may migrate and colonize the lower respiratory tract, causing pneumonia."

As a solution to the failings of closed suction, the MGH researchers studied the endOclear device on its patients.

What's endOclear?

According to the researchers, the "endOclear catheter is a novel medical device designed to clean the endotracheal tube without interrupting mechanical ventilation. Essentially, it consists of a flexible central tube and a smooth disc-shaped wiper at its distal end. In operation, the device is inserted into an ETT through a dedicated adapter, until touching the adjustable blue safety stop, therefore preventing over-insertion. The patient continues to be mechanically ventilated throughout the procedure thanks to the particular Y-shape of the adapter. The red safety toggle is then disengaged to allow subsequent active deployment of the distal end of the device. Firmly grasping the handle, the trigger is fired in order to deploy and expand the smooth wiper end. When activated, the distal cleaning apparatus shifts from a closed, to an open position. Once deployed, the wiper can firmly engage the inside walls of the endotracheal tube. The endOclear device is then pulled back out of the ETT, thereby removing secretions and biofilm from inside the lumen and placed inside the collection adapter which can be sent to the lab for analysis. Overall, the process of insertion, activation, and clearing of the ETT (distal to proximal end) requires 3 to 5 seconds."

Improved Outcomes

The MGH researchers concluded that the endOclear "was used effectively to remove ETT occlusions when standard methods to clean ETT had failed...In all cases, the use of the device was associated with a rapid improvement of the clinical condition of the critically ill patients, avoiding risky and otherwise inevitable reintubation."

A three-year retrospective study from 2011 to 2013 by researchers at McLaren Northern Michigan (2) also found positive results using a "mucus shaver clearing device" (endOclear) as opposed to closed suction—with improved patient outcomes and significant savings to the medical facility.

The study's results said this: "583 cases were reviewed during year one, 516 cases in year 2, and 662 cases in year three. Prior to the initiation of the endotracheal tube being cleared with the mucus shaver clearing device, ventilator days were 4.3, ICU LOS was 5.2, and hospital LOS was 9.7. After the initiation of the

Chris Campbell is with Respiratory Therapy.

REAL AND REPRODUCIBLE RESULTS FOR BETTER AIRWAY MANAGEMENT IN THE ICU

ETT biofilm and pathogen-laden secretions are damaging to a patient's body and potentially life threatening. Such buildup increases the risk of infection, work of breathing and may cause emergency airway restoration. All of which increases vent days, ICU days and total cost of care.

There is a quick, safe and cost-effective solution: endOclear®. This innovation is proven by clinical research.⁽¹⁾⁽²⁾ The endOclear patented wiper blade is designed to effectively clean ETT's. The process of cleaning the ETT takes a mere three to five seconds.

Partner with Mercury Medical in the endOclear PROCESS IMPROVEMENT PROGRAM. Hard dollar cost savings, reduced MV days and improvement in patient outcomes are guaranteed. Call Scott Horowitz at 800.237.6418, ext. 3023, to discuss this special program.



1. Removal of Endotracheal Tube Debris Obstructions by a Clearing Secretion Device, Massachusetts General Hospital, Cristina Miletto MD, Kevin Foley RRT, Lindsay Salerno RRT, Jenna Oleksak RRT, Riccardo Pinciroli MD, Jeremy Goverman MD, Lorenza Berra MD.

2. The Use of a Unique Mucus Shaver Clearing Device to Improve Ventilator Weaning, Linda Schofield RN PhD, Gary W. Saur MBA RRT, Jeffrey Washington MD, McLaren Northern Michigan.

mucus shaver clearing device, there was a decrease in average ventilator days by 1.1 days. ICU LOS decreased from 5.2 to 3.7 and the hospital LOS decreased from 9.3 to 8.0. Our VAP rate went from 1.2 to 0, and the first 6 months of 2013 there were zero ventilator-associated events (VAE). There was an estimated savings of \$1,962,532 with the addition of the mucus shaver clearing device to daily weaning trials.”

Where can the endOclear device be found?

The good news is that the endOclear device is now commercially available in the US, and will be supplied exclusively by Mercury Medical, which believes it is the answer to improving patient outcomes when it comes to cleaning ETTs. Mercury recently exhibited endOclear at the NTI meeting sponsored by the American Association of Critical Care in Denver and received an overwhelming response to the product’s capabilities and advantages. It will also be displayed at the AARC meeting held in Las Vegas.

Linda Schofield, RN, PhD, from McLaren Hospital testifies that endOclear delivers the goods for patients. “endOclear has proven to deliver tremendous clinical and economic value to McLaren system patients. Over the last two and a half years using endOclear, our system has reduced vent duration, ICU length of stay and total length of stay by over two days, at three different McLaren Hospital locations. This has translated into several millions of dollars of savings and a 30% improvement in our NHSN/CDC/CMS quality metrics. As results are reproducible and non-disruptive to current workflows, endOclear will be as part of a process improvement program, projected to save the McLaren system, \$7 to \$8 million per year.”

For more information, visit mercurymed.com.

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- 2 The Use of a Unique Mucus Shaver Clearing Device to Improve Ventilator Weaning, Linda Schofield, RN, PhD, Gary W Saur, MBA, RRT, Jeffrey Washington, MD, McLaren Northern Michigan.

Alarm Management...continued from page 30

tens of thousands of alarms clinicians encounter daily.¹ By creating solutions that reduce nuisance alarms while detecting intervention-required alarms, device manufacturers can help reduce the problem of alarm fatigue and help ensure patient safety.

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Biphasic Cuirass Ventilation Personal Perspectives

Gary Mefford RRT

A quiet paradigm shift related to care of patients needing cardio-pulmonary support is underway. Since shortly before the FDA cleared the United Hayek RTX Biphasic Cuirass Ventilator for use in the US a new and powerful narrative related to this unique clinical tool has been developing. This device and the cardio-pulmonary supportive interventions it provides patients have been cited frequently in the medical literature over the last 20 years. These data in the form of journal articles from around the world relate the benefits provided to many differing types of patients by the RTX and its predecessor the Hayek Oscillator (HO). The RTX and the HO function utilize the same physiologic principles known now as biphasic cuirass ventilation (BCV). Previously referred to as external high frequency chest wall oscillation (HFCWO) or occasionally mistakenly confused with negative pressure ventilation (NPV), BCV offers all of the advantages of NPV and then some. A true clinical game changer for many patients, BCV can provide several modes such as continuous negative extrathoracic pressure (CNEP), control ventilation, synchronized ventilation, and a secretion clearance treatment mode. The secretion clearance mode incorporates a timed high frequency chest wall oscillation to thin and mobilize secretions with an assist cough cycle that can be set to repeat in sequence per patient needs. All is applied via a cuirass interface that comes in 12 different sizes and can be customized to patients from 1-180 kg.

In this article rather than the standard presentation of the data a more personal picture will be drawn via a format that will present the personal stories generated by patients' individual experiences using BCV as well as testimonials, which have been provided to the distributor by enthusiastic family members of patients and clinicians that have benefited from BCV use.

Tyler

(This story took place just prior to the device used to provide BCV, the United Hayek RTX Ventilator, was cleared by the FDA. Prior to FDA clearance in the US the RTX had been used extensively in the UK where it is manufactured and hospitals worldwide.)

Midsummer in a small upstate New York town a young man was out playing golf. Nothing is so unusual about that except this young man had spent a good part of his life fighting the battles that a life with cystic fibrosis had placed before him.

His last pulmonary function test showed a FEV1 of only 33% of what would be predicted for someone his age and height. He constantly lived on the edge of losing his health and on this day out playing golf the damage to his lungs that has been done by chronic secretion retention, and reoccurring pneumonias become acutely clear as he developed severe right sided chest pain and acute shortness of breath on the golf course. Tyler was taken to the local hospital where staff were caring, but not specialized in caring for his unique mixture of symptoms. They identified that he had a severe right sided pneumothorax and they placed a chest tube. Considering Tyler's complicated illness and the acuity of his situation he was moved to a facility that had an adult Cystic Fibrosis care unit for more intensive medical management. The initial x-ray there revealed he still had a pneumothorax and that the chest tube that had been placed at the outlying facility was not evacuating the air that was trapped in his pleural space adequately. So the first chest tube was removed and a second larger one was placed. Two days later the chest tube number two that had replaced the original one was found to be intraparenchymal. The second chest tube was removed and another was placed. Tyler though still quite sick was fairly stable. After five days with the third chest tube and his chest x-ray showing his lung was reinflated well, his chest tube was changed to water seal. His x-ray following this change was unchanged so the chest tube was removed after twenty-four hours on water seal. Tyler continued in poor but stable condition through the following week at which time he developed sudden right sided chest pain and worsening respiratory distress. Chest x-ray showed a complete right sided pneumothorax and a fourth chest tube was put in place and Tyler stabilized. Three days later Tyler underwent a blood pleurodesis on the right. This procedure is done to help the visceral and parietal pleura adhere thus decreasing chances of the lung collapsing again. Three days following the blood pleurodesis the chest tube was moved to water seal to assess the lungs ability to remain inflated. All remained well on water seal so the chest tube was removed. The following day Tyler again experienced increased shortness of breath and chest pain and he was again experiencing a pneumothorax. At this point a Fuhrman catheter was placed in the right pleural space to allow air to evacuate and keep the lung inflated. Four days later, day twenty five of Tyler's hospitalization a Bleomycin pleurodesis and a video assisted thoracic surgery (VATS) with bleb resection were done in an attempt to eliminate the reoccurring pneumothoraces. Shortly thereafter a broncho-pleural fistula was noted near the area of resection. At this point AM blood gas on NIPPV pH 7.22, pCO₂ 72, pO₂ 51, HCO₃ 32. Tyler was subsequently unable to come off of NIPPV for more

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than a few minutes without severe increase in dyspnea and demonstrating an acute rise in PaCO₂. He became unable to take nutrition orally and less and less communicative due to having to keep the mask on at all times and the toxic rise in CO₂ levels when the mask was removed. Tyler was started on gastric tube feedings and hyperalimentation but his nutrition remained compromised since he could not take nutrition normally. He was unable to come off the mask NIPPV for any period of time and his white blood count was rising. On day 29 Tyler was counseled regarding the seriousness of his condition. He was also introduced to the concepts offered by BCV. He consented to give it a try. The medical team considered BCV for Tyler due to the following reasons:

- The Hayek RTX is an external respiratory assistance device that augments efforts in both phases of respiration (BiPhasic). It is NOT solely an NPV
- The RTX is capable of providing external chest wall oscillation to assist with secretion clearance and external cough assist
- He was having respiratory distress off of positive pressure support
- Tyler was having ineffective cough and sputum evacuation despite aggressive manual CPT and nebs
- The persistence of the pneumothorax and bronchopleural fistula with ineffective sputum evacuation was not being helped by positive pressure efforts
- No further surgical intervention was recommended due to tenuous nature of his condition

Since the RTX had not yet been cleared for use in the US, special FDA approval had to be granted. FDA, hospital IRB and administration were consulted and all cooperated to permit import of this non-FDA approved device from the UK for compassionate use for Tyler.

On day forty-one of Tyler's hospital course BCV was started. Settings selected were -32/6. Secretion clearance with cough assist was started. Tyler immediately felt it easier to breathe. He was able to communicate with his family and caregivers. By the next day he was off NIPPV, his chest X-ray showed improved aeration. His initial blood gas was a venous sample that showed 7.35/75/16/41. The following day another venous sample showed 7.41/64/43. On day forty-four the inspiratory pressure was increased to -35 to increase tidal volume somewhat. Tyler's use of BCV advanced gradually from continuous use for both support and secretion clearance to slowly decreasing durations of use. On day fifty-six the chest tube was removed and Tyler's lung stayed inflated. Seventy-three days after Tyler's admission to the hospital and thirty-two days following the start on BCV Tyler was discharged to home needing only low flow oxygen and no other pulmonary support. Tyler's story was a dramatic first success story of the many other near miraculous results that have been obtained by patients that have had the opportunity of using BCV as a clinical intervention here in the US since the RTX received FDA clearance.

Jada

My daughter, Jada is eight years old with Spinal Muscular Atrophy (SMA). Almost five years ago she was in the hospital with pneumonia. We were discharged at that time with a Trilogy ventilator. The Trilogy machine was not effective for her. Jada still experienced respiratory issues while using the Trilogy and it meant she had to wear a face mask. The mask would make her nose blister. We had to fight with that constantly until my

daughter's pulmonary doctor recommend we try BCV. What a great recommendation that turned out to be for us!

As a mother I will be the first to admit having the curraiss "shell" around my daughter's stomach was not something I was thrilled about, neither was my child. At the beginning of the initial start it was a life changing experience to go through as a family, but I have to commend the respiratory therapist (RT) that came to start us out. She spent endless hours helping my child adjust to the BCV. Yes, the RT caregiver would play cards, board games etc. to make my child feel comfortable while adjusting to the BCV. The RTs that see us regularly make my daughter feel more than just a "patient", my daughter calls RT Denise Fernandez her Best Friend! Never did I expect or imagine the sincere care they have shown over the years for my child. The care we receive from them with Hayek is remarkable. On several occasions we have had urgent questions about the operation of the machine, and all I have to do is call and it is taken care of. I love the fact I can get a person to assist!

While using the BCV Jada has been helped in numerous ways. Before she had BCV her muscles would normally fatigue in the afternoon. Since using BCV she is now able to raise her arms in the afternoon! The Trilogy just did not rest her muscles like BCV does. Another very important difference for our entire family I must mention is that my child has been able to stay out of the hospital since we switched to BCV! I truly believe using BCV has made a huge difference in my child's health care needs. — Jada's mom



Jada and Denise playing between uses of BCV.

Asthma Girl

The patient a 9-year-old female presented to the emergency department midday in respiratory distress. Pt was retracting with very minimal air movement. Pt started on 15mg continuous Albuterol. Pt was admitted into the PICU with minimal improvement and still on continuous Albuterol. HR is 170-180. RR upper 40's to low 50's. Breath sounds remain the same with minimal air movement. Chest Cuirass is ordered and placed on patient with CNEP -10. Continuous Albuterol remains. Within five minutes, work of breathing is decreased, RR 21-24, HR is 160, pt looks comfortable. In half an hour, vitals remain improved and patient remains comfortable and is sleeping. In an hour, air movement is significantly improved. On night shift, the chest cuirass is discontinued as patient is now much improved, alert, anxious, and irritable. By next afternoon patient is on Q3 Albuterol and sent to the general pediatric floor. I believe eventual interventions were avoided such as extensive use of

continuous Albuterol, Heliox, BiPap, and intubation. — Pediatric Clinical Supervisor, A Children's Hospital.

Sophia

My mother is very sick and she is going through so much. She has COPD and BCV has essentially helped her function. What I believe it did was it definitely improved her ability to breathe to the point where she was able to have her necessary surgery. BCV definitely improved her breathing. — Sophia's daughter

Janelle

Basically I was introduced to the cuirass machine during my regular admission to the hospital. I always had trouble getting off ventilator machines when they tried to wean me off with the CPAP. Hospital staff just talked to me about the cuirass machine and they said they are willing to try it if I was willing to, and I said ok. They said that "it is a new machine and they heard good things about it; so I said that I am willing to try it. Once they got it there, they started me using it. It was a little uncomfortable at first, and then I slowly got used to it and then it was not so bad. Then I got comfortable with it and I was able to get off of the regular ventilator, which was really good. I felt that my breathing has gotten better than it has ever been before. I feel that I have influenced other people with using the machine because now when they hear my story they want to try it too. My hospital admissions decreased ever since. Now I am using different modes. For example I use the secretion clearance mode on it and that helps me to bring the secretions up. Also other modes which is the continuous negative which also helps me out along with control mode. I feel a difference with it compared to me using BiPAP and other machines, and the regular ventilator that I used to use before. I feel a major difference and it gives me more freedom. I do not feel that I have to be stuck to a machine all day and I feel that I can move around. I can be on a trach collar for most part of the day, which I am, and for nighttime, I use the cuirass. I have freedom with it, which I feel good with. I just feel that if there is anybody who has trouble with breathing and they have trouble weaning they should really give BCV a try and see if that will work out for them. Just give it a try because you never know.

June

I do not know why it happened, but I have diaphragmatic paralysis and within a three month period I started from being little short of breath to not being able to finish a sentence. The paralysis caused part of my lung to collapse and everything they tried failed. They tried vest, the one that you put on and it vibrates and that did not work. My Pulmonary Function Tests (PFT's) were awful. I have been through round after round. I have been to neurosurgeons and neurologists and everywhere and nothing was helping and nobody could tell me why. I was back in pulmonary clinic and they wanted to operate and put pacemaker on my diaphragm and I was not ready for that so I decided to alter my life and live with it. When my doctor heard about BCV and the other doctor in with her said that she didn't know if it would be approved by insurance but she tried and it did. My respiratory therapist from Hayek/Personal Support Medical Supply came and set up the equipment. They showed me how it works and everything I needed to know. That night I wore it and I slept so sound and I got up the next day and I did more in a day then I was able to do in a week before. So what I do is I wear it at night and I am free do whatever I need to do during the day. It actually does make my lung inflate at night. I wear my oxygen too and between the two my oxygen levels come up and

I feel so much better. When the day goes on, of course the more I do the more I get tired, but if I get to that I just put BCV back on during the day. I am still not allowed to go back to work but I do so much more and I would not be able to talk normally like I do without it. Where I am from, the majority of doctors are not receptive to it yet and I appreciate my doctor for trying to find something to use that would help me. I do know very few people that have it in my area but I think it is a very beneficial, would be beneficial to a lot of people and less invasive. I am very thankful for it. The quality of life is what it is about.

Liam

What I think BCV has mostly improved for Liam is to remove CO2 from his body. That is in Liam's case where it has been most effective. It all started about a year and a half ago when Liam was in the hospital, and he was having problems with his CO2 levels. They were awfully high where he was becoming toxic. The hospital had one of these BCV machines there. They tried it on Liam and it began to do its job helping him to breathe and exhaling all this carbon dioxide. Since then he has been on this machine which he is generally on for twenty-two hours a day. Also it's been helpful with his chest secretion clearance and helps to mobilize any junk in his lungs and it helps to loosen it up and move it around. It helps him to cough. — Liam's mom

Grace

I am such a fan. My mother has been on antibiotics pretty much all the time. If she had seven day break it was a lot. The minute she would go off of them she would get pneumonia. My mother also had atelectasis and her last x-ray showed improvement since using BCV. Last time she was admitted to the hospital, they put her on Levaquin again, and took a chest x-ray thinking it was pneumonia, but due to BCV it wasn't. Sure enough it was UTI. With BCV it is a huge, massive improvement. We are talking months and months and months of pneumonia over and over again. She has not had pneumonia since June which is 5 months and for her that is amazing. The other thing is if she is really junky in the morning and she has a lot of congestion, before she was really struggling. We used to do neb treatments, breathing exercises, throw mucinex down her throat while trying to get it all out. It would take us all day to clear it. Now when we do the BCV treatment she gets all the secretions up. During the secretion clearance mode on the fourth cycle she is starting to cough and she gets it up and we suction it out of her. She is good for the rest of the day. I cannot say enough. It is helping her quality of life so much. She is just so weak that she could not get it out on her own. When people get weak like her they can't cough well on their own. BCV gave her the extra help that she needed and she is able to cough it up on her own. Also, I know that by using CNEP more often she got over a pneumonia that I could tell was just starting. Her nurse comes and checks her every Monday and she told us recently that her upper and lower lobes are congested and if it does not clear by tomorrow to take her to hospital, we did even more BCV therapy that's what helped clear up her lungs so we could keep her home. — Grace's Daughter

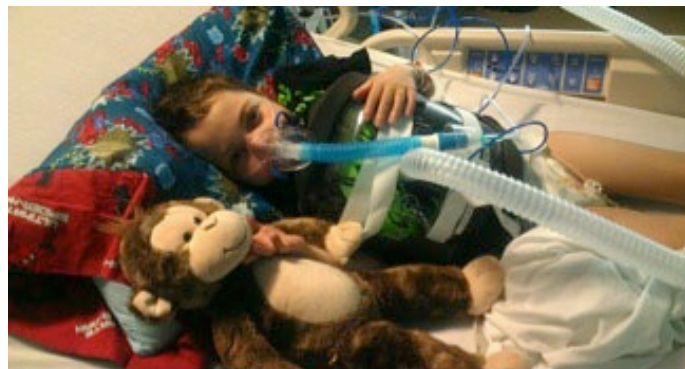
Marco

Some times as parents we do the impossible for our kids. When we think that all hope is gone something comes along to restore it...well our life had a 360 degree turn. As parents of three children (one girl and two boys) life hasn't been easy for us. Our two boys are nine years apart yet both have been diagnosed with SMA. With all of the challenges we face, we never stop for anything.

Well let me tell you a small story that most people won't believe until they hear it or see it. Our son Marco was diagnosed at age eighteen months and we were told he had four months to live. Years have passed and now he is thirteen years old. Life hasn't been easy for him. Marco would always have a hard time breathing and tired easily. He was under weight because he didn't have the strength to eat or do much else and has been wheelchair bound. Winters were very hard as Marco would always get pneumonias and RSV and Bronchiolitis. One day during an appointment with his pulmonologist we were told about the Biphasic Cuirass Ventilator. The more she explained, in my mind was the word HOPE. She asked if we were interested, and it was a big YES!!!! Soon after we got to meet our RT that brought the Hayek RTX BCV. As she explained to us the functions and purpose of the medical equipment our eyes and ears got amazed. It finally got to the time for our son to try it. Guess what!!!! After two hours of test using it and the shell was removed we noticed he had more strength. He didn't struggle to breathe as much and was able to bring phlegm on his own. This was my son's BIG BREAK in life. Finally after insurance approval we received one. Now let me tell you one thing; when we got the Cuirass Marco was hospitalized and almost ended with a ventilator. As soon as he began using BCV, Marco started to get out of his crisis faster than ever. It was an improvement from one day to the next. You may think it's just another medical equipment, but it is not. Children with SMA have a weak cough and fatiguing is very easy for them. Their lung function is very weak. For the past two years my son has only been hospitalized once thanks to the cuirass. He's able to last longer without getting tired and has more energy than ever and sleeps well at night. Most of all he's home and not at a hospital every other month. I wish to thank my son's pulmonologist and the team at Hayek. Thank you so much for introducing my family to the Cuirass. BCV has taken over of other equipment he has used and has never done the function it does on it's own. — Thank You from, Marco's Family

Scotty

Eight year old Scotty was all boy, but his life had always been a matter of stoically overcoming challenges to live life like any other boy since he had been diagnosed with Cystic Fibrosis shortly after birth. Scotty lungs had become severely packed with secretions and he had been placed in ICU. One of his lungs was hyperinflated and the other was very poorly aerated. Scotty was requiring NIPPV via mask around the clock. He was losing weight due to his not being able to eat because when the mask came off he became very short of breath and had to put it back on, and he was facing many other physical challenges. Scotty was accepted as a candidate for a lung transplant, but he needed to be stabilized enough to move from the hospital where he had originally been admitted to a transplant center. BCV was tried for Scotty due to the NIPPV seemingly only being able to expand the already expanded lung. It was also hoped that BCV would expand the atelectatic lung and allow him to eat and speak while supported. BCV also provided secretion clearance and assistance to his cough efforts. At first he was a little scared, but once he got started and began to feel the difference he told everyone how much he liked it. Some of the staff were uncertain that BCV would work. One of his doctors was heard to remark that he would not make it to the transplant center, that he was just too unstable with or without the cuirass. Shortly after BCV was started for him Scotty took a good nap. His nap ended right at the time his dinner tray arrived. He had not been needing the tray for some time as he could not eat with the mask on before.



Scotty's first day using BCV



Scotty's x-ray just before using BCV and the next morning after using all night. Images sent to the author by Scotty's father.



Scotty had put on eleven pounds after using BCV.

He was asked if he wanted to take the cuirass off to eat and he adamantly declined. On the tray was a large plate of one of Scotty's favorites, macaroni and cheese. While the cuirass ventilator cycled away on Scotty's chest he ate the first real meal he had had in days and consumed the full plate of mac n cheese. Within a week Scotty's improvement became more and more apparent. After a month on BCV he was able to get along by using BCV part time only most of the day rather than continuously. He also continued to use BCV for his secretion clearance sessions. By this point his

nutritional status had also improved and he had experienced significant weight gain. He was eating like a hungry boy should not via tube feedings only. A little over eight weeks after starting on the cuirass Scotty was safely moved to the transplant center where he continued to use BCV while awaiting his new lungs.

More studies on the benefits of BCV are coming to the medical literature all the time. This presents the stories behind the studies from a different perspective, that of those benefiting from this most natural form of pulmonary support. These patients, caregivers and patient's families will attest to why they say "BCV, it's just better."

Waste Not, Want Not, Part 1: Understanding Aerosol Delivery System Efficiency

Michael McPeck, RRT FAARC

Small volume medication nebulizer (SVN) technology has one major problem that is yet to be completely overcome: namely, it is very inefficient. Efficiency is often defined as Output / Input and represented as a percentage. With respect to nebulizers, fundamental nebulizer efficiency would concern the percentage of the loading dose (Initial Charge) that was emitted from the nebulizer (Output Aerosol) and not left behind in the device (Retained Charge). Chatburn and McPeck¹ have proposed a useful lexicon for aerosol delivery and its terminology and descriptions of aerosol delivery system efficiency are referenced throughout this paper.

Inefficiency typically occurs within the device itself, but may be compounded depending on the type of delivery system with which the SVN is coupled for aerosol drug delivery to the patient. Contemporary vibrating mesh nebulizers, on the other hand, are inherently efficient devices, but their cost and complexity renders them unsuitable for many situations where a less-expensive alternative ought to be used. Therefore, this 2-part paper addresses the inefficiency of plastic, disposable SVNs, explores the causes and offers a unique solution that allows the SVN to be used in a more efficient manner to conserve cost and retain the simplicity of pneumatic nebulizers with which most patients are already familiar.

Most common SVNs, including breath-enhanced and breath-actuated types, leave half or more of their Initial Charge behind in the device after it ceases to emit aerosol. This Retained Charge can be represented either as residual volume or, more importantly, as residual drug mass. Residual drug mass remaining in the nebulizer is essentially drug that was placed into the device for administration, but not administered, and therefore represents the first stage of SVN inefficiency, as shown in Figure 1.

It is frequently thought that Retained Charge of a nebulizer is merely a function of the inability of the device to completely aspirate fluid from the bottom of the nebulizer cup. In many cases the inability of the device to completely aspirate all the fluid contained in the bottom of the nebulizer cup is related to the design of the cup and/or the siphon tube or mechanism. For example, if the cup is not angled sharply, it may not allow liquid to collect in sufficient volume to meet the nebulization rate of the device. If the siphon tube orifice is not configured properly, or the tube or mechanism is not properly positioned

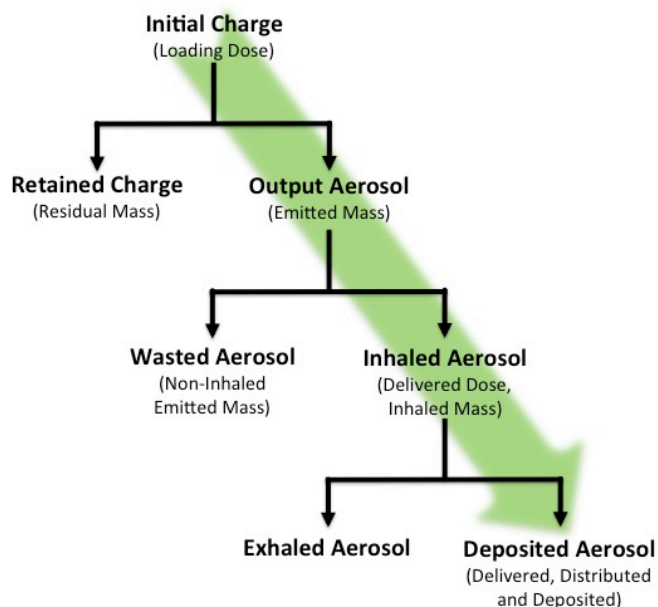


Figure 1. Basic nomenclature to describe the sequential stages of aerosol delivery. (Adapted from Ref. 1).

in the accumulated liquid, it may not aspirate efficiently. These issues may or may not be influenced by the effect of tilting the device away from its vertical center axis. Consequently, SVN manufacturers are well aware of this issue and strive to optimize device performance in this area.

While this is a part of the problem, it is not the entire problem. An oft-overlooked aspect of nebulizer performance is the contribution of the physical phenomenon of cohesion. Do not confuse cohesion with adhesion. Adhesion is defined as the tendency of dissimilar particles and/or substances to cling to each other. Glues, cement, mucilage and paste are examples of adhesives that allow dissimilar materials to bind together and resist separation.

Cohesion is strongly related to the phenomenon of surface tension. Surface tension is the property of the surface of a liquid that allows it to resist an external force. This property is caused by cohesion of similar molecules in the fluid and is responsible for many of the behaviors of liquids. Cohesive force is the action or property of like molecules sticking together and being mutually attractive. Surface tension keeps liquids from “spreading out.” Instead the liquid tries to form droplets as its

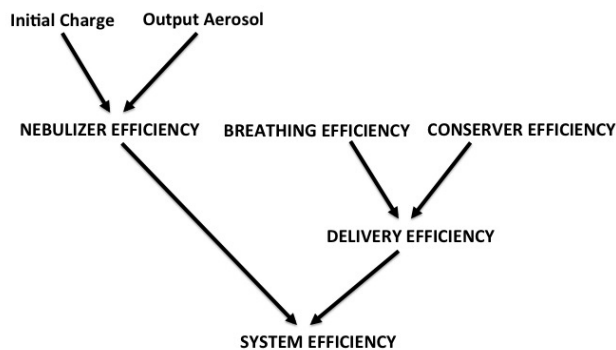


Figure 2. Schematic of the compound efficiencies that comprise the overall efficiency of an aerosol delivery system with small volume nebulizer. Conserver Efficiency can compensate for poor nebulizer efficiency and insufficient breathing efficiency to increase the overall System Efficiency. (Adapted from Ref. 1).

molecules are attracted to each other and its outer surface is pulled inward from all directions. It is surface tension, along with cohesion, that act together to create spherical or spheroid droplets of liquid, such as droplets of morning dew on the leaves of plants, or submicronic droplets of aerosolized medication emanating from a medication nebulizer.

Interestingly, it is also surface tension and cohesion that act together to cause even very large droplets of medication to stick to the inside surface of SVN. Droplets of this nature are anything but submicronic; they are typically very large, highly visible, and represent a substantial portion of the Initial Charge when summed with that portion of the Retained Charge that cannot be aspirated.

It may be underappreciated that physically larger nebulizers, like the tall “tower-type” devices, such as breath-actuated and breath-enhanced type devices, have much more internal surface area and therefore have a greater amount of Retained Charge than smaller, more compact devices such as the “acorn” type of nebulizers. These larger devices, such as the breath-actuated device as an example, obviously have a greater internal surface area on the inside of the nebulizer cup. But, in addition, they also have even greater internal surface area contributed by the surfaces of the internal mechanism that sits inside the nebulizer cup. All of this internal surface area contributes to an exceptionally large Retained Charge, often exceeding 60% or more of the Initial Charge placed into the device for treatment. That means that only 40% of the drug mass placed initially placed in the nebulizer will be emitted after nebulization. So, these devices are inherently inefficient by design.

When students of aerosol science are first presented with this issue, it is often suggested that the internal surface of the nebulizer cup be coated or treated with a surface-active substance that would repel liquid particles from cohering to it. Similarly, suggestions of adding surfactants, such as ethanol, to the medication, are frequently proposed. What these suggestions fail to take into account is that appending chemical additives to either the plastic surfaces or the medication itself would also change the surface active properties of the medication droplets that are formed by nebulization, likely rendering them too small to transport a significant amount of drug.

Fortunately, smaller, “acorn-type” SVN without the internal

triggering mechanism found in breath-actuated nebulizers, or the venturi air entrainment mechanisms found in breath-enhanced nebulizers, are inherently more efficient with respect to reduction of Retained Charge and enhancement of Output Aerosol. These devices have minimal internal surface area and are highly efficient, as plastic disposable SVN go. Because Retained Charge in the form of droplets on internal surfaces is minimized, largely due to the absence of a large area of internal surface, Output Aerosol frequently ranges between 50 and 60% of the Initial Charge. While this may seem, at first blush, to be insignificant, in the realm of SVN, it is quite meaningful.

The flip side of Nebulizer Efficiency, however, relates to what happens to the aerosol after it leaves the nebulizer. In actuality, there are a number of individual efficiencies that can be compounded to represent overall Treatment Efficiency, as shown in Figure 2. For example, as we have explored thus far, the interaction between the Initial Charge and the Output Aerosol results in the Retained Charge and leads to an understanding of the Nebulizer Efficiency, meaning just the efficiency of the nebulizer itself, independent of all other factors. However, for actual aerosol delivery to the airway opening to occur, Delivery Efficiency must be optimal. Delivery Efficiency, in turn, is dependent on the Breathing Efficiency of the patient as well as the Conserver Efficiency of the delivery system. The influence of any conserver, or reservoir, in the system will be discussed in greater detail in Part 2 of this paper.

What should be obvious at this stage is that plastic, disposable SVN, while economical to use, are not inherently efficient devices. And that some of the alleged design improvements vis à vis breath-actuation and breath-enhancement, actually diminish basic nebulizer performance due to excessive Retained Charge (elevated residual drug mass). Smaller devices are modestly more efficient due to smaller internal surface area and less Retained Charge thereby allowing greater Output Aerosol.

However, for maximum aerosol delivery, within the genre of the plastic, disposable SVN, greater Treatment Efficiency can be achieved by ensuring that a greater portion of the Output Aerosol is actually delivered to the patient. To accomplish that, the Conserver Efficiency must be increased. A unique way of accomplishing increased Conserver Efficiency will be discussed in Part 2 of this paper.

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The Benefits of Helium-Oxygen Therapy for Infants With Bronchiolitis

Chris Campbell

For many years, health professionals mainly relied on supportive care to deal with acute viral bronchiolitis in infants.

Many treatments had been studied, but in 2011 a team of researchers from Kentucky and Pennsylvania published some compelling evidence about the use of helium-oxygen therapy to greatly enhance the survival of infants with this deadly condition.

Acute viral bronchiolitis is the most common lower respiratory tract infection in the first year of life and represents a common cause of visits to the emergency department (ED) in the winter.¹ Despite recent advances in the treatment of patients with bronchiolitis, this disease continues to be associated with significant morbidity and mortality.²

An estimated 3% to 8% of hospitalized infants develop acute respiratory failure that requires mechanical ventilation.³ These findings highlight the continued need for new therapies targeting bronchiolitis.

Helium-oxygen inhalation is a re-emerging area of interest. It has been used in the treatment of pediatric asthma exacerbations and may also be effective for bronchiolitis.^{4,5}

Bronchiolitis is characterized by airway obstruction and turbulent gas flow, which may be improved by helium-oxygen because helium-oxygen improves gas flow through high-resistance airways.^{6,7} In contrast, many treatments for bronchiolitis have been studied, but there is a lack of evidence endorsing any specific treatment other than supportive care.⁸⁻¹⁰

The objective of the study—conducted between 2004 and 2008 at an urban children's hospital—was to conduct the largest controlled trial to date to evaluate the effectiveness of helium-oxygen compared with oxygen to deliver nebulized racemic epinephrine and as a component of inhalation therapy for infants with bronchiolitis. The study's designed hypothesized that infants with clinically significant bronchiolitis treated with helium-oxygen-driven nebulization followed by helium-oxygen inhalation therapy would have more clinical improvement, as assessed by clinical bronchiolitis score, than those who received conventional oxygen-driven nebulization followed by oxygen inhalation therapy.

The Patients

The patients in the study were infants aged 2 to 12 months with a Modified Wood's Clinical Asthma Score (M-WCAS) of 3 or higher.

Patients initially received nebulized albuterol treatment driven by 100% oxygen. Patients were randomized to the helium-oxygen or oxygen group and received nebulized racemic epinephrine via a face mask.

After nebulization, humidified helium-oxygen or oxygen was delivered by high-flow nasal cannula (HFNC). After 60 minutes of inhalation therapy, patients with an M-WCAS of 2 or higher received a second delivery of nebulized racemic epinephrine followed by helium-oxygen or oxygen delivered by HFNC.

Of 69 infants enrolled, 34 were randomized to the helium-oxygen group and 35 to the oxygen group. The mean change in M-WCAS from baseline to 240 minutes or emergency department discharge was 1.84 for the helium-oxygen group compared with 0.31 for the oxygen group ($P<.001$). The mean M-WCAS was significantly improved for the helium-oxygen group compared with the oxygen group at 60 minutes ($P=.005$), 120 minutes ($P<.001$), 180 minutes ($P<.001$), and 240 minutes ($P<.001$).

Comment

The researchers said that among a cohort of infants in the ED with bronchiolitis, treatment with helium-oxygen resulted in a “statistically significant reduction in M-WCAS and in RDAI scores compared with oxygen treatment at most time points. The helium-oxygen group scores decreased from baseline more than our pre-specified level of clinically significant change in M-WCAS (1.5) by 180 minutes and maintained that decrease at 240 minutes, whereas the oxygen group showed only a slight and irregular decrease during 240 minutes. At no point, however, was the difference between the 2 groups clinically significant.

“Interestingly, we observed both a statistical and clinical significance between groups using the respiratory distress assessment instrument (RDAI). One possible explanation for these contrasting findings between 2 different scoring systems is the difference in variables. The RDAI does not include pulse oximetry as a variable. In contrast, the M-WCAS includes pulse oximetry. Because most patients were receiving supplemental oxygen during the study with helium-oxygen or oxygen, this variable may have been less discriminating between the 2 groups. As a result, the RDAI may have been

Chris Campbell is with Respiratory Therapy.

able to differentiate a significant change in clinical scores more effectively than the M-WCAS.

“This study found that the administration of heliumoxygen-driven nebulized racemic epinephrine followed by helium-oxygen inhalation by HFNC to infants with bronchiolitis, early in their ED care, resulted in a substantial clinical improvement as indicated by 2 clinical scores. We did not observe a significant statistical difference in ‘readiness to discharge’ between the helium-oxygen and oxygen groups.”

The Future

The researchers also urged continued study of the subject: “Our small investigation demonstrated a statistically and clinically significant short-term improvement in clinical scores among a small group of patients with bronchiolitis compared with controls. These results will require confirmation with an expanded focus on masked short-term clinical outcomes, including ED length of stay, admission rates, and complications. Our findings suggest that helium-oxygen may serve a future role as an adjunct therapy for severe bronchiolitis. Future studies should focus on defining the role of helium-oxygen inhalation therapy in severe bronchiolitis and better determining optimal helium-oxygen mixtures, nasal continuous positive airway pressures, and delivery systems. From a practical consideration, patients with severe bronchiolitis are a challenging subset of patients to identify early and to study. Larger sample sizes may benefit future clinical trials.”

Study Authors

The study was designed, developed and written through the combined efforts of staff at the Department of Pediatrics, University of Louisville Medical Center, and Division of Pediatric Emergency Medicine, Kosair Children’s Hospital, Louisville, Kentucky (Drs Kim and Pendleton and Ms Sikes); Departments of Pediatrics (Drs Phrampus and Venkataraman and Mr Saville) and Medicine (Dr Corcoran), University of Pittsburgh Medical Center, and Divisions of Pediatric Emergency Medicine (Dr Phrampus), Pediatric Critical Care Medicine (Dr Venkataraman and Mr Saville), and Pulmonary, Allergy, and Critical Care (Dr Corcoran), Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania; and Department of Community and Preventive Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania (Dr Gracely).

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NIOV: A Breath of Fresh Air in a Stale Environment

Larry C Casey, MD, PhD, Keith Torgerud, RRT

The World Health Organization estimates that 65 million people worldwide have moderate to severe COPD. In 2005, more than 3 million people (5% of all deaths globally) died of COPD.¹ The National Heart, Lung and Blood Institute estimated that 24 million adults have COPD, half of them not even diagnosed.² COPD is the 3rd leading cause of death in the United States. Every four minutes, someone dies of COPD. In the US, more American women die of COPD than die of breast cancer + ovarian cancer + uterine cancer all added together.

Health care costs are skyrocketing. Approximately \$50 billion is spent each year directly or indirectly related to care for patients with COPD. A large percentage of the cost is likely related to hospitalizations, intensive care utilization, mechanical ventilation and end of life care. Efforts to reduce the utilization of high cost services are critical to the sustainability of affordable care.

Obviously, breathing is an important function. We take it for granted; unless you have COPD. The sensation of dyspnea is very very unpleasant. At some point in every healthcare providers training, an instructor has suggested to try breathing through a straw. In general, my guess is that you were able to breathe through the straw for about 15 seconds. After 15 seconds, the sensation, discomfort and increasing anxiety kicks in and you quickly take the straw out of your mouth. Go ahead and try it, but force yourself to continue for 1 minute. If you want to really challenge yourself, breathe through the straw for 2 minutes. That's 120 seconds. Now imagine living your life breathing through a straw. Not a very pleasant experience. In a survey conducted by EFFORTS, a non-profit patient support group, approximately 90% of patients with COPD thought about their condition every day and were limited in their ability to do routine household chores. More than 80% were limited in their ability to travel or participate in group activities. Almost 100% of patients with COPD want something that will improve their regular breathing and provide long lasting relief from their dyspnea.³

The non-invasive open ventilation (NIOV) system is FDA approved. The FDA description of the NIOV system is: "The Breathe Technologies Ventilator, with accessories, is a volume assist ventilator intended to aid adult patients with respiratory insufficiency. It is designed for patients who are capable of spontaneously breathing with minimum tidal volume of

3.5cc/kg of predicted body weight. The device is designed for continuous applications such as patient ambulation, physical therapy, occupational therapy, respiratory therapy, and other rehabilitation efforts in an institutional or home care environment. The device is intended for operation by trained personnel, patients, or caregivers under the direction of a physician."

The NIOV system increases tidal volume by providing positive pressure ventilation to patients, which significantly improves ventilation, reduces dyspnea, increases oxygenation, significantly enhances exercise endurance, and unloads respiratory muscle activity.

Compared to long term oxygen therapy, the NIOV System provides: 54% increase in exercise endurance; 28% reduction in Borg Dyspnea Scale; 46% reduction in accessory respiratory muscle activation; and increased and maintained oxygen saturation levels during exercise.⁴ Richard Casaburi, MD, PhD, Professor of Medicine and Associate Chief of Research at UCLA's David Geffen School of Medicine, has been quoted as saying "Our study indicates that the NIOV System dramatically prolongs exercise tolerance. The magnitude of this improvement is substantially greater than what we have observed with either bronchodilator or routine oxygen therapy."⁵

Patients using NIOV increase their exercise time by 213%, their 6 minute walk time by 73 meters and have a decrease in their Borg dyspnea score.⁶ NIOV has the potential to reduce hospitalization, ICU days, mechanical ventilation days resulting in substantial cost savings. My experience with using NIOV is that after a patient uses it once during the initial trial, they want to take it home and they don't want to give it up. With 30 years of academic Pulmonary Medicine, I've never seen such an immediate and profound impact on a patient's quality of life.

NIOV is FDA approved and is in use within the Veteran's Administration. Currently, not all insurance companies are providing coverage. Medicare assigned the NIOV system a code for a non-reimbursable oxygen tank regulator valve. In this era of accountability and affordable care, it is critically important that Medicare and Insurance Companies become accountable by providing appropriate payment and coverage for a device that not only improves quality of life but also drastically reduces the high cost associated with ER visits and hospital admission.

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Admission Prevention in COPD: Non-Pharmacological Management

Eui-Sik Suh, Swapna Mandal and Nicholas Hart

Abstract

Exacerbations of chronic obstructive pulmonary disease (COPD) are one of the commonest causes of hospital admission in Europe, Australasia, and North America. These adverse events have a large effect on the health status of the patients and impose a heavy burden on healthcare systems. While we acknowledge the contribution of pharmacotherapies to exacerbation prevention, our interpretation of the data is that exacerbations continue to be a major burden to individuals and healthcare systems, therefore, there remains great scope for other therapies to influence exacerbation frequency and preservation of quality of life. In this review, the benefits and limitations of pulmonary rehabilitation, non-invasive ventilation, smoking cessation, and long-term oxygen therapy are discussed. In addition, supported discharge, advanced care coordination, and telehealth programs to improve clinical outcome are reviewed as future directions for the management of COPD.

Financial and human cost

Management of chronic obstructive pulmonary disease (COPD) is a worldwide challenge. It has a prevalence of 1.5% in the UK [1] and 5.1% in the USA [2], while in China, which has about one-third of the world's smokers, the prevalence of COPD in patients aged over 40 years is estimated at 8.2% [3]. Current predictions estimate an annual COPD mortality rate in China of over 2 million by 2033 [4]. As expected, COPD imposes a substantial economic burden on healthcare systems. Data from the USA showed that in 1 year, COPD caused 1.5 million emergency department (ED) attendances, 726,000 hospitalizations, and 119,000 deaths [5]. Direct costs of COPD have been estimated at \$29.5 billion, with indirect costs of \$20.4 billion [6]. Studies in the UK have estimated an annual direct cost of treatment per patient of \$819 [7]. Given the heterogeneity of COPD, it is not surprising that acute exacerbations of COPD display a broad range of phenotypes, which can be categorized by their clinical, physiological, radiological, and etiological features [8]. These are discussed in detail in an earlier review on this subject in this journal [9]. Although exacerbation phenotyping can facilitate the targeting of treatments to individual patients, the severity of the exacerbation determines the urgency and location of treatment, and this pragmatic classification is in widespread use

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(Table 1) [10]. Up to 50% of exacerbations are mild and may go unreported, with 40 to 45% being classified moderate and less than 10% as severe [10].

Table 1 Classification of exacerbation severity [10]

Level	Description
Mild	An increase in respiratory symptoms that can be controlled by the patient with an increase in the usual medication
Moderate	Requires treatment with systemic steroids and/or antibiotics
Severe	Requires hospitalization or a visit to the ED

An acute exacerbation of COPD has detrimental effects on lung function [11-14], health-related quality of life (HRQL) [15-17] and exercise capacity [18]. Several studies have shown high mortality rates for patients with COPD who are hospitalized with an acute exacerbation [19-23]. The SUPPORT study reported an in-hospital mortality rate of 11% in patients with COPD admitted with hypercapnic respiratory failure, and 2-year mortality was 49% [23]. Soler-Cataluna et al. demonstrated, in a large Spanish cohort of patients with COPD, the relationship

Table 2 Predictors of early and late mortality in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (adapted from Singanayagam et al. [24])

Predictors of short-term mortality (up to 90 days after hospitalization)	Predictors of long-term mortality (up to 2 years after hospitalization)
Age	Age
Male sex	Low body mass index
Low body mass index	Cardiac failure
Cardiac failure	Diabetes mellitus
Chronic renal failure	Ischemic heart disease
Confusion	Malignancy
Long-term oxygen therapy	FEV ₁
Lower limb edema	Long-term oxygen therapy
GOLD stage 4 disease	P _a O ₂ on admission
Cor pulmonale	
Acidemia	
Raised plasma troponin level	

Abbreviations: GOLD Global Initiative for Obstructive Lung Disease, FEV₁ forced expiratory volume in 1 second, P_aO₂ partial pressure of oxygen in arterial blood.

between exacerbation frequency and mortality [19]. Whereas exacerbation-free patients had a survival rate of 80%, patients with three or more exacerbations per year had a 5-year survival rate of only 30%. A recent systematic review of 37 studies involving 189,772 hospitalized patients with COPD reported 12 factors (Table 2) associated with short-term mortality (90 days after hospital discharge) and 9 factors associated with long-term mortality (2 years after hospital discharge) (Table 2) [24].

Hospital admission and re-admission

Intolerable dyspnea is the major cause of hospital admission during an exacerbation of COPD [25]. This event is common, with hospitalization due to dyspnea accounting for one in eight hospital admissions in the UK and one in four admissions in Canada [26]. In the UK, such patients occupy a hospital bed for a median of 5 days [27], with a 20% re-admission rate within 28 days, and up to a third of patients re-admitted within 3 months [27,28]. These data differ from other parts of Europe and from the USA, where 30-day re-admission rate is estimated at 10.9% and 8.1%, respectively [29]. Despite these differences, this is clearly a burden to both healthcare systems and patients, and as of 2011, the UK National Health Service has limited the reimbursement to acute hospitals for patients who are re-admitted within 30 days. Similar key performance targets have been imposed in the USA [30]. Although inhaled and oral drug preparations play an important part in exacerbation prevention, the reduction with pharmacotherapy of severe exacerbations requiring hospitalization is limited. Non-pharmacological management therefore has an important role in the management both of patients with stable disease at risk of exacerbation and of those who are in the immediate recovery phase following an acute exacerbation.

Non-pharmacological management

Pulmonary rehabilitation

Physiological principles

Pulmonary rehabilitation (PR) is 'an evidence-based, multidisciplinary and comprehensive intervention for patients with COPD that is designed to reduce symptoms, optimize functional status, increase patient participation and reduce healthcare costs through stabilizing or reversing systemic manifestations of the disease' [31]. Exercise training is a major component of PR, and aims to modify skeletal muscle function to enhance exercise capacity [32,33]. Improved skeletal muscle performance and subsequent reduced lactate production throughout exercise enhances the relationship between respiratory muscle load and respiratory muscle capacity. This is achieved through modifications in breathing pattern, in the context of airflow limitation with optimization of pulmonary mechanics, which reduces exertion-related dyspnea, with a resultant improvement in exercise capacity leading to further improvement in skeletal muscle performance [34,35].

In addition to impaired exercise capacity and disuse in the stable state, several other mechanisms have been implicated in the muscle wasting and weakness associated with exacerbation [36]. Systemic inflammation, confirmed by an elevation in serum interleukin (IL)-6 and IL-8 levels during acute illness, has been shown to have an inverse relationship with quadriceps muscle strength [37]. In addition, oxidative stress is prominent in the peripheral skeletal muscle of patients during an acute exacerbation, which adversely affects mitochondrial function and the contractile properties of the skeletal muscle [38]. Furthermore, blood gas abnormalities affect skeletal muscle

function, with hypoxemia being associated with muscle weakness, inhibition of protein synthesis, and activation of proteolysis [39], while hypercapnic acidosis worsens skeletal muscle fatigability [40] and the endurance properties of the diaphragm [41]. Muscle wasting as a consequence of systemic corticosteroid treatment through the inhibition of protein synthesis, downregulation of the anabolic insulin-like growth factor-1 pathway, and activation of catabolic pathways, combined with appetite suppression and reduced dietary intake due to systemic inflammation during acute illness, drives the energy imbalance between supply and demand [42].

Although exercise training plays an important role in improving patient outcomes in COPD, other components contribute significantly to the benefits of PR. PR also addresses the nutritional deficits that are common in stable COPD and during acute exacerbations [43]. Low body mass index is associated with poor prognosis in patients with COPD [44], and caloric supplementation may help to maintain or restore body weight and fat mass, and ensure adequate protein intake. The patient education component of PR is aimed at self-management and enhanced autonomy, in order to encourage early self-identification and treatment of exacerbations. Education programs may also include breathing strategies to control dyspnea as well as bronchial hygiene techniques [43]. Psychosocial support may help to address the anxiety, depression, and other mental health problems that are often associated with chronic respiratory disease [45,46].

Pulmonary rehabilitation delivered in the post-acute exacerbation recovery stage

Although well established as part of chronic care in stable COPD [43,47], there is mounting evidence for the utility of PR in the early recovery period following an exacerbation [48]. Furthermore, data support the role of PR in preventing exacerbations and in reducing acute healthcare utilization, including unscheduled physician visits, ED attendances, and hospital admissions [49]. There are specific features of acute exacerbations that make them an important target for PR. Skeletal muscle dysfunction is evident, with a decline in quadriceps muscle strength of 5% between day 3 and 8 of hospital admission [37]. In the absence of any intervention, quadriceps force continues to decline for up to 3 months after hospital discharge [50]. Immobility and reduced physical activity are major contributors to muscle wasting and weakness, with hospitalized patients spending less than 10 minutes per day walking [51]. Furthermore, these patients remain inactive for up to 1 month after discharge compared with patients with stable COPD and similar disease severity.

Patients are at high risk of re-exacerbation and re-admission in the early recovery phase. Therefore, there is a potential role for an intervention in the post-exacerbation period after an acute episode to reduce the re-admission risk. A recent Cochrane systematic review of five randomized controlled trials (RCTs) of early PR post-acute exacerbation [48] concluded that there was a significant reduction in hospital admissions in patients enrolled in PR programs following an exacerbation (odds ratio 0.22, 95% confidence interval 0.08 to 0.58). More importantly, these data showed that only four patients need to receive PR in the post-acute phase in order to prevent one re-admission, with an overall reduction in mortality observed also (OR 0.28; CI 0.10 to 0.84). There were no serious adverse events in any of the five studies reviewed. Although Eaton et al. showed only a trend towards

a reduction in 90-day re-admission in the PR group compared with the usual care (UC) group (23% versus 32%, respectively), the adherence to the PR program was only 40% [52]. However, in the trial of Seymour et al., the effect of early outpatient PR on 3-month re-admission rate was investigated in patients enrolled within 1 week of hospital discharge [50]. The intervention group in this study received 16 exercise training sessions over a 3 month period rather than the standard PR approach of 2 sessions per week for 8 weeks. This ensured that the effect of the treatment was tested, whereas the results of the trial by Eaton et al. [52] were, in part, a consequence of the failure of delivery of the treatment rather than necessarily a failure of the treatment itself. In the Seymour study, re-admission rate at 3 months was lower in the early PR group compared with the UC group (7% versus 33%, respectively; $P=0.02$) [50]. Interestingly, Seymour et al. reported that the rate of ED attendances not requiring admission were similar between the two groups, but the rate of hospital attendance of any type was lower in the early PR group (27% versus 57%; $P=0.02$). The post-discharge frequency of exacerbations was lower in the early PR group (0.27 versus 1.1; $P<0.01$). Although informative, these trials were limited by a relatively short-term follow-up period. By contrast, Ko et al. investigated the effect on healthcare utilization at 12 months of an 8-week program of supervised outpatient PR in patients enrolled up to 3 weeks following hospital discharge [53]. Although the PR group showed improvement in health status at 3 and 6 months, this effect did not persist at 12 months, and there was no reduction in healthcare utilization at 12 months. Similarly, Puhan et al. reported, albeit in an underpowered study, that early PR failed to improve exacerbation rate at 18 months [54]. This is not surprising as the patients enrolled in such trials have severe and very severe COPD, and the interventions that are applied are unlikely to have effect on long-term benefit as the disease process progresses. Despite this, the short-term gains to the patient and acute healthcare providers are clear. In the future, we may target these patients during the exacerbation as inpatients. Acknowledging that these patients have very high levels of dyspnea during this period, which prevents exercise, novel use of technologies that accommodate for or modify dyspnea, such as neuromuscular electrical stimulation [55] and non-invasive ventilation [56], have been used as adjuncts to exercise training in pilot studies, but further work is required.

Pulmonary rehabilitation delivered in the stable state

Although uncontrolled cohort studies have found that PR reduces hospitalization frequency [57,58] and hospital bed days [57-60], RCTs of PR in patients with stable COPD have not shown such consistent results. Griffith et al. reported that despite fewer hospital bed days, there was no reduction in hospitalization frequency in the PR group [61]. Guell et al. found a reduction in hospital admissions over a 2-year period [62]; however, other studies have failed to show a reduction admission frequency and hospital bed days [63,64]. These contrasting data highlight the differing phenotypes of COPD, based on exacerbation frequency, and the requirement for clinicians to develop strategies to target the timing of PR based on the phenotype rather than on the current clinical state of the patient at the time of starting PR.

Non-invasive ventilation

Non-invasive ventilation (NIV) is well established as the treatment of choice for patients with COPD with acute decompensated hypercapnic respiratory failure (AHRF) who fail to respond to standard medical therapy [65,66]. Importantly, and in addition to a reduction in mortality, hospital length of

stay is reduced compared with standard treatment. Although NIV remains controversial as a domiciliary treatment to reduce hospital admission and improve survival in patients with COPD with stable chronic respiratory failure, the physiological mechanisms by which long-term NIV results in clinical improvement in patients with severe COPD and hypercapnic respiratory failure are well-described [67]. Indeed, Nickol et al. showed that 3 months of NIV enhanced gas exchange through alterations in pulmonary mechanics (shown as reduced gas trapping), and also increased ventilatory sensitivity to carbon dioxide. However, there was limited effect on non-volitional muscle strength [68]. Clinical manifestations of these physiological changes are reflected as reduced dyspnea and improved HRQL, and it is hypothesized that there will be an associated reduction in acute exacerbations and hospitalization, with a potential for improved survival. However, trial data are as yet inconclusive for this high-risk group of patients with severe COPD.

An observational study from Tuggey et al. showed that, following initiation of domiciliary NIV in a cohort of patients with COPD who were prone to recurrent admissions, there was a significant reduction in total hospital days and days spent in the intensive care unit. This was, not unexpectedly, associated with substantial cost savings [69]. This is in contrast to several RCTs that have failed to show a convincing benefit in terms of acute healthcare utilization. In the trial by Casanova et al., there was no difference in survival between patients with stable COPD randomized to NIV or UC [70], although the proportion of patients who required hospital admission at 3 months was reduced in the intervention group (5% versus 15%; $P<0.05$, respectively). Unusually, ventilator set-up in this trial was aimed at reducing accessory muscle use and reducing dyspnea, which explains, in part, the low inspiratory positive airway pressure (IPAP) of 12 cm H₂O applied. Clini et al. randomized 90 patients to long-term oxygen therapy (LTOT) alone or home NIV (IPAP 14 cm H₂O) with LTOT, as part of a multicentre trial [71]. Adherence to NIV was high in this study at 9 hours per day, but there was only a trend to a reduction in hospital admission comparing admission rate before and after enrolment (45% decrease in hospital admissions in the intervention group versus 27% increase in the UC group). More recently, McEvoy et al. found a significant improvement in survival in a combined NIV and LTOT group in both intention-to-treat and per-protocol (>4 hours NIV use per night) analyses (HR 0.63, 95% CI 0.40 to 0.99, $P=0.045$ and HR 0.57, CI 0.33 to 0.96, $P=0.036$, respectively) [72]. This was achieved with an adherence of 4.3 hours per night. Despite this beneficial effect, NIV in addition to LTOT treatment conferred no benefit in terms of HRQL or hospital admission, albeit the IPAP in this trial was again low, at 12.9 cm H₂O.

Patients with COPD are at greatest risk of death and re-admission immediately after an episode of AHRF. Indeed, the reported re-admission rate is 79.9% with a 1-year mortality rate of 49.1% [73]. Two recent trials have focused on this high-risk group [74,75]. In the trial by Cheung et al., patients who had required NIV for AHRF were randomized to domiciliary nocturnal NIV or continuous positive airway pressure (CPAP) of 5 cm H₂O. The intervention was shown to have a lower rate of recurrent AHRF compared with the control group (38.5% versus 60.2%; $P=0.039$, respectively) and a longer median time to first re-admission (71 days versus 56 days; $P=0.048$, respectively) [74]. CPAP as an appropriate control arm in patients with COPD is interesting. The methodological aim was to balance

the possible negative physiological effects of CPAP in patients with severe COPD against the concerns about using a control group that were not exposed to a mask interface. The use of interface with minimal pressure delivery allowed testing of the hypothesis that NIV is beneficial in COPD patients with post-acute hypercapnic respiratory failure. In a separate trial, Funk et al. enrolled patients who had required NIV for AHRF, but randomized the patients, after a run-in period on NIV of 6 months, to either continuation or withdrawal of NIV. The primary endpoint was escalation of ventilation. They found that the rate of ventilation escalation was lower in the NIV continuation group compared with the withdrawal group (15% versus 77%; $P = 0.0048$, respectively) [75]. These studies suggest a benefit of using domiciliary NIV in patients who are recovering from a recent acute exacerbation complicated by acute hypercapnic respiratory failure.

At present, there is controversy about the use of domiciliary NIV, and there are currently no widely accepted criteria for commencing domiciliary NIV in stable COPD, despite the practice being widespread [76]. The available data indicate that patient selection is important. Specifically, the patients most likely to benefit from long-term domiciliary NIV are those who exhibit symptomatic chronic hypercapnic respiratory failure and those with severe episodes of acute exacerbation requiring acute NIV during hospital admission [77]. Because the prognosis is better for patients who have hypercapnia that is reversible during the post-exacerbation recovery phase [78,79], it is important to target long-term NIV to patients who remain hypercapnic following their acute episode, as shown by the studies of Cheung et al. and Funk et al. [74,75]. Preliminary screening data in 25 patients from a UK RCT of post-exacerbation domiciliary NIV suggest a prevalence of persistent severe hypercapnia (arterial partial pressure of carbon dioxide > 7 kPa 2 weeks after an episode of AHRF) of over 40% [80]. However, further studies are needed to elucidate the trajectory of hypercapnia in a large cohort of patients with COPD treated with acute NIV.

Two RCTs are ongoing in the UK [81] and the Netherlands [82] to establish the effect of domiciliary NIV in reducing mortality and hospital admission for patients with COPD who are hypercapnic. The UK trial is focused on patients following an acute hospital admission requiring NIV, and the trial from the Netherlands is focused on patients with stable COPD who are hypercapnic. There are, however, several challenges in conducting such studies. Firstly, the absence of a true placebo for NIV makes it difficult to have a robust control group for comparison. Most studies to date have compared NIV with UC, with or without LTOT [70-72,75], but a limitation of this approach is that it does not take into account the placebo effects of being given a mask interface. Cheung et al. attempted to address this by administering nasal CPAP at 5 cm H₂O to patients in the control group [74]. However, as the authors acknowledged, the possibility remained that the CPAP had a beneficial physiological effect on the control group, and could not therefore be considered to be a true placebo [83,84]. Secondly, the interpretation of the potential benefits of NIV are hampered by relatively short follow-up periods in the trials published to date; only two studies [71,72] have followed patients up for 2 years or more. Clearly, as patients established on domiciliary NIV are likely to remain on it for several years, it would seem advantageous for future studies to assess its benefits over the longer term.

Smoking cessation

Smoking cessation is one of the few interventions shown to reduce mortality in patients with COPD. However, there are relatively few data showing the benefits of smoking cessation in reducing exacerbations. In the Lung Health Study, there was no significant difference in the risk of hospital admission between current smokers and ex-smokers [85]. Furthermore, Kessler et al. reported that smoking status had no effect on hospitalization risk [86], and Garcia-Aymerich et al. showed that current smoking was associated with a reduced risk of hospitalization in a small cohort of patients with COPD [87], suggesting that patients with very advanced disease and high risk of hospital admission quit tobacco consumption as a result of their significant symptom load. By contrast, Godtfredson et al. reported that, in a large prospective population study in Denmark, previous smokers had a lower risk of hospitalization for COPD (HR 0.57, 95% CI 0.73 to 1.18) compared with current smokers [88]. Interestingly, tobacco consumption (low versus high) had no effect on hospital admission. This study is supported by a population study by Au et al., who reported a reduced risk of COPD exacerbations in ex-smokers compared with current smokers when adjusted for comorbidity, markers of COPD severity, and socioeconomic status (adjusted HR 0.78, 95% CI 0.75 to 0.87) [89]. Importantly, the duration of smoking abstinence significantly influenced the magnitude of the reduced exacerbation risk.

Long-term oxygen therapy

Although LTOT is well established as a treatment to improve survival in patients with COPD and hypoxemia, there was no effect on exacerbation or hospitalization rates in early studies [90,91]. The benefits of LTOT in reducing acute healthcare utilization have been shown in the EFRAM cohort, with appropriate LTOT utilization being associated with lower risk of admission [87]. Further evidence was given by Ringbaek et al., who showed in a Danish COPD cohort that LTOT reduced admission rates and hospital days by 23.8% and 31.2%, respectively [92].

Risk stratification and physiological monitoring

Early recognition and treatment of exacerbations, and timely detection of treatment failure during an exacerbation are key factors that may reduce in hospital admissions, facilitate early discharge, and avoid re-admissions. The development of clinical tools to achieve this should be a priority for COPD research. Although there has been a considerable focus on molecular biomarkers, the predictive value of the data has been disappointing [93]. However, more encouraging data have shown that fibrinogen levels, as a biomarker of severity of systemic inflammation, combined with forced expiratory volume in 1 second (FEV₁) predicted moderate to severe exacerbations in the following year [94].

Despite the limited clinical usefulness of the molecular biomarkers, basic and advanced physiological measurements have been shown to have increased utility in monitoring the course of COPD. Stevenson et al. showed that inspiratory capacity, as a marker of dynamic hyperinflation, changed significantly during the course of recovery from an exacerbation, while the impedance of the respiratory system, as measured by impulse oscillometry, was unchanged [95]. Murphy et al. investigated the use of a novel technique using electromyography of the second intercostal space parasternal muscle as an advanced physiological biomarker of neural respiratory drive in patients with COPD admitted to hospital

with an exacerbation. Indices of neural respiratory drive were shown to be superior to standard bedside clinical measures and spirometry in detecting clinical deterioration [96]. Furthermore, when the neural respiratory drive between admission and discharge were compared, this physiological biomarker had the sensitivity and specificity to identify those patients who were re-admitted within 14 days. Advanced physiological technology that monitors the clinical status of the patient during hospital admission will not only identify treatment failure early but will also allow risk stratification for early re-admission. Furthermore, the technology has the potential to be used as part of a home telehealthcare program.

Supported discharge and telehealth programs

Supported discharge and hospital-at-home programs have been introduced to improve the quality of life of patients by reducing hospital attendance and admission. This has potential benefits both for the patient and for reducing the expenditure within acute healthcare organizations. Studies have shown that in patients with uncomplicated acute exacerbations, early supported discharge is safe, and reduces length of stay without an increased re-admission rate, which was an initial clinical concern [97,98]. However, a meta-analysis of hospital at-home programs, as an alternative to continued hospitalization, concluded from eight trials that there was only a small benefit in terms of re-admission risk (risk ratio 0.76, 95% CI 0.59 to 0.99, $P=0.006$) [99]. Furthermore, only a third of all patients were eligible for enrolment in the program, and there was no significant reduction in mortality (RR 0.65, 95% CI 0.4 to 1.04). Importantly, there was also no evidence of a cost saving.

With advances in information technology, advanced care coordination telehealth systems have been developed. These aim to facilitate transfer of clinical data about the patient through telecommunication networks. These data are reviewed remotely by a trained healthcare professional, who provides advice on the basis of the transmitted data [100]. In patients with COPD, such systems are aimed at early recognition and treatment of exacerbations in order to reduce healthcare utilization through admission avoidance, which will be reflected as an enhanced quality of life for the patient [100]. Although bodies such as the European Commission have highlighted the potential of telehealth in the management of chronic diseases, there is limited evidence for its effectiveness in COPD [101]. Although systematic reviews investigating the role of telehealth in patients with COPD have reported reductions in ED attendance and hospital admission [100,102,103], there has been a wide variation in the nature of the interventions themselves, with some of the studies being underpowered [102], such that clinical effectiveness has not been established. A meta-analysis reported that telemonitoring actually appeared to increase the mortality rate compared with UC, suggesting that patients may have delayed seeking urgent medical attention because of false reassurance from the remote assistance [103]. The Whole System Demonstrator study, a UK project funded by the Department of Health, was designed to establish whether integrated care supported by telehealthcare was effective in reducing healthcare utilization and mortality in a large number of patients with chronic illness, including COPD [104]. Primary care practices were randomized to provide either telehealth or UC, and patients were enrolled across three UK regions. Telehealth reduced the hospital admission and mortality [104], but interestingly, there was no improvement in either quality of life or psychological outcomes [105]. In a subsequent economic analysis, telehealth

was not shown to be cost-effective in patients with COPD [106]. The results of a large UK RCT in patients with COPD are awaited [107]. In the interim, as part of a European Commission Innovation Partnership project, clinicians, researchers and engineers are working together identify the specific technological, physiological, behavioral, and clinical components that should be included in an advanced care coordination and telehealth deployment program to provide the most benefit to patients [108].

Conclusions

Attention has been focused on the development of non-pharmacological strategies to improve health status and quality of life, and to reduce healthcare utilization and costs by preventing the frequency and severity of acute exacerbations of COPD. These non-pharmacological strategies, although they show potential, need further supporting data before widespread implementation can be suggested.

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Physical Activity Level and its Clinical Correlates in Chronic Obstructive Pulmonary Disease: a Cross-Sectional Study

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Abstract

Background: Decreased physical activity is associated with higher mortality in subjects with COPD. The aim of this study was to assess clinical characteristics and physical activity levels (PALs) in subjects with COPD.

Methods: Seventy-three subjects with COPD (67 ± 7 yrs, 44 female) with one-second forced expiratory volume percentage (FEV1%) predicted values of 43 ± 16 were included. The ratio of total energy expenditure (TEE) and resting metabolic rate (RMR) was used to define the physical activity level (PAL) ($\text{PAL} = \text{TEE}/\text{RMR}$). TEE was assessed with an activity monitor (ActiReg), and RMR was measured by indirect calorimetry. Walking speed (measured over 30-meters), maximal quadriceps muscle strength, fat-free mass and systemic inflammation were measured as clinical characteristics. Hierarchical linear regression was applied to investigate the explanatory values of the clinical correlates to PAL.

Results: The mean PAL was 1.47 ± 0.19 , and 92% of subjects were classified as physically very inactive or sedentary. The walking speed was 1.02 ± 0.23 m/s, the quadriceps strength was 31.3 ± 11.2 kg, and the fat-free mass index (FFMI) was 15.7 ± 2.3 kg/m², identifying 42% of subjects as slow walkers, 21% as muscle-weak and 49% as FFM-depleted. The regression model explained 45.5% ($p < 0.001$) of the variance in PAL. The FEV1% predicted explained the largest proportion (22.5%), with further improvements in the model from walking speed (10.1%), muscle strength (7.0%) and FFMI (3.0%). Neither age, gender nor systemic inflammation contributed to the model.

Conclusions: Apart from lung function, walking speed and muscle strength are important correlates of physical activity. Further explorations of the longitudinal effects of the factors characterizing the most inactive subjects are warranted.

Background

Chronic obstructive pulmonary disease (COPD) is characterized by non-reversible airflow limitation and systemic effects [1]. In addition to respiratory impairments reduced exercise capacity, systemic inflammation, loss of muscle mass and reduced physical activity are common [2-6].

The impaired exercise capacity can be improved through pulmonary rehabilitation, but whether this increased functional reserve will lead to subjects utilizing their capacity in everyday life is still uncertain [7,8]. Both decreased exercise capacity and decreased physical activity are associated with higher mortality from COPD [9-11], indicating that further exploration of the factors involved in this complex interrelationship is warranted. If mediating factors are identified that contribute to variations in activity, they would be possible targets for interventions [12,13].

We hypothesized that using a combination of objectively measured clinical characteristics would be useful for assessing physical activity levels in subjects with COPD. Therefore, the aim of this study was to explore the clinical characteristics of physical activity in patients with moderate and severe COPD, with special emphasis on variables that are amendable through rehabilitation efforts.

Methods

Design and subjects

A cross-sectional study was performed, and a sample of 73 subjects with COPD was consecutively recruited from the Department of Respiratory Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden. The inclusion criteria were: clinical diagnosis of COPD with a ratio of forced expiratory volume in one second (FEV1) by forced vital capacity of two standardized residuals below predicted value, smoking history ≥ 10 pack-years and stable disease. The exclusion criteria were: other conditions known to affect muscular tissue or physical performance (e.g., chronic heart failure, renal failure, rheumatic disease, diabetes, severe arthritis). The study was approved by the regional ethics review board in Gothenburg (Dnr: 408/05).

Lung function

Post-bronchodilator lung function values from the subjects' medical records were used if results from within six months were available; otherwise, dynamic spirometry was performed (SensorMedics model 922, SensorMedics Co., Palm Springs, CA, USA) [14]. Reference values from the European Community for

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Steel and Coal were used [15]. The severity of airflow limitation was based on post-bronchodilatory FEV1 using the criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1].

Energy expenditure

Resting metabolic rate (RMR) was measured by indirect calorimetry using a ventilated hood system (Deltatrac II Metabolic Monitor, Datex, Helsinki, Finland). Measurements were taken after an overnight fast, in a temperature-neutral environment with the subject in supine position and after 30 minutes of rest. The measurement period was 30 minutes, and the last 25 minutes were used for determining the RMR.

Physical activity

The ActiReg activity monitor (Premed AS, Oslo, Norway) was used to measure physical activity [16]. The monitor consists of a storage unit (measuring 85×45×15 mm, weight 60 g) worn at the waist to which two pairs of sensors are attached: one pair at the front of the right thigh, the other at the chest. Each pair consists of a position sensor and a motion sensor. The position sensors discriminate between four body positions (lying, sitting, standing and bending forward) and the motion sensors between four states of motion (no motion, motion at chest or leg, and motion at both location). Information from the sensors are checked every second and by combining this information with the energy requirements of different body positions and activities [17], an estimate of total energy expenditure during the measurement period is possible in the software. Data were analyzed using the ActiCalc computer software (Premed AS, Oslo, Norway), with which total energy expenditure was analyzed and physical activity level calculated. The ActiReg system is validated for use in subjects with COPD and has shown high agreement with the doubly labeled water method for energy expenditure estimates

[18]. The ActiReg was worn for seven consecutive days, except during the night or when taking a shower.

Physical activity level

The physical activity level (PAL) was calculated as the ratio of the total energy expenditure (TEE) from the ActiReg divided by the RMR from indirect calorimetry ($PAL = TEE/RMR$). The World Health Organization proposes that the resulting ratio can be used to classify the lifestyle patterns of subjects as very inactive [$PAL < 1.40$], sedentary or lightly active [$PAL 1.40 - 1.69$], active or moderately active [$PAL 1.70 - 1.99$] or vigorous or vigorously active [$PAL 2.00 - 2.40$] [17].

Walking speed

Walking speed was assessed by the 30-meter walk test [19]. The test was performed at two walking speeds, self-selected (usual) and maximal. Subjects were instructed to start from a standstill and walk 30 metres in both speeds with three minutes of rest in between. The mean walking speed at both the self-selected and the maximal speeds was calculated (distance/time, m/s). The cut-off for normal walking speed was set at 1.0 m/s [20].

Quadriceps strength

Maximal voluntary isometric knee extensor strength was assessed using the Steve Strong dynamometer (SteveStrong HB, Gothenburg, Sweden). The outcome was maximal strength measured in Newtons (N). In a seated position with back support, hip and knee in 90 degrees, with the subject secured to the seat by a strap to minimize engagement of the muscles of the hip, three maximal efforts per leg were performed with vigorous encouragement. The highest result obtained from three maximal efforts was used. Data were converted into kg, and predicted values based on the equation by Seymour et al. [21] were used to classify muscle weakness.

Table 1 Description of sample. Numbers are means \pm standard deviations, medians (IQRs) or numbers (%)

	Total sample (n = 72)	1 st tertile of PAL (n = 24) (1.15 – 1.38)	2 nd tertile of PAL (n = 24) (1.40 – 1.51)	3 rd tertile of PAL (n = 24) (1.52 – 2.21)
Age, years	65 \pm 7	65 \pm 7	66 \pm 7	65 \pm 7
Gender, n male/female	28/44	8/16	10/14	10/14
Current smoker, n (%)	20 (28%)	7 (29%)	7 (29%)	6 (25%)
Dyspnea, mMRC	3 (1)	3 (1)	2.5 (2)	2 (2)
FEV ₁ , percent of predicted	43 \pm 16	35 \pm 11	42 \pm 16	52 \pm 14
FVC, percent of predicted	83 \pm 20	73 \pm 19	85 \pm 21	92 \pm 20
GOLD grade 1/2/3/4, n	1/18/37/16	0/1/15/8	0/6/11/7	1/11/11/1
BMI, kg/m ²	24.4 \pm 4.7	23.2 \pm 5.0	23.9 \pm 4.0	26.0 \pm 4.8
FFMI, kg/m ²	15.7 \pm 2.3	15.0 \pm 2.4	15.5 \pm 1.9	16.6 \pm 2.3
FFM depleted, n (%)	35 (49%)	17 (71%)	12 (50%)	6 (25%)
Quadriceps strength, kg	31.3 \pm 11.2	27.2 \pm 10.7	30.2 \pm 10.0	36.3 \pm 11.3
Quadriceps strength, percent of predicted	81.8 \pm 24.8	73.8 \pm 28.0	80.8 \pm 20.8	90.9 \pm 23.1
Quadriceps weakness, n (%)	15 (21%)	6 (25%)	5 (21%)	4 (17%)
Walking speed, self-selected (m/s)	1.02 \pm 0.23	0.89 \pm 0.21	1.00 \pm 0.23	1.14 \pm 0.17
Walking speed, maximal (m/s)	1.54 \pm 0.30	1.42 \pm 0.29	1.57 \pm 0.29	1.66 \pm 0.30
Low self-selected walking speed, n (%)	30 (42%)	15 (63%)	11 (46%)	4 (17%)
CRP	1.86 \pm 2.85	2.38 \pm 3.24	1.47 \pm 2.55	1.85 \pm 2.75

mMRC = modified Medical Research Council scale (0-4), FEV₁ = Forced expiratory volume in one second, FVC = Forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, BMI = body mass index, FFM = fat-free mass, FFMI = fat-free mass index, FFM depleted = FFMI \leq 15 in women, \leq 16 in men, Slow walkers = < 1.0 m/s self-selected speed, CRP = C-reactive protein (anti-logged values).

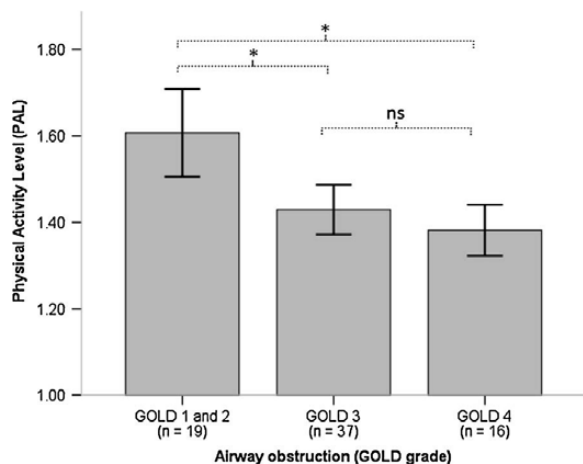


Figure 1 Physical activity level (PAL) presented across the airway obstruction classification from the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Bars are the mean PALs (with 95% CI) in respective GOLD grades.

* = $p < 0.05$, ns = $p > 0.05$.

Anthropometrics and body composition

Height (m) and body weight (kg) was measured, and body mass index calculated as weight/height² (kg/m²). Fat-free mass (FFM) was assessed in grams (g) by dual-energy x-ray absorptiometry (Lunar Prodigy, GE Healthcare, United Kingdom). The fat-free mass index (FFMI) was calculated as FFM/height² (kg/m²). Fat-free mass depletion was defined as FFMI ≤ 15 for women and ≤ 16 for men [5].

Systemic inflammation

Venous blood samples were taken in the morning after 12 hours of fasting. C-reactive protein (CRP) was used to assess systemic inflammation and analyzed according to standardized procedures at the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg, Sweden.

Dyspnea

Dyspnea during daily activities was assessed using the modified Medical Research Council scale, ranging from 0–4 [22].

Statistics

The analyses were performed using IBM SPSS statistics version 20. Descriptive statistics are presented as the means (standard deviations) for continuous and normally distributed variables or as the medians (interquartile ranges) for categorical variables (or

non-normally distributed variables). Skewed variables were log-transformed prior to analysis. Using PAL as a grouping variable, the sample was split into tertiles to explore whether a linear trend would be evident in the independent variables. Pearson product-moment correlation coefficient, r and Spearman rank correlation, r_s were used to assess associations. The Kruskal-Wallis test was used to test for differences in PALs between GOLD grades with the Mann-Whitney U test used for post hoc pairwise comparisons and gender differences.

Hierarchical multiple linear regression analysis was used to investigate the explanatory values of age, gender, FEV₁% predicted, self-selected walk speed, quadriceps strength, FFMI and the log of CRP (independent variables) on PAL (dependent variable). In the case of missing values for independent variables, the multiple imputation technique was used to complete the data set. No variable had missing values in $> 6\%$ of cases. The significance level was set at $p < .05$. Due to the exploratory nature of the study no sample size calculation was performed.

Results

Data from one subject's activity monitoring were faulty and therefore excluded, leaving a total of 72 subjects (44 female) for analysis. The subjects' mean age was 65 ± 7 years, and FEV₁% predicted was 43 ± 16 (Table 1). Airway obstruction according to GOLD was grade 1 ($n = 1$), grade 2 ($n = 18$), grade 3 ($n = 37$) or grade 4 ($n = 16$).

The mean PAL was 1.47 ± 0.19 . There was a negative correlation between PALs and GOLD grades, $r_s = -0.447$ ($p < 0.001$), indicating less physical activity with worsening airway obstruction. The differences in PAL were significant between GOLD grades 2 and 3 ($p < 0.001$) but not between GOLD grades 3 and 4 ($p = 0.358$) (Figure 1). Sixty-six subjects (92%) were very inactive or sedentary, four were active or moderately active and two subjects were vigorously active. Subjects who were more physically active were characterized by better pulmonary function; higher Body Mass Index, FFMI, walking speed and muscle strength; and less dyspnea (Table 1). Forty-nine percent of the sample (27 female, 8 male) was classified as FFM-depleted. Forty-two percent (19 female, 11 male) did not reach normal walking speed. The maximal quadriceps strength was 31.2 ± 11.2 kg, corresponding to $82 \pm 25\%$ of predicted values.

Univariate associations with PAL

The explanatory values of FEV₁, walking speed and quadriceps strength were almost similar (ranging from 16 to 20%) (Figure

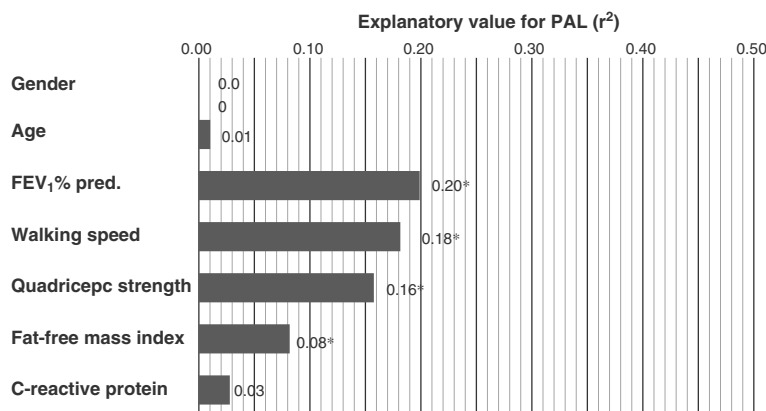


Figure 2 Figure shows the univariate associations with PAL. The x-axis represents the explanatory value (r^2) of PAL from the independent variables. FEV₁ = Forced expiratory volume in one second in percent of predicted, * = $p < 0.05$.

Table 2 Correlation matrix of the variables used in the regression model

	PAL	Age	Gender	FEV ₁	Walking speed	Quadriceps strength	FFMI
PAL							
Age (years)	−0.101						
Gender (female = 1)	−0.012	−0.207					
FEV ₁ (percent predicted)	0.446**	0.075	0.093				
Walking speed (m/s)	0.426**	0.046	−0.172	0.253*			
Quadriceps strength (kg)	0.397**	−0.088	−0.410**	0.120	0.315**		
FFMI (kg/m ²)	0.286*	0.098	−0.591**	0.089	0.147	0.524**	
CRP (log values)	−0.167	0.139	−0.058	−0.006	−0.038	0.063	0.106

Note: N = 72. FEV₁ = Forced expiratory volume in one second in percent of predicted, FFMI = fat-free mass index, CRP = C-reactive protein **p < .001,

*p < .05 (two-tailed).

2), whereas the correlation for FFMI was considerably lower. No significant associations were identified for age, gender or CRP. Moderate correlations were identified between quadriceps strength and FFMI and between gender and FFMI, whereas all other correlations between independent variables were weak or statistically non-significant (Table 2).

Multivariate model for explanation of PAL

In a hierarchical multiple regression analysis, FEV₁ accounted for 22.5% of the variation in PAL when adjusting for age and gender (Figure 3). Further improvements to the model were gained by the inclusion of self-selected walking speed (10.1%), quadriceps strength (7.0%) and FFMI (3.0%), details of the model is presented in Table 3. Age and gender did not contribute significantly to the model; nor did CRP when adjusting for the previous variables entered. The fit of the final regression model was R² = 0.45, (p < 0.001).

Discussion

The new information added from this study is that variations in physical activity can be explained only to a degree by lung function but by adding information from simple tests of walking speed and lower extremity strength, substantial improvements in the explanation of the variability in PAL is possible.

In this study, FEV₁ explained approximately 20% of the variability in PAL. Previous studies have shown moderate associations between higher GOLD grades and both lower PALs [23] and lower numbers of steps/day [24] and with not performing the recommended amount of physical activity [25]. Walker et al. [26] reported that changes in both overall activity and lower limb activity were related to FEV₁ and that there were higher levels of leg activity among subjects with better FEV₁. The mechanism behind this association could be dynamic hyperinflation [27]. The altered mechanical properties of the lungs and airways in COPD reduce expiratory flow and limit the time for expiration, especially during physical exertion, leading to increased end-expiratory lung volume [28]. If increased discomfort is apparent in physical activities, subjects are likely to limit their activity to avoid negative experiences of dyspnea, thereby contributing to a worsening of the condition from the disuse of muscles [29]. This model is supported by our data, given that both dyspnea and lung function worsened as PAL decreased. It is reported that walking distance from a 6-minute walk test (6MWT) is a stronger determinant of daily activity than FEV₁, self-efficacy and health-status [30].

A novel finding in the present study was that the explanatory value of self-selected walking speed towards PAL was of the

same magnitude as the explanatory value of FEV₁. In this study, walking was measured as walking speed over 30 meters. The 30-meter walk test has been shown to correlate well with the 6MWT [19]. Pitta et al. showed that patients with COPD spent less time walking in daily life than did age-matched controls and also walked at lower walking speeds [31]. Furthermore, the authors concluded that the 6-minute walk distance (6MWD) was the best surrogate marker for inactivity in COPD. Our results are therefore in accordance with the results of previous studies confirming the value of walking performance with regard to daily activity [31]. However, to our knowledge, the finding of walking speed as an independent predictor of daily physical activity has been reported in only one previous study [32]. DePew et al. measured walking performance using the 4-meter gait speed test and the 6MWT in a sample of chronic lung disease subjects. In agreement with our present results, the association between walking speed and PAL was modest (r 0.32), but DePew et al. did not present a multivariate prediction model for PAL, so further comparison is not possible. In the present study, 42% of the participants had a lower than normal walking speed (< 1.0 m/s). A slow walking phenotype has been described in COPD, characterized by both worse exercise capacity and health status [33], but the impact of slow walking on physical activity levels has not been reported previously. The mechanism behind the reduction in speed with COPD is likely quite complex, but a feasible explanation is that it reflects a global sign of the constraints imposed by the airway obstruction and dyspnea. Lower speed likely results in less oxygen consumption in the muscles and thereby less ventilatory stress and dyspnea. In this scenario, muscular dysfunction must also be considered because it could impact both walking performance and physical activity.

The proportion of variability of PAL explained by quadriceps strength in the present study was almost of the same magnitude as the variability explained by lung function and walking speed. An association between quadriceps strength and daily activity was also reported in the study by Pitta et al. [31]. However, the maximal muscle strength in our sample was well preserved at the group level (82% predicted) compared with the reference values [21], which is somewhat contradictory to the results of the Pitta study. However, it is important to consider that muscular performance might be affected despite preserved maximal strength [34,35]. Coronell et al. found that the endurance of the quadriceps muscles was more impaired than was maximal strength and that impairment was present even in subjects with mild to moderate disease without sedentarism. Borst et al. [35] showed that reduced oxidative phenotype in COPD was related to reduced quadriceps endurance, but not with total activity or its intensity. Lower PALs were not associated with lower

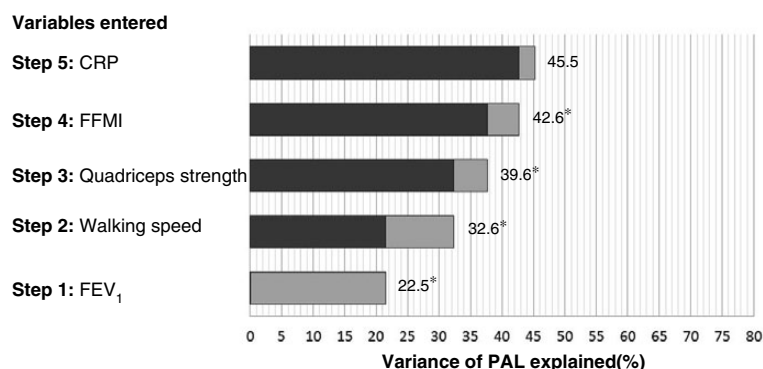


Figure 3 Graphical presentation of the evolving regression model adjusted for age and gender. The darker color represents the proportion of variance explained (R^2) from the previous step, and the light grey represents the R^2 change from the variable entered at that step. Numbers outside of the bars are the total R^2 at the current step, * = significant improvement from previous step, CRP = C-reactive protein, FFMI = fat-free mass index, FEV₁ = Forced expiratory volume in one second in percent of predicted.

quadriceps force in newly diagnosed subjects, as shown by Van Reemortel et al. [36].

Nearly half of the participants were FFM depleted with the least physically active subjects being most affected. FFM depletion was more prevalent among women than men (61% vs. 29%), with a substantially larger gender discrepancy than was described in a Dutch outpatient sample [5]. In the present study, the explanatory value of FFMI towards PAL was relatively low. The reasons may be that we included quadriceps strength in our model and that our subjects had well-preserved quadriceps strength. In our study, there was a relatively strong association between quadriceps strength and FFMI ($r = .52$), which is in accordance with the findings of a previous study [5].

Systemic inflammation has previously been linked to muscle dysfunction in COPD [37] but was not confirmed in our study. Perhaps the large proportion of subjects displaying low FFMI contributed to this finding. Eagan et al. [38] reported that patients with low FFMI did not have increased levels of CRP or soluble TNF-receptor 1; instead, they found the opposite to be true.

Methodological considerations

We used an activity monitor that operated on the basis of motion sensors, in contrast to the more recent literature, in which accelerometers have been used. We considered the choice of the monitor to be a strength of the study because of

its proven validity in measuring energy expenditure in COPD [18]. Furthermore, the sampling method used was not random, which could have introduced selection bias into the study. However, the aim was to include a relatively homogenous sample of COPD subjects by excluding many of the common co-morbid conditions observed in COPD. Other lung function variables than FEV₁ and forced vital capacity would have been needed in order to assess whether the association between low FEV₁ and low PAL was related to dynamic hyperinflation or not. The cross-sectional design does not permit any cause-effect relationships to be determined but allows for the generation of new hypotheses. The method for quantifying quadriceps strength was not tested rigorously for validity or reliability, which should be taken into account when interpreting the results. Body composition and FFM depletion were assessed by dual-energy x-ray absorptiometry, a valid method for assessing body composition.

Our findings suggest that incorporating measures of physical function into clinical practice would be of great value. Activity monitoring suffers from being costly and technically challenging. Having simpler measures for identifying subjects who are sedentary would open new possibilities for interventions. It is also important to note that two of the three major correlates of PAL, walking speed [39,40] and muscle strength [41], can be improved by pulmonary rehabilitation. A novel finding is that in a sample not burdened by comorbidity, impairments in walking speed rather than muscle strength seem valuable for identifying the most sedentary subjects. These subjects can be characterized by reduced walking speed, FFM depletion and poor lung function. Because impairments in one of these factors have been shown to impact mortality, the combined impacts of simultaneous impairments in all three factors should likely be of extra concern for clinicians.

Conclusions

We conclude that apart from lung function, walking speed and muscle strength are important correlates of physical activity. Further explorations of the longitudinal effects of the factors characterizing the most inactive subjects are warranted.

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Table 3 Independent predictors of physical activity level (PAL)

Variable	PAL				
	B	SE	95% CI	Sig.	Beta
Age (years)	-0.002	0.003	-0.007, 0.003	0.489	-0.054
Gender (female = 1)	0.089	0.048	-0.004, 0.183	0.062	0.221
FEV ₁ (percent predicted)	0.004	0.001	0.001, 0.006	0.002	0.305
Walking speed (m/s)	0.232	0.087	0.062, 0.402	0.008	0.282
Quadriceps strength (kg)	0.004	0.002	0.000, 0.008	0.041	0.242
FFMI (kg/m ²)	0.021	0.011	0.000, 0.042	0.047	0.240
Log of CRP	-0.032	0.017	-0.066, 0.002	0.065	-0.174

Note: N = 72. FEV₁ = Forced expiratory volume in one second in percent of predicted, FFMI = fat-free mass index, CRP = C-reactive protein, CI = confidence interval, FEV₁ = forced expiratory volume in one second.

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Nitric Oxide Synthase Polymorphisms, Gene Expression and Lung Function in Chronic Obstructive Pulmonary Disease

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Abstract

Background: Due to the pleiotropic effects of nitric oxide (NO) within the lungs, it is likely that NO is a significant factor in the pathogenesis of chronic obstructive pulmonary disease (COPD). The aim of this study was to test for association between single nucleotide polymorphisms (SNPs) in three NO synthase (NOS) genes and lung function, as well as to examine gene expression and protein levels in relation to the genetic variation.

Methods: One SNP in each NOS gene (neuronal NOS (NOS1), inducible NOS (NOS2), and endothelial NOS (NOS3)) was genotyped in the Lung Health Study (LHS) and correlated with lung function. One SNP (rs1800779) was also analyzed for association with COPD and lung function in four COPD case-control populations. Lung tissue expression of NOS3 mRNA and protein was tested in individuals of known genotype for rs1800779. Immunohistochemistry of lung tissue was used to localize NOS3 expression.

Results: For the NOS3 rs1800779 SNP, the baseline forced expiratory volume in one second in the LHS was significantly higher in the combined AG + GG genotypic groups compared with the AA genotypic group. Gene expression and protein levels in lung tissue were significantly lower in subjects with the AG + GG genotypes than in AA subjects. NOS3 protein was expressed in the airway epithelium and subjects with the AA genotype demonstrated higher NOS3 expression compared with AG and GG individuals. However, we were not able to replicate the associations with COPD or lung function in the other COPD study groups.

Conclusions: Variants in the NOS genes were not associated with lung function or COPD status. However, the G allele of rs1800779 resulted in a decrease of NOS3 gene expression and protein levels and this has implications for the numerous disease states that have been associated with this polymorphism.

Background

Nitric oxide (NO) is a molecule that is involved in many physiological and pathological pathways and can have either beneficial or detrimental effects. Many studies have shown that NO has protective effects on human airways such as muscle relaxation, attenuation of airway hyper-responsiveness to bronchoconstrictor stimuli, and the killing of invading

microorganisms [1]. In contrast, adverse effects of NO have also been observed, such as vasodilation of the bronchial circulation, increased airway secretions and the promotion of pro-inflammatory pathways, as well as necrosis and apoptosis [1].

Endogenous NO is primarily synthesized by enzymes known as NO synthases (NOS) which catalyze the cellular production of NO from arginine. There are three known NOS isoforms: neuronal NOS (NOS1), inducible NOS (NOS2), and endothelial NOS (NOS3). In humans, NOS1 can be found in neurons and endothelial cells in the lung [2], while NOS3 is found in bronchiolar epithelial cells and the endothelium [3,4]. NOS2 is expressed in the human airway epithelium [5], lung endothelium [2], and alveolar macrophages [2].

Due to its pleiotropic effects, it is likely that NO is a significant factor in the pathogenesis of lung diseases such as chronic obstructive pulmonary disease (COPD), which is characterized by airflow limitation that is not fully reversible. There is evidence to suggest that NOS genes are associated with COPD. Recently, the mRNA and protein expression of NOS1 and NOS2 were observed to be increased in the peripheral lung tissue of smokers with COPD compared with nonsmoker controls, whereas the opposite effect was detected for NOS3 expression [6].

Another study reported that the numbers of NOS2+ and NOS3+ cells were increased in the bronchial submucosa of smokers with COPD compared with nonsmoker controls [7]. Furthermore, deficiency of NOS2 has been shown to be protective against cigarette smoke-induced emphysema in a mouse model [8].

To further determine the effects of NOS in COPD, it is important to determine whether single nucleotide polymorphisms (SNPs) in NOS genes are associated with phenotypes related to the disease. It has been widely acknowledged that genetic factors account for some of the variability of lung function among smokers [9,10], suggesting an interaction between genetic and environmental influences on disease progression. The aim of this study was to determine whether NOS gene variants were associated with phenotypes related to COPD. We examined the rate of decline of lung function and baseline lung function in smokers with mild to moderate airflow obstruction from the Lung Health Study (LHS) in relation to polymorphisms in three NOS genes. The LHS was a randomized trial of an anti-smoking intervention and bronchodilator treatment in volunteer smokers [11]. We selected polymorphisms in NOS genes that had previously been associated with gene function or COPD-

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Table 1 Characteristics of the 4132 Lung Health Study participants (2611 male, 1521 female)

Characteristic	Total
Age (mean ± SD), years	48.5 ± 6.7
Smoking history (mean ± SD), pack-years ^a	40.4 ± 18.4
Baseline FEV ₁ post-bronchodilator (mean ± SD), % predicted ^b	78.55 ± 9.10
FEV ₁ post-bronchodilator rate of decline (mean ± SD), % predicted / year ^c	−0.97 ± 1.78

^aNumber packs of cigarettes smoked per day × number of years of smoking.

^bLung function at the start of the study measured as forced expiratory volume in 1 second (FEV₁).

^cChange in lung function over a five-year period measured as forced expiratory volume in 1 second (FEV₁).

related traits [12–14]. We sought to determine whether these polymorphisms were associated with lung function decline and baseline level in COPD patients in the LHS as well as with COPD and lung function in four replication case–control sets.

Methods

Ethics statement

The investigation of the LHS and lung tissue samples was approved by the University of British Columbia/Providence Health Care Research Ethics Board and all subjects review boards and all subjects provided written informed consent. For the NAS, anonymized data were used, as approved by the institutional review boards of Partners Healthcare System and the Boston VA.

Study participants

The participants in the primary analysis were from the National Heart, Lung, and Blood Institute sponsored LHS cohort [11], consisting of smokers who had mild/moderate lung function impairment at the start of the study. Table 1 provides the characteristics of the LHS participants. Of the 5887 total participants in the LHS cohort, 4132 individuals of Caucasian descent had DNA samples available for the study. Lung function at the start of the study was expressed as forced expiratory volume in 1 second (FEV₁) as a percentage of predicted value. The change in lung function, measured as change in FEV₁ % predicted per year over a five-year period, was also an outcome measure of this study. For gene expression in lung tissue, genomic DNA, mRNA and protein were isolated from lung tissue from Caucasian patients who had undergone lobar or lung resection surgery for a localized lung cancer (n = 27). These samples were obtained from the James Hogg Research Centre Lung Registry. SNPs that showed association with lung

function in the LHS cohort were genotyped in four Caucasian case–control cohorts: 1) the first 1000 COPDGene study subjects, 2) the COPD cases and smoking controls of the ECLIPSE study, 3) the NETT cases and NAS controls, and 4) the GenKOLS case–control population from Norway (Table 2) as described previously [21].

Gene variants and genotyping

SNP selection was based on previous genetic associations with disease and function (Table 3). The NOS1 SNP (rs41279104) is located in the exon 1c regulatory region. Both the NOS2 SNP (rs8078340) and the NOS3 SNP (rs1800779) are located in their respective promoter regions. DNA from blood samples of the LHS participants was whole genome amplified using the REPLI-g Mini Kit (Qiagen, Mississauga, ON, Canada) prior to genotyping.

The following TaqMan assays (Applied Biosystems, Foster City, CA, USA) were used: assay ID for rs41279104 = C_86363451_10; rs8078340 = C_29024700_10; rs1800779 = C_7599687_1. For each assay, 5 ng of DNA was used for allelic discrimination. For genome-wide SNP genotyping in the COPDGene, ECLIPSE, NETT-NAS, and GenKOLS populations, all cohorts were genotyped on Illumina platforms (Human Hap550, Quad610, and Omni1 Quad). Quality control in each cohort included subject missingness, discordances, relatedness, and sex; and marker missingness, discordances, singletons, and Hardy-Weinberg equilibrium.

Quantitative polymerase chain reaction (PCR)

RNA was extracted from lung tissue samples using the RNeasy Mini Kit (Qiagen) and cDNA was synthesized using SuperScript®III Reverse Transcriptase (Life Technologies, Grand Island, NY, USA). The cDNA samples were used to determine the gene expression of NOS3. The reference gene used was GNB2L1 as this was previously shown to be stably expressed in lung tissue [22]. Gene expression assays for NOS3 (Hs01574659_m1) and GNB2L1 (Hs00272002_m1) were purchased from Applied Biosystems. Gene expression was calculated using cycle threshold (CT) values for NOS3 and GNB2L1, as previously described [23].

Protein expression levels

Human lung tissue fragments (30 mg) were homogenized in protein extraction buffer with protease and phosphatase inhibitors (Sigma-Aldrich, St. Louis, MO, USA). Protein lysates were resolved by SDS-PAGE and transferred to nitrocellulose membranes, and probed with anti NOS3 rabbit polyclonal antibody NOS3 (C-20): sc-654 at a concentration of 200 µg/mL (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) and anti-

Table 2 Characteristics of the case–control replication study groups

Characteristic	COPDGene		ECLIPSE		NETT/NAS		GenKOLS	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Number of participants	499	501	1764	178	373	435	863	808
Age (mean ± SD), years	64.77 ± 8.12	60.20 ± 8.66	63.63 ± 7.10	57.48 ± 9.44	67.47 ± 5.78	69.8 ± 7.49	65.53 ± 10.03	55.62 ± 9.71
Smoking history (mean ± SD), pack-years ^a	54.76 ± 26.69	38.87 ± 21.07	50.29 ± 27.42	32.11 ± 24.84	66.43 ± 30.68	40.66 ± 27.85	31.98 ± 18.46	19.66 ± 13.58
FEV ₁ (mean ± SD), % predicted ^b	48.73 ± 18.41	97.98 ± 11.32	47.63 ± 15.62	107.83 ± 13.56	28.12 ± 7.38	99.97 ± 13.20	50.63 ± 17.44	94.91 ± 9.24
Sex (% male)	49.5%	50.1%	67.0%	57.9%	63.8%	100%	60.1%	50.1%

^aNumber packs of cigarettes smoked per day × number of years of smoking.

^bLung function was measured as forced expiratory volume in 1 second (FEV₁) as a percentage of the predicted value.

Table 3 Description of the polymorphisms studied

Gene	SNP	Protein	Allele change	Location	Association
NOS1	rs41279104	Neuronal NOS	C => T	Promoter for exon 1c	Reduced gene expression [12]
NOS2	rs8078340	Inducible NOS	G => A	Promoter region	Decreased DNA-protein complex [13]
NOS3	rs1800779	Endothelial NOS	A => G	Intronic	Lower FEV ₁ % predicted in COPD patients [14]

β -tubulin monoclonal antibody clone AA2 at a concentration of 1 mg/mL (Upstate Co., Lake Placid, NY, USA). Detection was performed with IR700 and IR800 anti-mouse and anti-rabbit antibodies (Cell Signaling Technology, Danvers, MA, USA). The density of the bands was analyzed with the Odyssey Infrared Imaging System (LI-COR Biotechnology, Lincoln, NE, USA) using two infrared channels independently. The results were expressed as NOS3 / β -tubulin density ratios.

Immunohistochemistry

Sections were de-paraffinized, rehydrated, and antigen retrieved by autoclaving (15 min, 120°C, 30 psi) for 20 min in citrate target retrieval solution (Dako, Mississauga, ON, Canada). Endogenous peroxidase was quenched with 3% H₂O₂ and non-specific interactions blocked for 20 min with 10% goat serum. Antibody directed against human NOS3 (NOS3 (C-20): sc-654, Santa Cruz Biotechnology, Inc.) at 200 μ g/mL was added overnight at 4°C in 5% goat serum. Sections were then incubated with biotinylated goat anti-mouse (1:100, Vector Labs Burlingame, CA, USA) for 60 min followed by a 10 min treatment with Streptavidin-HRP (Dako). The NOS3 antigen was visualized using the brown chromogen 3, 3'-diaminobenzidine (Dako) and counterstained with Harris Hematoxylin Solution (Sigma-Aldrich). Finally, sections were then dehydrated and mounted with Cytoseal 60 (Richard-Allan Scientific, Kalamazoo, MI, USA). Antibody dilutions and all washes were in TRIS-buffered saline solution.

Statistical analyses

The JMP 5.1 statistical software package (SAS Institute Inc., Cary, NC, USA) was used for analysis of the relationship between the genetic variants and the measures of lung function in the LHS. Agreement of the genotype distributions with Hardy-Weinberg equilibrium was assessed using a χ^2 goodness-of-fit analysis. The two outcomes used in the LHS were baseline and rate of decline of post-bronchodilator FEV₁, expressed as a percent of predicted value. Statistical analyses were performed by multiple linear regression. For the COPDGene, ECLIPSE,

NETT-NAS, and GenKOLS, after removal of principal component outliers, genotype imputation within each study was performed using MaCH and CEU samples from HapMap2 and the 1000 Genomes Project as a reference population. Association analysis of SNPs with case-control status was performed in each cohort using logistic regression, adjusting for age, pack-years of cigarette smoking, and genetic ancestry using PLINK 1.07. Results were combined among the four cohorts using fixed effect meta-analyses using METAL and R 2.12 (manuscript submitted). Differences in gene expression and protein levels between the three genotypes were assessed using two-tailed t-tests.

Results

Allelic discrimination in the lung health study

None of the three SNPs were in Hardy-Weinberg equilibrium for their genotypic distributions in the Caucasian LHS population (rs41279104, p-value = 0.04; rs8078340, p-value = 0.008; rs1800779, p = 0.003). We did not detect any association of either the rs41279104 or the rs8078340 polymorphisms with baseline FEV₁ or rate of decline of FEV₁ (Table 4). However, there was an association of the rs1800779 SNP with baseline lung function (p = 0.0018) (Table 4). This result remained significant (p = 0.0108) after Bonferroni correction for multiple comparisons (3 SNPs and 2 outcomes). In particular, subjects with the GG genotype had higher baseline FEV₁ compared with subjects who had the AA genotype (p = 0.0273). Furthermore, with the AG + GG genotypes combined, an association with an increase in baseline FEV₁ was observed compared with the AA genotype (p = 0.0042). No significant association, however, was observed with rate of decline of FEV₁. An association study of this SNP was then performed in the four replication case-control populations; however no significant findings were observed (Table 5). In addition, we examined the relationship of rs1800779 to FEV₁ % predicted in the four replication populations but there was no significant association with lung function in either the cases or the controls (Table 6).

Table 4 Genotype frequencies of NOS polymorphisms among participants in the LHS cohort and their associations with lung function

Gene	SNP	Genotype	N	Mean \pm SE Baseline FEV ₁ (% predicted)	p-value ^a	p-value ^b	N	Mean \pm SE Rate of Decline in FEV ₁ (% predicted)	p-value ^a	p-value ^b
NOS1	rs41279104	CC	2650 (79%)	78.39 \pm 0.17	Referent	0.1424	2602 (79%)	-0.97 \pm 0.04	Referent	0.3530
		CT	650 (19%)	78.84 \pm 0.37	0.7688		635 (19%)	-1.02 \pm 0.07	0.5332	
		TT	55 (2%)	79.33 \pm 1.19	0.3825		52 (2%)	-1.27 \pm 0.26	0.3434	
NOS2	rs8078340	GG	2760 (76%)	78.64 \pm 0.17	Referent	0.1118	2705 (76%)	-0.96 \pm 0.03	Referent	0.1838
		AG	794 (22%)	78.28 \pm 0.32	0.7166		781 (22%)	-1.03 \pm 0.07	0.8221	
		AA	81 (2%)	77.82 \pm 1.00	0.2977		81 (2%)	-1.12 \pm 0.20	0.4215	
NOS3	rs1800779	AA	1448 (41%)	77.97 \pm 0.24	Referent	0.0018	1425 (41%)	-1.05 \pm 0.05	Referent	0.3838
		AG	1552 (44%)	78.81 \pm 0.23	0.8034		1521 (44%)	-0.92 \pm 0.05	0.1149	
		GG	516 (15%)	79.31 \pm 0.39	0.0273		504 (15%)	-1.02 \pm 0.07	0.7133	

^ap-values were adjusted for age, sex, and smoking history (pack-years).

^ap-value for comparison to the wild type homozygous genotype.

^bp-value for the additive model.

Table 5 Genetic association of NOS3 rs1800779 SNP with COPD affection status in each case–control study

Genotype	COPDGene β coefficient (SE) p-value*	ECLIPSE β coefficient (SE) p-value*	NETT/NAS β coefficient (SE) p-value*	GenKOLS β coefficient (SE) p-value*	Meta-analysis β coefficient (SE) p-value*
AA	Referent	Referent	Referent	Referent	Referent
AG	0.03 (0.15) 0.83	0.01 (0.19) 0.95	0.36 (0.19) 0.06	0.03 (0.13) 0.81	0.08 (0.08) 0.30
GG	0.15 (0.22) 0.49	0.13 (0.28) 0.6310	0.10 (0.27) 0.70	−0.05 (0.19) 0.79	0.07 (0.12) 0.57

*p values were adjusted for age, pack-years of cigarette smoking, and genetic ancestry.

NOS3 mRNA expression in lung tissue

Since we had observed an association between the NOS3 rs1800779 polymorphism and lung function levels in the LHS, a follow-up experiment was performed to determine the effect of rs1800779 on NOS3 gene expression in lung tissue. Individuals were closely matched for age and sex among each genotype (7 males and 2 females for each genotype; average age 60 ± 6 years in all 3 groups). Of the subjects where smoking status was known, they were either ex-smokers ($n = 12$) or current smokers ($n = 9$). No association with NOS3 gene expression was observed when all three genotypes were analyzed. However, as shown in Figure 1, subjects with the AG + GG genotypes combined demonstrated significantly lower NOS3 gene expression in comparison with the AA genotype ($p = 0.0366$).

NOS3 protein levels in lung tissue

The same lung tissue samples used for NOS3 mRNA expression were subsequently utilized for protein analysis by western blot. As shown in Figure 2, subjects with the rs1800779 AG + GG genotypes combined demonstrated significantly lower levels of NOS3 in comparison with individuals who had the AA genotype ($p = 0.0002$). We then used immunohistochemical analysis of lung tissue from three randomly selected donors of each genotype to localize NOS3 expression. As shown in Figure 3, the staining demonstrated NOS3 protein expression predominantly within the airway epithelium and again subjects with AA genotype demonstrated higher NOS3 expression compared with AG and GG individuals.

Discussion

In this study we investigated three polymorphisms in the NOS genes in relation to cross-sectional lung function and rate of decline of lung function in COPD patients. Although we observed a significant association with rs1800779 in NOS3 with baseline lung function in the derivation cohort we were unable to replicate the association in additional patient groups. Nevertheless, we were able to demonstrate that the rs1800779 SNP has a functional effect on the expression of the NOS3 gene and this has implications for the numerous disease states that have been associated with this polymorphism [24–27].

The NOS gene variants that we investigated were limited to those that had strong a priori evidence for involvement in regulation of gene expression or in a trait related to COPD. We utilized this approach to maximize power by limiting the number of comparisons that were made. If a tag SNP approach had been used, a total of 137 polymorphisms would have had to be genotyped (using a minor allele cut off of 1 %, an r^2 cut off for linkage disequilibrium of 0.8 in the European population, and a region 10 kb up and downstream of each gene). Thus, the correction for multiple comparisons would be substantially more severe and the power of the study greatly reduced. The rationale for the SNP selection is described below.

The NOS1 rs41279104 polymorphism that was selected for this study was previously shown to be associated with reduced gene expression [12]. The minor (T) allele was associated with a 30 % reduction in expression in a reporter gene assay [12]. The minor (A) allele of the NOS2 rs8078340 polymorphism was associated with considerably decreased affinity for nuclear protein(s) [13] suggesting that it has functional significance. We prioritized these polymorphisms for investigation in this study, as we reasoned that these functional effects could be relevant to a variety of traits, including COPD. The rs1800779 polymorphism in NOS3 was associated with COPD status and lower FEV₁ % predicted in COPD patients [14]. This is the only published report of a NOS polymorphism associated with our disease of interest in the Caucasian population.

The rs1800779 polymorphism has been previously associated with a number of additional phenotypes but only one of these traits, cytokine responses in children at risk for asthma, was related to respiratory disease [24]. rs1800779 is in strong LD ($r^2 > 0.8$) with ten other polymorphisms but none of these have been associated with phenotypes related to lung function or pulmonary disease.

Other NOS polymorphisms have been investigated with respect to phenotypes related to COPD. Arif et al. [14] studied four NOS3 polymorphisms in north Indian COPD patients and controls: -786 T/C (rs3918161), -922A/G (rs1800779), 894G/T (rs1799983), and

Table 6 Genetic association of NOS3 rs1800779 SNP with FEV₁ % predicted in each case–control study

Group	Genotype	COPDGene β coefficient (SE) p-value*	ECLIPSE β coefficient (SE) p-value*	NETT/NAS β coefficient (SE) p-value*	GenKOLS β coefficient (SE) p-value*	Meta-analysis β coefficient (SE) p-value*
Cases	AA	Referent	Referent	Referent	Referent	Referent
	AG	0.75 (1.84) 0.68	−1.43 (0.85) 0.09	−1.46 (0.84) 0.08	1.50 (1.30) 0.25	0.80 (0.52) 0.12
	GG	2.08 (2.60) 0.42	−0.52 (1.23) 0.67	−1.42 (1.17) 0.23	−2.03 (2.04) 0.32	−0.88 (0.75) 0.24
Controls	AA	Referent	Referent	Referent	Referent	Referent
	AG	1.69 (1.10) 0.12	3.53 (2.35) 0.13	−0.49 (1.37) 0.72	−0.98 (0.68) 0.15	−0.09 (0.52) 0.86
	GG	−0.73 (1.64) 0.66	0.36 (3.47) 0.92	−1.62 (1.81) 0.37	−0.12 (1.05) 0.91	−0.51 (0.78) 0.51

*p values were adjusted for age, pack-years of cigarette smoking, and genetic ancestry.

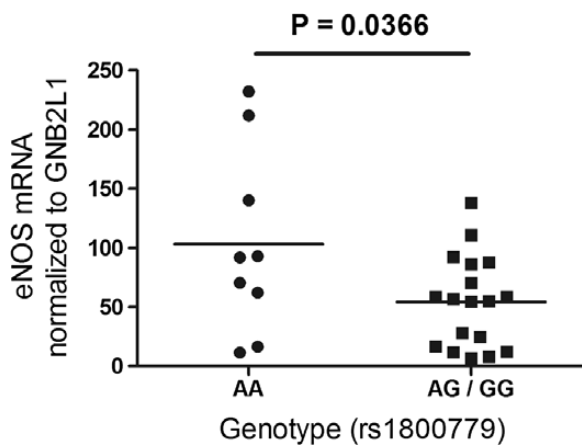


Figure 1. The effect of rs1800779 on NOS3 mRNA expression in lung tissue.

the 4B/4A variable number of tandem repeats (VNTR). rs3918161, rs1800779 and the VNTR were associated with COPD. However, data from the HapMap project (<http://hapmap.ncbi.nlm.nih.gov/>) show that rs3918161 is not polymorphic in individuals of

European descent. It was not feasible to genotype the VNTR with the large sample sizes in this study and therefore rs1800779 was the only relevant polymorphism in our study populations.

Ahsan et al. investigated NOS3 rs1799983 in 27 COPD patients and 66 controls but there was no significant difference ($p = 0.18$) in genotype frequency between the groups [28]. An earlier study that examined the NOS3 VNTR did not find an association with COPD although there was an association with pulmonary hypertension in the patients [29]. Novoradovsky and colleagues genotyped six NOS3 SNPs in patients with α 1-antitrypsin deficiency and found that rs1799983 and rs1549758 were increased in severely affected cases compared with healthy controls [30]. However, these associations were not confirmed by a subsequent study of α 1-antitrypsin deficient patients [31] and none of our patients were α 1-antitrypsin deficient. NOS2 polymorphisms have been investigated in the context of lung function growth and childhood asthma [32]. These investigators

included 24 SNPs in their analysis—seven of which were in the NOS2 promoter. The haplotype block including the promoter SNPs was associated with incident asthma and impaired lung function growth during adolescence. However, as the associations were seen in children and were with asthma, the relevance to COPD, a disease affecting an older demographic with a different pathology, is not clear. Several studies have examined the relationship between NOS gene variants and the fraction of exhaled NO in asthmatics and/or healthy subjects but the results have not been consistent [33–40] and therefore we did not consider them in this study.

The NOS1 and NOS2 polymorphisms that we investigated were both associated with functional effects on their respective gene expression [12,13]. Therefore, we hypothesized that these variants could be important factors in COPD, and that an association of these variants with FEV₁ would be observed in smokers. However, we found no significant associations between the NOS1 and NOS2 polymorphisms and lung function in COPD patients.

The rs1800779 polymorphism in the promoter of NOS3 was associated with lung function in the LHS participants. This SNP was not in Hardy-Weinberg equilibrium; however this could be due to several factors including random chance, genotyping assay failure, population stratification or because the SNP has a true genetic effect. In this study, it is unlikely a genotyping assay failure occurred since the positive controls were in 100% concordance with genotypes from the HapMap database ($n = 73$). The HapMap genotypes were generated with different technologies than the one used in this study and therefore the concordance is strongly indicative that the genotypes are accurate. Furthermore, approximately 13% of the subjects were re-genotyped and were in 100% concordance with the initial genotype results ($n = 573$). In addition, the LHS subjects were selected based on the presence of mild/moderate COPD and therefore the testing for Hardy-Weinberg equilibrium in this cohort may not be appropriate.

The results of the study in the LHS cohort demonstrated that the rs1800779 G allele was associated with a higher baseline FEV₁. Although we found an association in the LHS we did not find any association of this SNP with COPD in four case–control populations. This may indicate that the association in the LHS is a false positive result, even though a limited number of polymorphisms were tested. Alternatively, the lack of replication may be a reflection of the different recruitment strategies and hence demographic factors in the cohorts involved e.g. the LHS participants were younger and had less severe airflow obstruction than the subjects in the other cohorts. The data presented in this study are contradictory to results in a previous paper which reported that the G allele of the SNP is associated with reduced lung function in COPD [14]. A reason for this discrepancy could be differences in the study populations. The cohort used in the previous study was composed of Indian subjects, whereas the cohort in this study only included Caucasian subjects.

A follow-up experiment was performed to determine the effect of the rs1800779 SNP on NOS3 gene expression in lung tissue. It was observed that subjects who had the AG + GG genotypes had lower NOS3 gene and protein expression compared with the AA genotype. In addition, immunohistochemical analysis demonstrated higher NOS3 expression in the airway epithelium

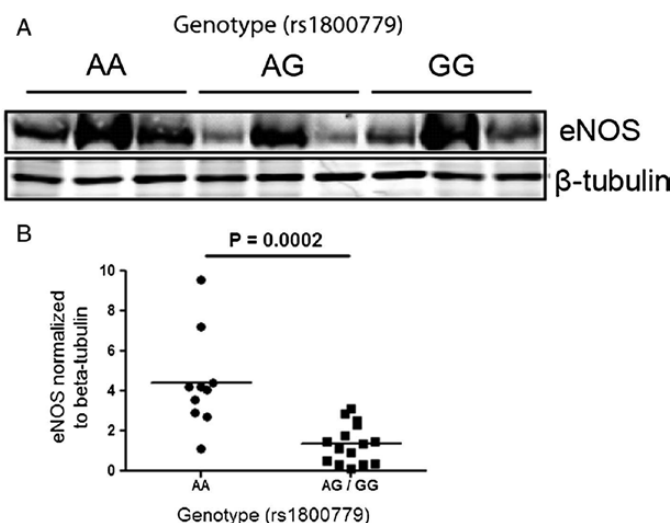


Figure 2. The effect of rs1800779 on NOS3 protein levels in lung tissue. A) Representative western blots of NOS3 protein levels in lung tissue using 3 randomly selected subjects from each genotype. B) NOS3 protein levels normalized to β -tubulin in different rs1800779 genotypic groups.

Genotype (rs1800779)

AA AG GG

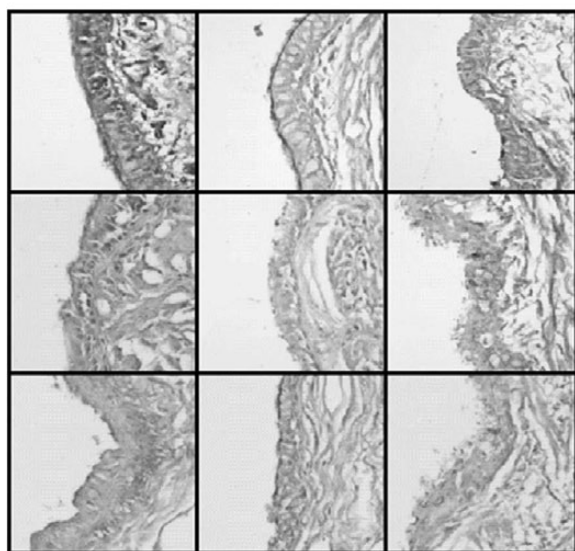


Figure 3. NOS3 expression in the epithelium of lung tissue from subjects stratified by rs1800779 genotype (NOS3 positive staining denoted in brown).

of COPD patients with the AA genotype. Taken together, these results strongly suggest that the G allele is associated with decreased NOS3 expression.

The function of NO as a deleterious pro-inflammatory or protective anti-inflammatory agent has yet to be fully understood. However, there is evidence that NO is implicated in the pathogenesis of lung diseases such as COPD. NO is a radical molecule that can rapidly react with superoxides, yielding a cytotoxic molecule known as peroxynitrite. This compound has been shown to be an important factor contributing to tissue damage in chronic inflammation, as well as impairing key cellular functions [41]. In particular, nitrosative stress mediated by peroxynitrite is evident in patients with COPD, suggesting the toxic compound is a key contributor to the pathogenesis of the disease [7]. Therefore, it can be speculated that once exposed to an environmental pollutant, such as cigarette smoke, airway cells and tissues experience oxidative and nitrosative stress due to production of endogenous NO.

Conclusions

Variants in the NOS genes were not associated with lung function or COPD status. However, the G allele of rs1800779 resulted in a decrease of NOS3 gene expression and protein levels and this has implications for the numerous disease states that have been associated with this polymorphism. The rs1800779 polymorphism is also an excellent candidate for traits that are influenced by NO levels.

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