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News

■ Winter 2016

Device Maker Finds Way to adapt

Passy-Muir (Irvine CA), the leading manufacturer of the No Leak speaking valve is introducing two adapters to provide clinicians with a way to easily connect the Passy-Muir Valve inline while the patient is mechanically ventilated. The adapters are designed to provide a secure connection between the Passy-Muir Valve and a tracheostomy tube, ventilator tubing, closed suction systems, or other adapters. Each adapter is latex free, color coded for easy identification, and provided in re-sealable, multiple unit packaging. The PMV-AD1522 is a stepdown adapter to connect the PMV 007 (Aqua Color) to a T-piece type closed suction system. The flexible, PMV-AD22 adapter is designed to be used with the PMV 2001 (Purple Color). All Passy-Muir's products are proudly made in the USA. Both adapters will be available for purchase through Passy-Muir. In other company news, Passy-Muir recently released a new user-friendly app for iPhone and iPad designed to facilitate patient communication, provide valuable information regarding tracheostomy and foster patient participation in care. The app includes a number of useful features including: Pre-recorded responses & phrases which enable communication at a touch of a button, user-defined male or female voice, child voice option, attractive and intuitive menu, and custom phrase record option. Clinicians attending the 2015 ASHA conference may have caught a glimpse of some exciting revisions to the Toby Tracheasaurus pediatric program. The enhancements include new dinosaur cartoon characters, new therapeutic activity cards, and a clinically improved Toby Tracheasaurus Coloring & Activity Book that is sure to appeal to tracheostomized children, their caregivers and clinicians. Each Toby Tracheasaurus pediatric program kit comes with a draw-string backpack containing a Toby Tracheasaurus Plush Toy, the Toby Tracheasaurus Coloring & Activity Book with crayons, and a Toby Tote with an assortment of therapeutic

toys. Featuring a pediatric tracheostomy tube and Passy-Muir Valve for the purpose of demonstration and education, the Toby Tracheasaurus Plush Toy provides therapists with a lighthearted method to introduce children to tracheostomy and the Passy-Muir Valve, while facilitating vocalization and enhancing therapeutic activities.

Landmark Study Results In

Inspire Medical Systems, Inc., announced the results of a landmark long-term clinical study for its Inspire Upper Airway Stimulation (UAS) System, the first FDAapproved implantable neurostimulation treatment for people diagnosed with Obstructive Sleep Apnea (OSA). OSA affects more than 18 million Americans and can have devastating effects on heart and brain health, impair quality of life and increase accident risk. Inspire therapy is for some people diagnosed with moderate to severe OSA who are unable to tolerate or get relief from Continuous Positive Airway Pressure (CPAP). In contrast to CPAP, Inspire therapy works inside the body and with a patient's natural breathing process. Controlled by the patient sleep remote, the system includes a breathing sensor and a stimulation lead powered by a small battery. During sleep, the system senses breathing patterns and delivers mild stimulation to the tongue and other soft tissues of the throat to keep the airway open. Inspire therapy is currently available at more than 60 leading medical centers across the United States and Europe. The Stimulation Therapy for Apnea Reduction (STAR) trial was conducted at 22 leading sleep medicine centers across the United States and Europe. One-year STAR trial outcome measures, published in the January 9, 2014 edition of the New England Journal of Medicine, showed that sleep apnea patients receiving Inspire therapy experienced significant reductions in sleep apnea events and significant improvements in quality of life measures. The new long-term study outcomes showed that the improvements observed

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⁴⁴ In our experience, the amount of material drained increases by up to 10 times over what we were seeing with manual suctioning by our staff. It has saved time for our staff and reduced our contact with infectious material. And it has been beneficial to our patients, with less force put on the tracheal wall and no trauma from repeated endotracheal suctioning. To date, we have successfully treated over 300 patients using the SIMEX automated intermittent system.³⁷

> Dr. med Marcus Wolf Senior Physician Weaning Station, Department of Pneumology and Intensive Care Askepolis Klinik Bambeck, Hamburg, Germany

> > The SIMEX *cuff* M and *cuff* S are the only suction pumps designed and indicated for intermittent aspiration of subglottic secretions.



For more information contact us at: info@flosuretechnologies.com, or 914-909-6577 ©2015 FloSure Technologies' LLC, all rights reserved. at one-year were sustained at the three-year follow up mark. The outcomes include a 78 percent reduction in apnea-hypopnea index (AHI) from baseline, an 80 percent reduction in oxygen desaturation events from baseline, 80 percent of bed partners reported soft or no snoring as compared to 17 percent of bed partners sleepiness and functioning, showed clinically meaningful improvements and a return to normal levels over baseline. The biggest challenge for OSA patients is that many are unable to tolerate or get relief from CPAP. Published studies show that CPAP adherence rates are less than 50 percent. In contrast, new data from the STAR Trial demonstrate that more than 80 percent of the patients with Inspire therapy report nightly use after three years of being prescribed the therapy.

System Offers Better Suction

Ciel Medical, a medical device start-up focusing on unmet needs of those caring for the intubated patient, has announced the launch of the Sherpa Suction System, a tool to give nurses and respiratory therapists greater confidence in suctioning secretions pooling above the endotracheal tube's inflated cuff. Caregivers want to remove these mucus secretions to avoid aspiration into the lungs and the subsequent risk of acquiring ventilator associated pneumonia (VAP). The Sherpa Suction System is a single-patient product and includes the Sherpa Suction Guide and Suction Line. The Guide is a single molded unit that includes a locking feature, handle, soft tip and compatible with ETT sizes from 7.0 to 8.5 mm. Sherpa Suction Guide is easily clipped to the underside of the endotracheal tube and advanced until the handle is at the patient's teeth. The integrated Suction Line easily threads through the Guide, is advanced through the opening in the handle and guided to the optimal position for removal of secretions. The Sherpa Suction System allows for selective and cost-effective use of above-the-cuff suctioning in targeted patients.

Measuring Lung Function at Home

Using ndd Medical Technologies' EasyOne spirometer, Chronic Obstructive Pulmonary Disease (COPD) patients enrolled in the WISDOM study were as adept in monitoring lung function at home as the professionals who performed their baseline measurements in the clinic when the trial began. Results of the 2,161-patient clinical trial were recently presented in a poster at the American Thoracic Society meeting in Denver. Previous WISDOM (Withdrawal of Inhaled Steroids During Optimized Bronchodilator Management) study results were published in the New England Journal of Medicine (NEJM). Most patients in the study had severe or very severe COPD. The EasyOne spirometers used in the WISDOM and other clinical trials are portable spirometers employing advanced TrueFlow ultrasonic technology. There are no moving parts, no codes to enter, no screens to catch sputum, and no disposables to calibrate. The ultrasonic flow measurement is independent of gas composition, pressure, temperature, and humidity thus eliminating errors due to these variables. ndd Medical also manufactures the mobile EasyOne Pro and EasyOne Pro LAB, which perform most functions of a hospital-based PFT lab and have been found to be as accurate.

Early Warnings Go Wireless

SensiumVitals is a revolutionary new wireless early warning system that enables early intervention by continuously and accurately monitoring vital signs of heart rate, respiration rate and axillary temperature every two minutes, and alerting

the nursing staff when pre-set thresholds are exceeded. The system is based on a disposable, single-use, wearable patch that monitors patients. By notifying clinicians of changes in patients' vital signs, SensiumVitals brings the nurse to the deteriorating patient, allowing intervention before the condition worsens, resulting in improved patient outcomes, shorter hospital stays, and lower treatment costs. It is currently in trials in two leading National Health Service (NHS) hospitals at St. James's University Hospital in Leeds and Queen Elizabeth Hospital in Birmingham. An abnormal respiration rate is a strong indicator of serious underlying illness. SensiumVitals measures respiration rate using the technique of Impedance Pneumography (IP), which involves the direct measurement of thoracic impedance changes associated with respiration. The respiration rate algorithm used in SensiumVitals also ensures that irregular measurements caused by motion, eating, talking, sneezing, and so forth are not reported, reducing the occurrence of false alarms. The SensiumVitals digital patch is an FDA-cleared, lightweight (weighing only 1/2 ounce), energy-efficient, battery-powered device that uses a proprietary digital radio chip to monitor a patients' vital signs. It is designed for in-hospital use, particularly in general care, post-surgical areas, and emergency rooms, and can be easily attached to the patient's chest by means of two selfadhesive conventional ECG electrodes. The SensiumVitals patch has unique roaming capabilities, which means that patients' vital signs can be transmitted as they move around, helping patients recover more quickly.

Ventilation Device Addresses Transporting Neonates

The HAMILTON-T1 with neonatal option is a high-end transport ventilator that provides the best possible ventilation therapy for your smallest and most vulnerable patients. During transport, the HAMILTON-T1 delivers the same performance as a fully featured NICU ventilator at the bedside. Its unique features make it one of the best transport ventilators for neonates. Hamilton Medical has specially adapted the HAMILTON-T1 hardware and software to optimally meet the needs of ventilated neonates. Supporting tidal volumes of just 2 ml, the HAMILTON-T1 allows for effective, safe, and lung-protective ventilation for even the smallest preemies. The reliable and robust 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. With approvals and certificates for most types of transport and situations the HAMILTON-T1 is an ideal escort for your tiniest patients, reliable everywhere, both inside and outside the hospital, in the air as well as on the ground. The builtin high-performance turbine makes it completely independent of compressed air, gas cylinders or compressors. This saves

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- Sleep and Critical Illness: Bridging the Two Pillars⁺⁺

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Ventilator Circuit Stabilizer Launched

As many ventilator patients have become more mobile, both in long-term care centers and at home, increased safety has become an issue. One of the areas that is most important is to secure the patients ventilator circuitry and prevent accidental dislodgement. A more mobile patient, moving from bed to wheelchair and through everyday life, presents a unique challenge in not only providing proper ventilation but also in providing a safe method in securing the life sustaining ventilator tubing. In these critical moments of movement, the tubing and circuitry may easily find itself ensnared in bed sheets, on wheelchair railings or other hazards, which can result in serious injury or death from ventilator disconnections. Pepper Medical has introduced two products that will eliminate this issue and provide a safer environment for these patients. The first is the 701VCS (ventilator circuit stabilizer). The 701VCS is a harness style belt made of soft cotton laminate that fits comfortably around a patient's waist. Incorporated into the harness is a tubing securement strap that reliably secures the ventilator tubing getting it out of harms way and positioned close the patient's chest. The second product is the 701VCS/NG offering the same circuitry securement but also adds a second strap used to secure a nasal gastric (or oral gastric) tube keeping it secure and avoiding decannulation thereby reducing these difficult reinsertions. Find out more at www.peppermedical.com.

FDA grants priority review of Rapamune

The FDA has accepted a supplemental new drug application for priority review of Rapamune for the treatment of lymphangioleiomyomatosis, according to a press release. "If approved, Rapamune would be the first FDA-approved treatment option for patients living with (lymphangioleiomyomatosis [LAM])," Steve Romano, MD, senior vice president of Global Medicines Development at Pfizer, said in a press release. The application acceptance was based on results from the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial. LAM is a rare, progressive lung disease occurring in women of childbearing age that often is fatal. The trial involved 89 patients with LAM who had moderate lung impairment and were randomized to receive sirolimus or placebo for 12 months, followed by an additional 12-month observational period. Patients treated with sirolimus for 1 year experienced stabilization of lung function as measured by forced expiratory volume in 1 second. "The results of the MILES trial demonstrated that Rapamune has the potential to stabilize lung decline in patients suffering from LAM," Francis X. McCormack, MD, director of pulmonary, critical care and sleep medicine at the University of Cincinnati School of Medicine, said in the release.

Use of 3D Printed Splints for Infants

Three infants with an often-fatal airway disease have been treated by implanting a 3D printed medical device that improves breathing and changes shape as the children grow, the researchers reported. All three custom airway splint devices were designed to fit the anatomy of each child, researchers at the University of Michigan and colleagues reported in the journal Science Translational Medicine. The splints were

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hollow, porous tubes that could be stitched over the affected airways, forming a scaffolding that helped support the weakened structures. They were made with a "bioabsorbable" material known as polycaprolactone that dissolves in the body over time. Researchers at the University of Michigan made the devices using 3D printing, in which materials are added in layers to create custom products. Such printers are already used in medicine to create a number of custom implants, creating new jaws, hips and hearing devices, for example.

Looking at GERD

Gastroesophageal reflux disease (GERD), being female, and certain scores on the St. George's Respiratory Questionnaire (SGRQ) were associated with exacerbations of chronic obstructive pulmonary disease (COPD) in subjects using longacting controller medication, according to a study presented at the 2015 American Thoracic Society International Conference. "Knowing these factors can help clinicians identify subjects at risk for acute exacerbations of their COPD," said Robert Busch, MD, Brigham and Women's Hospital, Boston. Although inhaled medications can decrease the risk for exacerbations, some COPD patients still experience them, Dr. Busch said. Researchers aimed to determine the prospective risk factors for acute exacerbations (AE) of COPD among subjects in the COPDGene study, which focuses on genetic factors relating to COPD. A total of 2489 adults with COPD on tiotropium (TIO), long-acting beta-agonist inhaled corticosteroids (LABA/ICS), and/ or short-acting bronchodilators (SAB) alone or in combination were studied using retrospective data from the COPDGene study and prospective data from the telephone and web-based biannual Longitudinal Follow-Up program. Researchers divided subjects according to medication use groups (TIO/LABA/ICS, TIO, LABA/ICS, and SAB); exacerbators and nonexacerbators were identified by the frequency of AECOPD (one or more AECOPD a year compared with zero AECOPD for nonexacerbators). In multiple medication groups, the presence of GERD, female gender, and higher total SGRQ scores were significant predictors of exacerbator status, according to the researchers. Subjects in the LABA/ICS or TIO groups had similar characteristics, such as forced expiratory volume in one second, 6-minute walk distance, percent emphysema by CT scan, and pack-years of smoking. There was a trend toward significantly lower rates of exacerbations in subjects taking TIO compared with those taking the LABA/ICS combination. This was especially true in subjects who did not have a doctor's diagnosis of asthma.

The Benefits of Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) treatment could be a valuable addition to comprehensive therapy in patients with obstructive sleep apnea (OSA) syndrome, according to a new study. The study was presented at the 2015 American Thoracic Society International Conference. "In our study with 40 newly diagnosed OSA patients and a control group, pulmonary rehabilitation helped reduce body mass index, certain body circumferences, and improve pulmonary function," said researcher Katerina Neumannova, MSc, PhD, Palacky University, Faculty of Physical Culture, Olomouc, Czech Republic. The classic treatment for patients with OSA is continuous positive airway pressure, often called CPAP or CPAP therapy. Treatment via PR, which is used for conditions such as chronic obstructive pulmonary disease (COPD), has not been thoroughly studied in OSA, even though patients with OSA often have respiratory symptoms associated with a decreased health-related quality of life and a diminished functional capacity. The study included 40 patients with OSA

who were randomly assigned to either the PR group (n=20)or the control group (n=20). All patients involved in the study received CPAP therapy as their apnea/hypopnea index (AHI) was higher than 15. The PR group had 6 weeks of 60-minute individual rehabilitation sessions twice a week. The sessions consisted of education, exercise training, breathing retraining, respiratory muscle training, and oropharyngeal exercises. At baseline and then after 6 weeks of CPAP-only use or CPAP with the PR, researchers tracked a number of parameters, including pulmonary function, AHI, body mass index (BMI), percentage of body fat; and neck, waist, and hip circumferences. The final study included 15 patients in the PR group and 20 in the control group, as 5 patients did not complete PR. Although OSA severity was significantly decreased in both groups after the treatment, significant reduction of BMI, neck, waist and hip circumferences was confirmed only in the PR group. That same group also had an improvement in pulmonary function. Patients in both groups had decreased body fat, although body fat loss was higher in the PR group. "Patients with OSA can benefit from pulmonary rehabilitation treatment," Dr. Neumannova said. "We can determine on a patient-by-patient basis which patients would benefit most from pulmonary rehabilitation based on their individual disease and clinical judgment."

COPD Worse in Rural, Poor Areas

Living in a rural area and being poor are risk factors for chronic obstructive pulmonary disease (COPD), said Sarath Raju, MD, MPH, Johns Hopkins School of Medicine, Baltimore, Maryland, lead author of a study presented at the 2015 American Thoracic Society International Conference. The researchers used a nationally representative sample to pinpoint COPD risk factors. "We wanted to identify the prevalence of COPD in urban and rural areas in the U.S. and determine how residence, region, poverty, race and ethnicity, and other factors influence COPD rates," Dr. Raju said. Using data from the National Health Interview Survey, the U.S. Census, and the National Center for Health Statistics Urban-Rural Classification Scheme, the 87,701 participants included a population-based sample of adults older than age 40. The study's main outcome was the prevalence of COPD, defined as self-reported emphysema or chronic bronchitis. The researchers looked at both community-based and individual-based factors that are potential predictors of COPD, such as region, census level poverty, urban/rural residence, fuel sources, age, sex, race/ethnicity, smoking years, household income, home ownership, and education status. The prevalence of COPD in the study was 7.2%. However, in small metro/ruralpoor communities, the prevalence was 11.9%. Rural residence, southern residence, and community poverty were all associated with a greater prevalence of COPD. When the researchers added individual income to the model, community poverty was no longer significant. Researchers found an association between biomass fuels and COPD in the South, but there was no association in an overall multivariate model. "Findings suggest regional differences and the need for future disparities research to understand the potential contribution of occupational exposures, fuel sources, and indoor air pollutants to COPD prevalence in poor, rural areas," the researchers concluded.

The People's Choice

Dräger announced that the American Association for Respiratory Care (AARC) has honored the company with its esteemed Zenith Award for delivering outstanding products and services to the respiratory care profession. This is the seventh straight *Continued on page 37...*



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1 Than their prescribed mask; survey of U.S. patients 2 In a retrospective review conducted by Philips Respironics of approximately 15,000 patients using System One, those patients who used DreamMapper demonstrated 22% greater adherence to the therapy than patients who did not use DreamMapper. To see a list of compatible DreamMapper devices, go to www.sleepmapper.com/compatible.





Hospital Benefits of Using the Astral Ventilator

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview from Hospital for Special Care is Pamela Held, MEd, RRT, Respiratory Operations Manager.

Respiratory Therapy: Please tell us a little about Hospital for Special Care.

Pamela Held: Hospital for Special Care is a private, not-forprofit 228-bed rehabilitation long-term acute and chronic care hospital, widely-known and respected for its expertise in physical rehabilitation, respiratory, neuromuscular, cardiac, and spinal cord care, and medically-complex pediatrics. We have the following patient units:

- \bullet Weaning Unit for 30-45 day stays
- \bullet Rehabilitation Unit for 2-6 wk stays
- Chronic Care Unit-until death

RT: Can you explain your role?

PH: I am the respiratory operations manager responsible for the day to day operations of respiratory care services.

RT: What type of patients are you primarily treating with Astral? **PH:** We treat both adult and pediatric patients with the youngest patient being 3 months old. The primary patient diagnoses have been ALS, spinal cord injuries, respiratory failure and Poland syndrome. We are also using the Astral ventilator for patients being discharged to home.

RT: What types of treatments or devices have you been using in the patients that you are now placing on Astral?
PH: Historically we used LP10s, which were retired 2yrs ago, and many patients are currently using LTV ventilators. Some are using oxygen in addition to their ventilator. Transitions from older devices has been seamless for patients so far, in fact, we now have patients specifically asking for "the new ventilator"

RT: What are the key factors that led you to try the Astral ventilator?

PH: The possibility of improved portability within the facility for patients, as well as the quality of life improvements related to the battery life. Our clinicians love the battery reporting Astral provides, as it gives them peace of mind when taking patients down to recreational activities, or off the unit to designated sitting areas. The facility offers recreational activities 7 days a week and we've found the fact that Astral is so quiet really allows patients to be engaged in activities without having others distracted by the typical noises of a ventilator.

RT: Are there any other feature sets of Astral that have proven to be helpful to your clinicians?

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstien at s.gold4@verizon.net.

PH: Astral is simplistic for use in a wide range of patients, which is particularly important given our staff supports home ventilation discharges as well. I had an initial training on Astral and it was adequate to prepare me to provide a "train the trainers" session for staff. Our staff has had no challenges working with the device. The most important benefit we've found is that Astral provides an additional safety component we had not expected. When Astral is placed on the back of the wheelchair, because the circuit comes out of the top of the device we have decreased incidences of decannulation and circuit tears, as patients will often run into things with their wheelchairs. With Astral, the tubing comes up over the patients shoulders so we have none of our old safety concerns when patients are mobile.

RT: Could you tell us about a specific patient's experience on Astral?

PH: Glenn is a 56 year old male with C1-C2 quadraplegia due to a trampoline accident. He is ventilator dependent with chronic respiratory failure. Prior to his injury, Glenn was a very active man, who enjoyed restoring his old home, golfing, and was an avid traveler. As a resident at Hospital for Special Care, Glenn initially gained some freedom and portability on the LTV ventilator, but was frustrated with the battery life on the LTV.

RT: Please tell us a little about Glenn's transition to the Astral ventilator.

PH: When Glenn was approached about trialing the Astral, he was very excited. Glenn stated he hoped for greater independence with the Astral, which would improve his level of quality of life. Glenn's transition to the Astral was immediate and uneventful. We did not do trials, we simply switched ventilators. He loves this ventilator. I asked him why and he said it improved his quality of life. He stated it is extremely quiet, it is easier to breathe on, he can be on it the entire time he is up and the mobility bag offers protection to the vent itself. Since the transition to the Astral, Glenn has enjoyed full day trips to the casino, his home on the shore, and shopping.

RT: Is there anything else you'd like to add about your experiences with Astral?

PH: I would have to echo Glenn's feelings. It is well protected in its case, very quiet, the battery length fits our patient needs without having to worry about external batteries being charged and length of life. Furthermore, it is very easy to use and educate families on. Our patients have experienced greater freedom and mobility using this device.



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New Resusa-Tee[®], T-Piece Resuscitator Promises Many Hospital Benefits

In this feature, Respiratory Therapy interviews Scott Horowitz, Senior Product Manager for Mercury Medical about the application of a new product

Respiratory Therapy: Can you please tell me about this new T-piece, Resusa-Tee?

Scott Horowitz: The name of the new T-piece device is called Resusa-Tee. It is a new product but is a complementary, "sister" product to Mercury's Flagship Neo-Tee[®], the world's only disposable infant T-piece resuscitator that has gained worldwide acceptance for providing consistent infant ventilation around the globe. Many clinicians have asked if we had, or it would be nice if we did, offer a similar product for patients with a higher weight range over 10 kgs...expanding the offering to children and adults. I believe, if history of a T-piece repeats itself with a different patient population, this innovation can be revolutionary.

RT: How does it work?

SH: We recommend clinicians review the entire directions for use prior to using the device. Basically it's very easy to set-up or in-service and works very much like the Neo-Tee.

RT: Are there special features that make it stand out on the market?

SH: There is no other disposable T-piece resuscitator on the market today that simply handles kids and adults. More importantly, when compared with other products/technologies that are available for resuscitating such as self-inflating and flow dependent bags, (BVM's—bag, valve, masks, hyperinflation bags), you may not get consistent PIP and PEEP pressures. Also, some manual resuscitators do not come with manometers or PEEP valves. The Resusa-Tee comes standard with a manometer and PEEP valve. Best of all, the product is very lightweight and ideal for transport. While the device is a "resuscitation device," some clinicians that have seen it in demonstration say, "it works like a manual ventilator." Then they say, "please send me some samples as soon as possible."

RT: Can you describe its ease of use for clinicians? Is there any special training that has to be completed before using it? **SH:** As mentioned previously, the product is very easy to set pressures and use. A brief in-service on the product is really all that is needed. If one is familiar with the Neo-Tee, it makes it even easier to in-service. When RT students visit our booth at conventions, they try the CPR and hyperinflation bags, but when they demonstrate the Neo-Tee, they see first-hand how easy a T-piece is to set-up—and it's much less intimidating for them; also, they realize how safe it is to use.

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstien at s.gold4@verizon.net.

RT: Can you describe its efficacy? Have there been any studies to measure this? If so, can you describe it and give me the reference to the study?

SH: We do have studies on the Neo-Tee which are on the Mercury website, www.mercurymed.com, and we anticipate receiving similar results with the Resusa-Tee as it gets utilized in the marketplace.

RT: Are there cost savings associated with the device for clinicians, patients or payers?

SH: The savings could be realized in a variety of situations. For example, many CPR bags (BVM's) do not come with masks, manometers and PEEP valves and cost extra to purchase and then can be cumbersome to add them. While the Resusa-Tee may come with or without a mask, the manometer and PEEP valve are standard and integrated into the product design. Additionally, the Resusa-Tee can be used for two different patient populations, children and adults. With that said, clinicians can save money by not having to purchase two different sizes of CPR bags (BVM's) and can streamline their inventory. Additionally, there is no capital cost with the Resusa-Tee. Purchasing portable ventilators (that offer settings for PIP and PEEP pressures) can be expensive for a hospital, clinic or EMS agency. The Resusa-Tee offers these features at an extremely low cost.

RT: If the device is yet to be FDA approved, when do you expect it to be on the market?

SH: The Resusa-Tee has a 510(k) and is cleared for market in the US. Our expectations on having the product commercially available for sale in the US is by mid-to-late 1st quarter of 2016. The device will also have the CE mark for selling in Europe and other countries that require either 510(k), CE or both.

RT: When will the product be available?

SH: As we handle the preliminaries, as mentioned, we're hoping that the Resusa-Tee will be commercially available mid-to-late first quarter of 2016.

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Spirometry in Primary Care: A Model Service Specification for Clinical Commissioning

Chris Campbell

The role of spirometry

Office spirometry is a physiological test measuring exhaled volumes of air as a function of time. It is of irreplaceable value as a test of respiratory health in the same way that ECG and BP provide important information about general cardiovascular health. Spirometry gives an objective measurement of lung mechanics to help make or exclude a diagnosis, though a diagnosis cannot be made on the basis of spirometry alone.

Spirometry is recommended primarily for helping to diagnose and manage asthma and COPD, as well as a range of other diseases which may affect respiration. Spirometry is, however, only one way of objectively assessing COPD disease severity. Other measures, such as the BODE Index and quality of life assessment, help to build a more complete picture.

The use of spirometers in primary care is increasing but many primary care physicians, nurses and other health care providers have had little formal training in spirometry. Where there are major concerns regarding the technical ability of operators to perform the test and interpret its results commissioners may consider a spirometry service that provides:

- Quality assured spirometry
- Validation of safety and effectiveness
- Longitudinal measurements to recognise exacerbations and long-term decline
- Support in the making of a prognosis

Types of Spirometers

There are different types of spirometer with a range of features and prices:

- Volume displacement spirometers are simple to use and very accurate. They are useful for training and are used in lung function laboratories.
- Desktop spirometers are typewriter size and have a builtin display and printer and produce a report on thermal paper.
- Hand-held spirometers are pocket sized, have a realtime graphical display and provide reports and/or synchronise data with a PC. They are battery operated and store data so can be used inside or outside the office.
- PC spirometers make your desktop or laptop PC into a spirometer when you run the software application provided with the device. Spirotrac is the most widely used software.
- Medical Workstations are stand-alone medical devices that

Chris Campbell is the Senior Editor of Respiratory Therapy.

can also be linked to your office network. A range of hardware can be connected to the device for different physiological measurements, including spirometers, BP, ECG, SpO2, medical scales, etc. One medical workstation, the Vitalograph COMPACT, has a built-in spirometer.

• Respiratory monitors are not true spirometers because they cannot produce spirograms Their measured indices are limited, but always include FEV1. However, for screening purposes they are accurate and very fast to use.

The role of spirometry

The standard spirometry test is a maximal forced exhalation (with greatest effort) after a maximal deep inspiration (completely full lungs). Several indices can be derived from this blow.

- **FEV1** Forced Expiratory Volume in One Second the maximum volume of air that the subject is able to exhale in the first second. This is the single most important index.
- **FVC** Forced Vital Capacity the total volume of air that the subject can forcibly exhale. This can take as long as 20s in subjects with obstructive lung disease.
- **FEV6** Forced Expiratory Volume in Six Seconds the maximum volume of air that the subject is able to exhale in 6s. FEV6 is a useful and validated surrogate for FVC.
- **FEV1 /FVC** the ratio of FEV1 to FVC expressed as a fraction (not a percentage).

Population predicted values are commonly used to compare to the current test results. This can have some value in a few specific applications, but mostly 'predicted values' create a smokescreen blinding the practitioner from the real valuable data within the spirometry report.

Too often the opportunity for intervention or recognition of lung damage is lost because the spirometry test report appears to show that the data are in 'normal range, above 80% of predicted'. The rate of decline of the FEV1 should be the focus of the practitioner. If a previous measure of FEV1 is available, 'predicted values' are relevant only to help determination of a normal rate of decline.

It is possible to find smokers with a rate of decline of FEV1 of >100mL per annum (normal is about 30mL) whilst they are still above 'normal range'. If the rate of decline is not recognised, such individuals are simply classified as 'normal' (for a while it could be years or even decades before they present with dyspnoea).

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Pictured below is a representation of the well known 'Fletcher-Peto diagram' illustrating the natural history of COPD. FEV1 is shown against age in years. It illustrates that an abnormal decline in lung function may not be detected for decades if the subject stars off with normal lung function.



Subjects B is normal and D could also be normal, falling into the 5% of 'normals' below LLN. Subject C is detected as abnormal after 2 decades. Subject A is abnormal (probably a smoker) but is not detected without serial measurement and plotting of FEV1. Modern spirometers (not screeners or monitors) show the Z-score (or SDS) and the LLN (lower limit of normality) instead of 'percent of predicted'. This is far better, but still assumes that the test subject is in the same population as the 'predicted value' population.

Quality Control

Attention to equipment quality control and calibration is an important part of good practice. At a minimum, the requirements are to:

- Maintain a log of accuracy check results
- Archive the documentation of the annual service and any repairs
- · Record the software issue, updates or changes
- Perform QC checks before resuming use if equipment malfunction is suspected,
- Wash your hands

Prepare the test subject

- Explain the test
- Ask about smoking, recent illness, medication use, etc.
- Loosen any tight clothing
- Measure weight and height without shoes
- Instruct and enthusiastically demonstrate the test to the subject
- Demonstrate correct posture with head slightly elevated
- Show how the mouthpiece is inserted into the mouth, not like a trumpet
- Demand complete and rapid inhalation and maximum exhalation

Commence testing

- Two slow vital capacity (VC) tests are recommended before FVC
- Commence FVC testing, minimum of three usable efforts
- If obstruction is present administer bronchodilator and wait for effect
- Perform post BD testing
- The spirometric criterion required for a diagnosis of COPD includes FEV1/FVC ratio below 0.7 after the use of a bronchodilator.

Note: The procedure above cannot be conducted by an untrained operator. See below for training organisations.



Opportunistic Population Screening

The need to confirm diagnosis of COPD early is increasingly appreciated by primary care physicians in whose hands the ability to make improvements in early diagnosis largely rests. Case-finding of patients with symptoms of lifestyle limitation is probably the most practical way to achieve early diagnosis. Case finding can be achieved quickly, easily and cost effectively by screening people who are at risk of COPD using low cost respiratory monitors. To make a good assessment FEV1, the FEV1/FEV6 ratio and FEV1 as a percent of predicted is required. All this might sound complicated, but modern respiratory monitors can do all this automatically in a simple two-minute test of respiratory function. Using FEV6 instead of FVC makes it much simpler to get a repeatable reading and for screening purposes is perfectly adequate to determine the presence and severity of airways obstruction.

Spirometry Training

Health care professionals who perform spirometry must complete an approved competency based training course in spirometry and will be expected to keep their skills up to date.

References

- 1 The BTS COPD Consortium Practical Guide To Using Spirometry In Primary Care
- 2 Standardisation of Spirometry
- 3 Global Initiative for Chronic Obstructive Lung Disease (GOLD)
- 4 Global Strategy for Asthma Management and Prevention 2013
- 5 Management of chronic obstructive pulmonary disease in adults in primary and secondary care
- 6 An Outcomes Strategy for COPD and Asthma
- 7 NICE Quality standard for asthma
- 8 Achieving quality spirometry in the office
- 9 Spirometry Can Be Done in Family Physicians' Offices and Alters Clinical Decisions in Management of Asthma and COPD
- 10 Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study
- 11 An Approach to Interpreting Spirometry
- 12 The use and abuse of office spirometry

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A Comparison of Nebulizer Brand On Delivered Tidal Volumes and Peak Inspiratory Pressure During High Frequency Oscillatory Ventilation

Christopher J. Russian, Ph.D., RRT-NPS, RPSGT, Joshua F. Gonzales, MHA, RRT-NPS, RRT-SDS, Hanah Schelde, Lauren A. Terry, Shireen Albanna, Renee Adams

Abstract

Introduction: Mechanical ventilation of neonates requires close attention to volume and pressure delivery. The high frequency oscillator creates a challenge because delivered volumes and peak inspiratory pressures are not provided. Aerosol medication delivery during high frequency ventilation further complicates the scenario. There is currently little research regarding the effects of nebulizer use during high frequency oscillatory ventilated neonates. This lack of knowledge could increase the risk of lung damage.

Methods: This bench top study used an experimental design that did not involve human subjects. Seven different nebulizers were inserted into the circuit. The tidal volumes and peak inspiratory pressures were recorded twice using a one-way valve and twice without the one-way valve. Pressures and volumes were recorded using the RespiTrainer Infant (IngMar Medical, Pittsburgh, PA). Nebulizer liter flow was adjusted per recommendation of particular modality. An analysis of variance (ANOVA) was used to analyze the data and a Tukey procedure for post hoc analysis. A p value of 0.05 was used to determine statistical analysis.

Results: Our one-way ANOVA results demonstrated a significant difference between nebulizer type and volume change (p=.0001) and pressure change (p=.002). On post-hoc analysis there was significant differences (p<.05) between the AeroEclipse and the NebuTech HDN, Hudson MicroMist, Mini-HEART, Uni-HEART, and EZflow MAX in terms of volume change and pressure change.

Jesse Cozean is a clinical researcher who has overseen the design and operation of six different clinical trials totaling more than 15,000 patients, has received FDA approval for Stage III clinical trials on both OTC and prescription drugs, and is the author of many peer-reviewed articles. A research team that he led was just awarded the winner of the Fighting Ebola Grand Challenge from USAID, the White House Science and Technology Office, the CDC, and the Department of Defense. Jesse received his Bachelor of Science in Physics from Westmont College, and his MBA from Western Governor's University. He has served as the Vice President of Research and Development for several companies, including Abela Pharmaceuticals and Innovative BioDefense, heading research teams into pharmaceutical and OTC drug products. Jesse holds multiple patents on medical device and drug products. The author consults with Flosure Technologies. **Conclusion:** The study findings demonstrated that nebulizer type produced very similar results, with the exception of the AeroEclipse nebulizer. Nebulizer type does not appear to produce a major advantage or disadvantage when considering pressure and volume changes with HFOV. These findings support a variety of nebulizer brands when considering aerosol delivery with HFOV.

Introduction

High frequency oscillatory ventilation (HFOV) is used to ventilate and oxygenate patients in an effort to protect the lungs. HFOV is most often used in the NICU to provide ventilatory support and to prevent lung injury that may result from conventional positive pressure mechanical ventilation. HFOV accomplishes this by using very small tidal volumessmaller than anatomical dead space—and supraphysiologic respiratory rates.¹ Despite very high respiratory rates and very low tidal volumes, HFOV can achieve stable mean airway pressure and uniformed lung inflation, potentially leading to lower FiO2 use, improved oxygenation and equal survival rates to conventional mechanical ventilation.²⁻⁵ HFOV began in the Neonatal Intensive Care Unit (NICU) to provide rescue support and reduce lung injury that may result from conventional mechanical ventilation. However, the need to deliver nebulized medications did not cease when transitioning to this type of ventilation. Currently there is very little research investigating the impact of nebulizer use on delivered volumes and pressures. The use of nebulization in HFOV is likely to be as effective as nebulization with traditional mechanical ventilation, but the extent to which tidal volumes and inspiratory pressures are altered due to several different nebulizer brands is unknown. This has been unchartered primarily because of the delicateness of the neonatal population being tested.6,7

The research question for this project was does nebulizer brand create significantly different changes in delivered tidal volume and inspiratory pressures when using the HFOV and a neonatal test lung? The null hypothesis states there will be no difference in delivered tidal volumes and pressures when different nebulizers are used in-line with HFOV and a test lung. While the alternative hypothesis states that there will be a difference in delivered gas volume and pressures with different nebulizers placed in-line with HFOV. These vulnerable patients require respiratory therapists to provide adequate support while still preventing long-term lung damage. When you have good timing, the rest is easy.

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1. Doorduin J, Sinderby CA, Beck J, et al. Automated patient-ventilator interaction analysis during neurally adjusted non-invasive ventilation and pressure support ventilation in chronic obstructive pulmonary disease. *Crit Care.* 2014 18(5):550. 2. de la Oliva P, Schüffelmann C, Gómez-Zamora A, et al. Asynchrony, neural drive, ventilatory variability and comfort: NAVA versus pressure support in pediatric patients. *Intensive Care Med.* 2012 May;38(5):838-46. 3. Delisle S, Ouellet P, Bellemare P, et al. Sleep quality in mechanically ventilated patients: Comparison between NAVA and PSV modes. *Ann Intensive Care.* 2011 Sep 28;1(1):42.

Methods

The experimental design allowed for a benchtop study that did not require human subjects. The use of a test lung versus actual cadaver lungs or human subjects allowed us to control for potential complications, ie air leaks, associated with HFOV in neonates.^{8,9} The project used the High Frequency Oscillatory Ventilator (HFOV) 3100A mechanical ventilator (CareFusion, San Diego, CA). Baseline settings for the HFOV were: mean airway pressure 21 cmH2O, amplitude 36 cmH2O, inspiratory time percent 0.33, hertz 15, bias flow 20 L/min. The experiment included seven different nebulizers that are commonly used in hospital settings. All nebulizers were placed on the inspiratory limb distal to the humidifier. These nebulizers included: PARI LCplus (PARI Respiratory Equipment, Inc, Midlothian, VA), NebuTech HDN (Salter Labs, Alvin, CA), Hudson MicroMist (Teleflex, Morrisville, NC), Mini-HEART Lo-Flo (Westmed Inc, Tucson, AZ), Uni-HEART (Westmed Inc, Tucson, AZ), AeroEclipse (Monaghan Medical, Plattsburgh, NY), and EZflow MAX (Mercury Medical, Clearwater, FL). AeroEclipse was operated in continuous nebulization mode. The RespiTrainer Infant (IngMar Medical, Pittsburg, PA) was used to measure the volume and pressure produced by the HFOV and nebulizers. Firstly, we intubated the RespiTrainer Infant with a size 3 mm endotracheal tube (SunMed, Largo, FL), and calibrated the RespiTrainer infant unit. Mean baseline values generated for the HFOV without a nebulizer inline were tidal volume of 67.5mL and peak inspiratory pressure of 19.4 cmH2O. Next, nebulizers were placed, one at a time, in the same position in the inspiratory limb of the HFOV circuit, distal to the humidifier. We performed two trials, without using a one-way valve between the nebulizer and circuit, to assess the effect of the nebulizer output on volume and pressure changes delivered to the RespiTrainer. Then a one-way valve was added between the nebulizer and the HFOV circuit and two more trials were performed, ultimately testing each nebulizer four times. Using and not using a one-way valve was implemented to remain consistent with clinical practice. The liter flow was adjusted according to the manufacturers' recommendations for each nebulizer using an air flow meter. The PARI LC plus was operated on 6 L/min, Nebutech HDN on 6 L/min, Hudson MicroMist on 6 L/min, Mini-HEART on 2 L/min, Uni-HEART on 2 L/min, AeroEclipse on 6 L/min, and the EZflow MAX on 6 L/min. Normal saline was added to the chamber of each nebulizer to mimic actual nebulizer function and output. A blue filter was added between the HFOV circuit and the ETT to limit aerosol delivery to the infant trainer. An analysis of variance (ANOVA) was used to analyze the data and a Tukey procedure for the post hoc analysis. A p value of 0.05 was used to determine statistical analysis.

Results

Our one-way ANOVA analysis demonstrated a significant difference between the nebulizer type and the volume change (p=.0001) and pressure change (p=.002). On post-hoc analysis there was a significant difference for volume change between the AeroEclipse nebulizer and NebuTech HDN (p=.001), between the AeroEclipse and Hudson MicroMist (p=.001), between the AeroEclipse and Mini-HEART (p=.002), between the AeroEclipse and EZFlow MAX (p=.001). On post-hoc analysis there was a significant difference for pressure change between AeroEclipse and Hudson MicroMist (p=.003), between AeroEclipse and Nebutech HDN (p=.003), between AeroEclipse and Hudson MicroMist (p=.014), between AeroEclipse and EZFlow MAX (p=.003). See Table 1.

There was no significant difference on post hoc analysis between the PariLCplus, NebuTech, MicroMist, Mini-HEART, Uni-HEART, and EZFlow. There was no significant difference between the PariLCplus and the Aeroclipse for volumes or pressures. All volume and pressure data were generated with and without a one-way valve between the nebulizer and the HFOV circuit to remain consistent with clinical practice around the country. There was no significant difference, per one-way ANOVA, in volume change or pressure change when using and not using the one-way valve.

Nebulizer	Volume (mL) ± SD	Peak Pressure (cmH2O) ± SD
Pari LCplus	65.35 ± 4.06	18.60 ± 1.04
Nebutech HDN	70.00 ± 0.57	19.80 ± 0.00
Hudson MicroMist	70.00 ± 0.57	19.80 ± 0.00
Mini-HEART	69.00 ± 0.57	19.40 ± 0.00
Uni-HEART	68.75 ± 0.96	19.40 ± 0.00
AeroEclipse	58.00 ± 7.51	16.90 ± 2.19
EZFlow MAX	69.50 ± 0.00	19.80 ± 0.00

Table 1: Nebulizer Volume and Pressure Mean Values

Discussion

The study findings demonstrated that nebulizer type produced very similar results, with the exception of the AeroEclipse nebulizer. We also discovered a negative change in volumes and pressures compared to baseline values for the Aeroclipse and the PariLCplus. The Aeroclipse had a lower reduction in peak pressure and volume compared to the PariLCplus. The most likely explanation for a negative change in data variables is a leak in the system. All nebulizers used similar connections between the nebulizer and the circuit. However, it is possible that a leak existed between the top of the each nebulizer and the body of the nebulizer. However, we did not investigate if a leak was present or the source of any leak. Another possibility is that the pressure in the HFOV circuit produced backpressure within the two nebulizers. In this case there would be a reduction in aerosol entering the HFOV circuit. We did not investigate aerosol output with this study.

Nebulizer type does not appear to produce a major advantage or disadvantage when considering pressure and volume changes with HFOV. These findings support a variety of nebulizer brands when considering aerosol delivery with HFOV. The one exception, the AeroEclipse, produced a significantly lower volume and pressure compared to the other brands included in this study. We don't believe nebulizer flow rate setting caused this significant difference because several of the other nebulizers were set at the same rate, eg 6 Lpm. In addition, a couple of nebulizers operated on lower flow rates, eg 2 Lpm. One possibility is the AeroEclipse put out a smaller amount of aerosol compared to the other nebulizers. A smaller amount of aerosol output could produce a lower volume and pressure delivery. However, there is no literature to support this conclusion. Equally, aerosol output was not investigated in this study. Another explanation is the possibility of a small leak within the manufactured components of the device. However, we did not notice any changes in baseline HFOV settings, ie mean airway pressure reduction or amplitude reduction. Additional research is needed to determine why AeroEclipse produced lower volumes and pressures compared to the other nebulizers used for this study. Based on these findings we rejected the null hypothesis.

This study has several implications for the medical community. First, the results contributed specific and novel information on the effects that nebulizers have on HFOV delivered ventilator parameters. It is important to the safety of the neonate to appropriately choose a nebulizer type that will allow for safe administration of aerosolized medications. It is known that this area of study is relatively new and uncharted.¹⁰ Second. our research could ultimately lead to advancement in equipment design, nebulizer set-up and policy development in regards to nebulizer use for neonatal patients on HFOV. Further investigation is needed to understand the reason for the negative change in peak pressures and delivered volumes. If backpressure or a leak are the cause then nebulizer design may need to be addressed. Lastly, respiratory departments can use this information when deciding on which nebulizer to purchase and use with HFOV. Other studies have focused on aerosol deposition amongst different nebulizer types for neonates, but not the delivered pressures and tidal volume.^{11,12}

These vulnerable patients require respiratory therapists and equipment to provide adequate support while still preventing long-term lung damage. Due to the limited amount of patient monitored variables with the HFOV 3100A there is uncertainty in the impact of aerosol administration on volume and pressure changes. This study provides an analysis of two important parameters during mechanical ventilation, ie delivered volumes and inspiratory pressures. Although amplitude is provided on the 3100A this pressure does not represent the peak inspiratory pressure.

Limitations

There are several limitations of this study. First, we did not investigate aerosol output for each device. Placing a "catch" filter distal to the nebulizer and then weighing the filter at the end of each trial would provide aerosol output data. Second, we did not investigate if similar pressure and volume changes would occur with different baseline HFOV settings. We do not know if the same pressure and volume changes would occur with lower mean airway pressure and amplitude settings. Third, we did not investigate all available nebulizer brands. Specifically, we did not include any vibrating mesh nebulizers. At the time of this project we did not have access to an Aerogen (Galway, Ireland). We attempted to use the Omron MicroAir (Omron Healthcare, Lake Forest, IL); however, the design of the nebulizer created a leak in the set-up circuit. The final limitation of this study involves the bench top design we selected. Although the data collected was reliable we do not know if similar findings will occur in human subjects. For this reason our results must be interpreted with caution when making clinical decisions about nebulizer selection with the HFOV 3100A.

References

- 1 Notter RH, Finkelstein JN, Holm BA, eds. Lung injury: mechanisms, pathophysiologic, and therapy. Boca Raton, FL: Taylor and Francis Group;2005.
- 2 Cools F, Askie LM, Offringa M, et al. Elective high-frequency oscillatory frequency oscillatory versus conventional ventilation in preterm infants: a systemic review and meta-analysis of individual patient's data. Lancet. 2010;375(9731):2082-2091.
- 3 Sood BG, Shen Y. Effective aerosol delivery during highfrequency ventilation in neonatal pigs. Respirology. 2010;15(3):551-555.
- 4 Oostveen E, Macleod D. The forced oscillation technique in

clinical practice: methodology, recommendations, and future developments. Eur Respir J. 2003;22(1):1026-1041.

- 5 Rettwitz-Volk W, Veldman A. A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. J Pediatr. 1998;132(2):249-254.
- 6 Ari A, Atalay OT. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in stimulated pediatric and adult lung models during mechanical ventilation. Respir Care. 2010;55(7):845-851.
- 7 Sedeek KA, Takeuchi M, Suschodolski K, Kacmarek RM. Determinants of tidal volume during high frequency oscillation. Crit Care Med. 2003;31(1):227-31.
- 8 Garner S, Wierst D. Albuterol delivery by metered-dose inhaler in a pediatric high-frequency oscillatory ventilation model. Crit Care Med. 2000;28(6):2086-9.
- 9 Hager, DN, Fessler HE, Kaczka DW, et al. Tidal Volume delivery during high frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med. 2007;35(6):1522-1529.
- 10 Cameron D, Clay M. Evaluation of nebulizers for use in neonatal ventilatory circuits. Crit Care Med. 1990;18(8):866-70.
- 11 Fink JB. Aerosol delivery to ventilated infant and pediatric patients. Respir Care. 2004;49(6):653-665.
- 12 Clay MM, Pavia D. Factors influencing the size distribution of aerosols from jet nebulizers. Thorax. 1983;38(1):755-759.

The Jewish Hospital Demonstrates Over 2-Day Reduction in ICU Length of Stay with GE Ventilation

Joseph M Robertson, RRT

The Situation

The Jewish Hospital – Mercy Health, is committed to making quality healthcare easy in helping their patients and community be well in body, mind and spirit. As a teaching hospital, their graduate medical education (GME) program has been shaping the next generation of physicians for more than 120 years. And The Jewish Hospital and the entire Mercy Health system has a history of partnering with technology companies to support improved patient outcomes.

So when considering a purchase of new ventilators for critical care, The Jewish Hospital saw the opportunity for improving the health of critically ill patients through a measured approach to nutrition. GE Healthcare presented their solution, which included use of the ventilator and respiratory gas module, for precise, real-time measurements of the critically ill patient's caloric requirements. They also presented the potential to significantly reduce length of stay with the implementation of the GE technology, which would result in significant cost savings in addition to potentially improving their patient's health. The Jewish Hospital challenged the GE team to prove that the length of stay savings were real.

The Challenge

Working closely with Joseph Robertson, the Respiratory Care Manager for The Jewish Hospital, GE placed 19 ventilators with the GE Respiratory Gas Module, for a 90-day trial. A commitment to reduce ICU length of stay for critically ill, ventilated patients by 0.5 days was the requirement for purchase of the products. As a baseline for the 90-day study, the prior 9-months of patient data for all ventilated patients was used, which included ventilator days, as well as, ICU length of stay.

The Solution

Both The Jewish Hospital and GE understood that technology was only one part of the equation needed to deliver a length of stay reduction. People and process were also critical to the 90-day evaluation. Training the multi-disciplinary care team comprised of respiratory therapists, physicians, nurses and dietitians was required to create a sustainable impact. A consistent process needed to be developed for the measurement of indirect calorimetry.

Joseph is the Manager of Respiratory Care, PFT and EEG services at The Jewish Hospital – Mercy Health, Cincinnati, OH. He manages 34 staff serving all respiratory care needs across The Jewish Hospital including inpatient and out-patient services.



Overview

With the GE Respiratory Gas Module integrated with the GE CARESCAPE R860 Ventilator, clinicians can:

- Easily assess the caloric requirements of the critically ill ventilated patient
- Optimize a nutritional plan that integrates the entire care team
- Use Spontaneous Breathing Trials to easily liberate the patient from the ventilator
- Help reduce the ICU length of stay for critically ill ventilated patients, potentially improving patient outcomes while saving significant costs for the hospital

About The Jewish Hospital

The Jewish Hospital has been offering the most innovative treatments and services for 165 years. US News and World Report has named The Jewish Hospital among the best hospital in Ohio for the fourth year running.

They offer unique and specialized services that no one else in Cincinnati has:

- Adult Blood Cancer Center
- Makoplasty robotic arm for total hip replacements and partial knee replacements
- Gamma Knife that offers precision brain surgery with no incisions
- Advanced heart care with the newest and lowest dose radiation equipment

To learn more visit: www.gehealthcare.com/carescape_R860

HOW THE JEWISH HOSPITAL – MERCY HEALTH AND GE HEALTHCARE HOPE TO TAKE A BITE OUT OF ICU COSTS

Admission rates to hospital Intensive Care Units (ICU) are rising dramatically – along with the cost of critical care.¹ Here's how nutrition can impact the cost of care for ventilated ICU patients.

GROWING I	CU ADM	ISSIONS	5.	
††††FIVE MILLIONICU Patients1	CREASE U Patients 006-2015 ²	UP TO 50% ICU Patient Malnourishe	ts ed ²	
Nutrition is critical in ICU recovery. Ge's critical care ventilators feature an automated nutrition assessment application to assist caregivers with their ventilated patients.	▲ ½	ICU Patients on ventilator ³ THE JEV RESULT MULTI-DISCIPLINAI	VISH HO S: 90-DAY S RY CLINICAL NUTR	SPITAL TUDY ⁴ RITION PROGRAM
		© 28% REDUCTION Average ventilated (CU patient LOS	-9k LESS Avg. cost reduction per ICU ventilated	LIII \$6 MILLION Projected annual savings
(ge)	-	-	patient	-

Extending this solution across all U.S. hospitals could potentially impact hospital's clinical and financial outcomes.

The Jewish Hospital

- 1. Department of Health Policy, George Washington University School of Public Health and Health Sciences, Washington, DC, USA. http://www.ncbi.nlm.nih.gov/ pubmed/23672362
- Reid, CL. Nutritional requirements of surgical and critically-ill patients: do we really know what they need? Proc Nutr Soc. 2004 Aug;63(3):467-72.
- 3. The American Association for the Surgery of Trauma: Trauma Source – Mechanical Ventilation in the ICU. Note: % ventilated ICU patients referenced is a single source – actual % may vary)
- 4. The Jewish Hospital Demonstrates Over 2-Day Reduction in ICU Length of Stay with GE Ventilation. 2015. Note: GE does not guaranty any cost savings. These results are specific to The Jewish Hospital only.

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"GE supported the project by providing on-site respiratory therapists and a registered dietician to train our team. The support was broad and inclusive and allowed my team to both learn the product and implement the study," states Joseph Robertson, director of Respiratory Care. "We had used metabolic carts in the past and understood the measurements, but due to the complexity and time required to get an accurate measurement, we were very limited in the number of patients

Joseph Robertson Manager of Respiratory Care

where metabolic measurements were made. In fact, our cart had broken and the cost of replacement was significant, so it had not been replaced when this opportunity presented. Having the measurements available in real-time, using the technology integrated in the ventilator, was a huge time saver and leveraged the same resources."

The respiratory therapist captured the steady state caloric requirements of the patient and provided the data to the dietitian, who then consulted with the physician/nursing when modifications to the patient's nutritional plan were required. They also worked closely with nursing to understand the number of calories that the patient received in IV's and sedation such as Propofol (Diprivan). Ignoring these extra calories often leads to overfeeding and delays in ventilator liberation.



Pulmonologist

The Results

As a result of implementing a data-driven nutritional assessment for ventilator patients, The Jewish Hospital realized a 0.59 reduction in average ventilator days and even more significant was the 2.98 reduction in ICU length of stay from the pre-evaluation average. "Metabolic measurements is only one of the tools that we have access to with the GE Ventilator," states Dr. Erich Walder. "Our ability to implement lung protection

"Supporting our expert caregivers

with state-of-the-art technology that delivers real value for our patient's and

community is my goal," states Pat Davis-

Hagens, The Jewish Hospital President and Mercy Health Central Market CEO.

"Our partnership with GE has delivered

result in a significant financial savings for

improved patient outcomes that also

strategies using FRC measurements, with the same respiratory gas module, will prove valuable for the management of our critically ill ventilated patients."



Pat Davis-Hagens Central Market CEO

As a result of this 90-day risk-sharing evaluation, The Jewish Hospital purchased the 19 GE Ventilators with Respiratory Gas Modules.

the hospital."

Why Nutrition Matters

Appropriate nutrition plays an important role in our everyday lives – keeping us healthy and helping us recover from illness and injury. When a person becomes critically ill, nutrition

Pre-evaluation LOS Data

Month	Average Vent LOS	Average ICU LOS	Average ICU Cost per Patient
January	4.94	12.49	\$38,241.81
February	4.71	9.36	\$34,952.61
March	4.24	10.62	\$33,788.70
April	3.61	8.99	\$31,918.46
May	4.41	9.93	\$32,953.34
June	3.46	8.83	\$33,339.08
July	3.12	8.99	\$30,372.73
August	2.89	8.67	\$29,256.73
September	3.26	9.74	\$33,873.27
Average January- September (Pre-eval)	3.69	9.81	\$32,441.29

Total Number of Ventilated Patients: 565 Total Cost: \$18,329,328.85

90 Day LOS Study Data

Eval Month	Average Vent LOS	Average ICU LOS	Average ICU Cost per Patient
October	2.69	6.31	\$21,315.90
November	2.89	6.85	\$24,589.00
December	3.73	7.32	\$24,434.00
Total LOS for Eval	3.10	6.83	\$23,446.30

Total Number of Ventilated Patients: 112 Savings: \$1,007,438.88 (estimated)

Note: The 90-day study was conducted from October 2014-December 2014 using the Engström Ventilator and E-COVX modules. Data was compiled by The Jewish Hospital Respiratory Care Team.

plays an even more crucial role in the recovery process. Today, approximately 40-50% of ICU patients are malnourished.¹

Malnutrition is associated with:

- Deterioration of lean body mass
- Poor wound healing
- Increased risk of pressure ulcer development as the deterioration of lean body mass, nature of bed rest, and increased infection rates with decreased immunity lead to this issue²⁻³
- Weakened respiratory muscles which impacts ventilator liberation
- Impaired immunity
- Organ dysfunction
- Increased morbidity and mortality⁴⁻⁹

Evidence-based nutrition assessment has been shown to potentially reduce LOS in the ICU as much as 2.9 days.¹⁰

About Nutrition Assessment

In most hospitals, clinicians use predicative equations when assessing the nutritional status of their patients. There is no consensus on how to select from the hundreds of equations available and equations tend to be a one-size fits all approach to patient care. Many research studies have shown that these predicative equations are only accurate $\sim 30\%$ of the time.^{11,12,13} The metabolic status of the mechanically ventilated patient is in a constant state of flux as their bodies respond to stress and illness.

An accurate assessment of patient's nutritional status can be conducted using a metabolic cart. While using the metabolic cart to measure indirect calorimetry is possible, clinicians often encounter a number of issues:

- Specially trained staff is required, which may be costly
- Cart has a large footprint and may require frequent calibrations
- Connection to the ventilator circuit requires opening the circuit and may result in leaks that impact the measurements
- Assessment may be time consuming since steady state is required for the measurement to be valid. This is often difficult to achieve during the more active daytime hours, when staff is available to make the measurement

With the GE Respiratory Gas Module integrated into the ventilator, clinicians realize a number of key benefits:

- Accurate and precise measurements of Energy Expenditure in kilocalorie and Respiratory Quotient
- Availability to 100% of your ventilated adult and pediatric patients
- Part of the normal respiratory therapy staff workflow
- Data is available on demand; simply review trends for steady state and record the data
- Modular solution allows the clinician to add Respiratory Gas Monitoring where and when it is needed, allowing costeffective implementation
- Same module provides Functional Residual Capacity (FRC) measurements to aid clinicians in lung protection strategies

References

- 1 Souba, W. Nutritional support. N Engl J Med 1997; 336: 41.
- 2 Dorner B, Posthauer ME, Thomas D. The Role of Nutrition in Pressure Ulcer Prevention and Treatment: National Pressure Ulcer Advisory Panel White Paper. National Pressure Ulcer Advisory Panel
- 3 Stratton RJ, et al. Ageing Res Rev. 2005;4:422-450
- 4 Rubinson L, Diette GB, Song X, Brower RG, Krishan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 2004; 32(2): 350-356.
- 5 Heyland DK, Schroter-Nopee D, Drover JW, Minto J, Keefe L, Dhaliwal R, et al. Nutrition support in the critical care setting: current practice in Canadian ICUs – opportunities for improvement? JPEN J Parenter Enteral Nutr 2003; 27(1): 74-83.
- 6 Zijlstra N, Dam SM, Hulshof PJM, Ram C, Hiemstra G, Roos NM. 24-hour indirect calorimetry in mechanically ventilated critically ill patients. Nutr Clin Pract 2007; 22(2): 250-255.
- 7 Campbell CG, Zander E, Thorland W. Predicted vs. measured energy expenditure in critically ill, underweight patients. Nutr Clin Pract 2005; 20(2): 276-280.
- 8 Benotti PN, Bistrian B, Metabolic and nutritional aspects of weaning from mechanical ventilation. Crit Care Med 1989; 17(2): 181-185.
- 9 Fraser IM. Effects of refeeding on respiration and skeletal muscle function. Clin Chest Med 1986; 7(1): 131-139.
- 10 Early and Sufficient Feeding Reduces Length of Stay and Charges in Surgical Patients Leigh A. Neumayer, M.D.,*,1 Randall J. Smout, M.S.,† Howard G. S. Horn,† and Susan D. Horn, Ph.D. †Department of Veterans Affairs (VA) Salt Lake City Health Care System, and University of Utah, Health Sciences Center, Salt Lake City, Utah; and †Institute for Clinical Outcomes Research, Salt Lake City, Utah. Presented at the 24th Annual Symposium of the Association of Veterans Administration Surgeons Meeting, Seattle, Washington, April 9-11, 2000; published online November 28, 2000
- 11 Malone AM. Methods of assessing energy expenditure in the

intensive care unit. Nutr Clin Pract. 2002; 17: 21-28.

- 12 Matarese LE, Gottschlich MM (eds). Contemporary Nutrition Support Practice: A Clinical Guide. 1998: 79-98.
- 13 Reeves MM, Capra S. Variation in the application of methods used for predicting energy requirements in acutely ill adult patients: a survey of practice. Eur J Clin Nutr. 2003; 57: 1530-1535

Emergency Oxygen Administration

Chris Campbell

We have received numerous questions regarding the use of supplemental oxygen in emergency situations, such as "Should we? Can we? How do we? What if we don't?" The first answer is easy, at least morally and ethically...OF COURSE. The question's legality aspect falls under "Can we?"

That answer is a little more complex. In general the FDA (Food Drug Administration) considers U.S.P. (United States Pharmacopoeia) oxygen to be a prescription drug to be administered by a physician. That means that normally we cannot legally administer oxygen. An exception is recognized for equipment that:

- 1. can deliver U.S.P. oxygen at a rate of at least 6 liters per minute for a minimum of 15 minutes;
- 2. is labeled FOR EMERGENCY USE ONLY WHEN ADMINISTERED BY PROPERLY TRAINED PERSONNEL FOR OXYGEN DEFICIENCY AND RESUSCITATION. FOR ALL OTHER MEDICAL APPLICATIONS, RX ONLY; and
- 3. is utilized in a manner consistent with its labeling.

The lack of definition of terms creates some ambiguity. Certainly a person needing CPR (cardiopulmonary resuscitation) qualifies as an emergency. Other instances of acute respiratory need may involve some judgment, but since EMERGENCY USE is undefined and oxygen is not lethal, it is certainly wiser to err on the side of use than non-use.

The statute (not the label), does not define PROPERLY TRAINED PERSONNEL per se, but does say "as authorized, certified, or licensed by state authorities." Thus, some states may have adopted legislation that requires specific training or otherwise restricts authorization. Lacking that, however, there is no legal impediment to administrating emergency oxygen by those who have been trained to utilize the equipment on hand.

Once past the "Can we?" the "How do we?" is again pretty easy... we use it as we have been trained.

Included in the "What if ..." category must also be the query "What if we do, and something goes wrong?" In many jurisdictions non-medical personnel are protected under Good Samaritan statutes if they have acted within the scope of their training. At the present time there is no legal requirement for us to have available or to administer oxygen to individuals in need. That will not keep us out of court, however, and the time appears

Chris Campbell is the Senior Editor of Respiratory Therapy.

to be coming where the standard of care (if not the law) will be that we must have oxygen available to administer if needed. Should we elect not to make such a provision and an oxygendeficient emergency occurs in our facility, we may find ourselves to be the precedent-setting case that establishes emergency oxygen administration as the standard of care in our area.



Highlights of Recent Experience in Long-term Care Settings with an Automated Intermittent Subglottic Aspiration System

Helmut Fendler, RN, Katja Fain, SLP, and Jerry Gentile, BSRT, BSHA, MBA, EdD(c), RT, RRT

Keywords: Mechanical Ventilation, Pneumonia, Respiratory Tract Infections, Ventilator Associated Pneumonia (VAP), Ventilator Associated Events (VAE), Subglottic Secretion Drainage (SSD), Automated Intermittent Subglottic Aspiration

Abstract

Subglottic aspiration is a standard requirement in protocols and guidelines to prevent serious respiratory infections in patients requiring mechanical ventilation, and for other dysphagic patients intubated with tracheal/endotracheal tubes with a ballooned cuff. Research in subglottic secretion drainage (SSD) using a variety of traditional suction methodologies comes from studies done in ICU settings. Many advances in SSD are directly applicable to long-term care. This paper summarizes various SSD approaches and presents recent clinical experience with an automated intermittent subglottic aspiration system in long-term care facilities in Germany and the United States.

Introduction

When mechanical ventilation is required and patients are intubated with a cuffed endotracheal or tracheal tube, secretions are known to accumulate above the ballooned cuff. Aspiration of these secretions is a top priority for a host of reasons, with the goal of preventing short- and long-term Ventilator-Associated Pneumonia (VAP) frequently being the primary concern. The more advanced and newer cuffed endotracheal and tracheal tubes include a separate integrated port (suction lumen), designed to facilitate suction of subglottic secretions.

In most long-term care settings, patients typically have been suctioned by staff members using 10 or 20 ml syringes recommended at hourly intervals, or via continuous or intermittent suction using general purpose suction devices. In long-term acute care hospitals, regulated wall suction also has been applied continuously and/or intermittently. These conventionally used suction methods have presented practical and multi-faceted challenges related to: applying appropriate suction pressures consistent with guidelines, maximizing secretion aspiration volume, reducing tissue damage, preventing cross-contamination and nosocomial infections, contributing to

Helmut Fendler is the Director at the Gesundheits Manager Institute for Wound Care, Nursing Care, Hygiene Management, and Respiratory Care, Nuremberg, Germany. Katja Fain is a speech therapist specializing in neurological disorders, based in Veitsbronn, Germany. Jerry Gentile is the Director of Respiratory Care Services at Eastchester Rehabilitation & Healthcare Center, Bronx, New York. patient comfort and rehabilitation, relieving staff burden, and reducing treatment costs.

In this paper we present retrospective information and highlights of five years' of clinical experience in Germany (as well as initial US experience) in long-term care with an automated system designed specifically for intermittent subglottic aspiration.

Goals and Evolution of Subglottic Secretion Drainage (SSD)

Most clinical experience and evidence to date related to mechanical ventilation and the use of different SSD methodologies come from studies conducted in intensive care settings. In the ICU, VAP is estimated to occur in 9% to 25% of patients,¹⁻³ with mortality attributed to VAP ranging as high as 27%.⁴ Each day of mechanical ventilation increases patient risk for VAP by 1% to 3%,⁵ and occurrences are associated with increased ICU and hospital stays. Increased hospital costs of over \$40,000 per patient have been estimated.³

Parallel incentives to improve subglottic secretion drainage (SSD) methodologies and outcomes exist in long-term care. Patients with neurological, traumatic or medical disorders such as ALS, hypoxic brain damage, traumatic head injuries, strokes, and bleeds, often correlate with severe dysphagia, among a number of obstacles to weaning from ventilation and successful rehabilitation. As in the ICU, SSD is required to remove accumulated secretions from the pool above the ballooned cuff of the tracheal tube. The secretions, a combination of salivary aspirate, oropharynx secretions, and gastric reflux aspirate, contain pathogens. Because of the anatomy of the trachea, some leakage around the ballooned cuff is inevitable, allowing for potential drainage into the lungs. Suboptimal SSD therefore increases the risk of VAP. Coma patients are at substantial risk for pneumonia.

VAP Reductions Across Methodologies in SSD Randomized Controlled Trials

Efforts to prevent, delay, and shorten VAP using SSD have evolved and been effective when applied according to the latest guidelines. In nine randomized controlled trials in a total of 2,172 patients, a majority expected to be ventilated for greater than or equal to 48 hours, the incidence of VAP was reduced significantly, with VAP reductions among SSD groups ranging from 37.2% to 64.25% compared to respective control groups.⁶⁻¹⁴ Reductions were significant for all SSD methodologies applied in the research (manual syringe suction, continuous suction, and intermittent suction). Syringes, general purpose pumps and regulated wall suction were all used as suction sources among the various studies.

Practical Issues Effecting SSD in Practice

Although controlled studies demonstrate the value of SSD in significantly reducing VAP, many practical issues associated with widely used methodologies and suction sources deserve attention and study. For example, continuous suctioning is sometimes used but is known to cause drying of the tracheal mucosa and tissue damage. Too much suction and too frequent suctioning are also known to stimulate the production of additional saliva and other secretions.^{12,13,20,21}

Guidelines established by the AARC suggest the use of -80 to -150 mmHg of suctioning pressure. Both 10 ml and 20 ml syringes have been shown to exert over -700 mmHg of pressure, many times higher than recommended.¹⁷ Guidelines also recommend hourly suctioning of patients when manual syringes are used. In practice as well as research, and because of patient-to-staff ratios and workloads, it often has been difficult to adhere to hourly suctioning. If spontaneous aspiration occurs around the stoma as a result of a buildup of secretions, maceration of the skin occurs, foul odors proliferate, clothing can be repeatedly soiled, and the patient may be stigmatized. In addition, relatively small volumes of aspirate (median average of 14 ml/day) are typically removed via manual syringe suction.¹²

Wall suction and general purpose suction pumps, widely used for SSD, serve a number of other purposes in the ICU and in long-term acute care. Neither were designed specifically for SSD. Actual pressures may vary from the regulated settings. In addition, studies have shown nosocomial infections can be spread through contaminated wall suction, despite protocol measures for cleaning of regulators and other parts.¹⁹

Unblocking a continuously blocked tracheostomy tube carries a high risk of pneumonia if any pooled secretions aspirate into the airways. At the same time, unblocking is essential and unavoidable for patients for normalizing airflow, key pharyngeal awareness training, rediscovering/relearning vital protective functions and developing laryngeal reflexes.

Application of Automated Intermittent Suction Technology to SSD: Development and Clinical Experience in Long-term Care in Germany [Helmut Fendler, RN and Katja Fain, SLP]

We began our collaboration more than 7 years ago, combining knowledge from backgrounds in long-term nursing care, wound care and respiratory care. Our goal was to improve subglottic secretion drainage in patients intubated with tracheal or endotracheal tubes -- tubes with an integrated suction lumen.

The Gesundheits Manager Institute for wound care, nursing care, hygiene management, and respiratory care, services the Intensive Care Clinic, IPK (intensive.pflege.klinik GmbH & Co. KG), an independent long-term care facility in Nuremberg, specializing in the care of traumatic brain injury patients, and other patients neurologically severely impaired. A staff of over 25 multi-disciplinary specialists cares for 60 patients at any given time in the IPK, 40 of whom on average are coma patients of two types.

Ninety percent of the patients are Awake Coma, patients who sleep at night and open their eyes in the morning. They cannot talk, but have day and night routines. The remaining patients are classified Coma, with eyes closed 24/7.

Our decision to explore and refine automated subglottic secretion drainage began as a logical response to dissatisfaction with traditional suction methods and the search for efficient alternative solutions. People produce 1-2 liters of saliva a day, equivalent to 333-666 ml every 8 hours.¹⁶ Those who are able to swallow, do so 1000-3000 times a day. For our impaired population, with severe dysphagia and even absent spontaneous swallow response, we were seeking a practical way to capture the saliva and other secretions above the ballooned cuff of the tracheal tube, to prevent VAP, skin problems around the stoma, and patient discomfort.

Over the past 5 years, at the IPK and in surrounding clinics in the Nuremberg area, we have treated 60 patients using automated intermittent aspiration of subglottic secretions by means of a new device, the SIMEX Subglottic Aspiration System. There are two SIMEX pump models, the cuff M and the cuff S, which are identical with respect to their modes of operation, and only differ in size and weight and different collection canisters. The cuff M is designed for mobile use, for example by wheelchair- bound patients. The cuff S is for stationary use, at the patient bedside and in surgical settings. In the clinics, we have used both models.

Beginning with our earliest experiences with the system, we focused primarily on three parameters: suction pressure, the duration of suction, and the interval between individual suctions periods. Our goal was to tailor the suction pressure to the needs of the individual patient depending on the amount of secretions and the viscosity, while keeping overall suction to a minimum and within the AARC recommended pressure guidelines. The SIMEX system allows for pressure settings ranging from -15 to -225 mmHg. Suction intervals can be set at from 5-60 seconds "ON," time and from 1-60 minutes "OFF" time. AARC recommends the use of -80 to -150mmHg.

We were encouraged by the initial responses observed. Secretions were readily collected in the canisters. We observed immediately that the amounts of secretions being collected were much higher (several-fold), than with the use of syringes. Maceration around the stoma of patients was reduced, and later frequently prevented, as experience with the system was gained. In contrast with the manual suctioning of patients using syringes, which frequently causes coughing, sometimes severe, and an increase in body tone, heart rate and respiration, the automated suctioning using the system was quiet and very well tolerated. Vital signs remained constant.

5-Patient Study and Caregiver Survey Results

In another step to quantify treatment results with the system as well as to gather data on the use of resources, and feedback from caregivers, Fain led the development and conduct of a study within the facility that included a survey of caregivers. From March 13-24, 2014, 5 patients requiring SSD were selected from the population in the clinic. Patients were observed for a total of 10 days. Each patient received manual suctioning by syringe for the first 5 days, followed by use of the SIMEX cuff S in the final 5 days. The system settings were determined according to each patient's condition, and ranged from -75 to -150mmHg. The "ON" time of aspiration was set at 10-15 seconds, and "OFF" time

Results

(Based on mean average of 5 patients who were observed for total 10 days. Manual aspiration used during initial 5 days and automated aspiration used in final 5 days. The system parameters tailored to each patient's condition. Aspiration pressure ranging between -100 to -200 mbar, aspiration ON time of 10-15 sec, and OFF time of 10-15 min.)

	Manual ballooned cuff aspiration using a 20 ml syringe	Automated Intermittent Subglottic Aspiration System – SIMEX <i>cuff</i> S
	Tracheostomy tubes used: Portex, BlueLineUltra	, Suctionaid Gr. 8 or 9
Mean aspirate volume removed	approx. 33 ml	approx. 400 ml
Duration	5 days => 8 times daily during 8 hour shift	5 days automatic intermittent aspiration
Materials used	40 syringes (20ml), 40 pairs of gloves, 50 dressings	1 cuff S aspirator, 1 aspirator collection container, 1 suction tube
Results	 aspiration only possible on an interval-type basis increased risk of sputum to microaspirate into the lungs time-consuming severe cough stimulus during aspiration stoma remains macerated and extremely damp as a result of the enormous amounts of sputum that come out due to overflow additional stoma care, need for dressings and changes of clothing and bedding erythematous skin around the stoma high frequency of endotracheal/ bronchial aspiration 	 automated intermittent aspiration - 24/7 minimized risk of any sputum to microaspirate into the lungs unobtrusive sounds during aspiration aspiration does not have a negative impact upon breathing, the cough stimulus or physical tone stoma is dry and less irritated from the first day onwards immediate positive feedback from nursing staff => see survey reduction in the frequency of endotracheal bronchial aspiration

at 10-15 minutes. A total of 26 nurses took part in the survey. Results are shown in the table above.

The clinic nurses were asked the following questions:

Survey Results

- 1. In your opinion, is the automated intermittent aspiration system beneficial to the patient? If so, what are the benefits?
- 2. Does automated intermittent aspiration make your job easier? How much and in what ways does it make the job easier?
- 3. Does automated intermittent aspiration bring you any benefits in your job? If so, what are the benefits? See survey results in graph below.



Longest Individual Patient Use

The SIMEX cuff S model was used in one of our first experiences with automated SSD, in an Awake Coma patient, beginning in January of 2010. Prior to that time, the patient was suctioned via syringe, with consistently small amounts of secretions removed. The patient's stoma at that time was moist, irritated and reddened. In November of 2012, after nearly 3 years, we compared aspiration volume removed with the system, to what had previously been removed with syringe. We also compared differences in materials used and nursing time. Remarkably, the patient remains on the system, after the 3 additional years since 2012, and continues to comfortably tolerate the suction and benefit from the improved environment provided by the system. The calculations from 2012 are shown in the table below.

Comparative Results

(Automated intermittent subglottic aspiration system versus conventional manual syringe sytem for long-term care coma patient)

Date: Jan 2010 to Nov 2012 (1,064 days)	SIMEX cuff S Actual Values Recorded	Manual Syringe Extrapolated Values
Total Aspiration Volume	118,334 ml	38,304 ml (est. 1.5 ml/hour)
Disposable Materials Used	132 collection bags 132 suction tubes	25,536 syringes 25,536 pairs of gloves
Nursing Time Spent for Aspiration	Minimal to none	127,680 minutes (2.91 months)(24 x daily 6 min)
Tissue/Skin Condition	Stoma dry	Stoma moist, irritated, macerated and reddened
Patient Reaction to Aspiration	No discomfort	Cough irritation, body tension
Not Considered		Nursing time requirements for • change of wet dressing • change of wet garment/ linen • paratracheal aspiration



Leakage of Secretions from Manual Aspiration



Dry stoma Following Treatment with SIMEX cuff S

Initial Long-term Care Experience in the United States Eastchester Rehabilitation and Healthcare Center, Bronx, NY [Jerry Gentile, BSRT, BSHA, MBA, EdD(c), RT, RRT] The facility specializes in Respiratory Care, consisting of a 40bed ventilator and a 15-bed tracheostomy step down unit. Our staff consists of 20+ Registered Respiratory Therapists (RRTs), as well as a Speech Pathologist and Registered Nurses that work closely with the Respiratory Care Department.

Sixty percent of the patients on the ventilator unit have Glasgow Coma Scores (GCS) of 12 or below. The remaining forty percent are patients with GCS of 12 or above that have daily interaction with staff, as well as rigorous physical, occupational, and speech therapy routines. These departments work closely with the respiratory therapists in the development of the therapies and care plans.

Ventilator Associated Events (VAE)

In 2013, the CDC developed the Ventilator Associated Events (VAE) surveillance definition algorithm to streamline and identify a broad range of conditions and complications that arise in mechanically ventilated adult patients. There are 3 definition levels with the VAE algorithm: (1) infection-related ventilator-associated complication (IVAC); (2) ventilator-associated condition (VAC); and (3) possible VAP.

The initial VAE rate on the ventilator unit peaked at 18%, with a resulting hospital transfer rate of 14%. In response to this high rate of nosocomial pneumonia, the Respiratory Care Department developed a new VAE protocol. In collaboration with the Department of Nursing, we instituted the new protocol for all 40 patients. This protocol consists of: (1) head of bed 30 to 45° ; (2) chlorhexidine 0.12% daily; (3) DVT prophylaxis; (4) proton pump inhibitor; and (5) daily weaning from mechanical ventilation.



Leakage of Secretions from Manual Aspiration



SIMEX cuff S Automated Intermittent Subglottic Aspiration System

The initiation of the VAE protocol had a moderate impact. The unit VAE rate dropped from 18% to 12%, with a hospital transfer rate of 7%. This was a significant improvement, but we felt this rate could be much lower.

Subglottic Suction Tracheostomy

In September, 2014, we decided to switch all tracheostomy tubes to subglottic suction models. We did this in anticipation of the VAE rate decreasing due to the promise of secretion removal from above the cuff. This wound up being labor-intensive for the Respiratory Therapists, as each subglottic port had to be suctioned manually via a 20 ml syringe. This method was not practical and presented many challenges, such as applying consistent suction pressure (according to AARC guidelines), ensuring maximal aspiration of secretion volume, patient comfort level, minimizing tissue damage, and risk of nosocomial pneumonia. Respiratory Therapists reported that the subglottic ports would frequently clog, resulting in saline lavages that further increase the risk of VAE. The addition of the subglottic suction tracheostomy tube resulted in no change of the 12% VAE rate over the course of five months.

SIMEX cuff M

In March, 2015, we instituted a trial of five SIMEX cuff M devices in our ventilator unit. We started the trial at -100 mmHg suction pressure/10-second suction duration/10-minute suction intervals. We adjusted the settings based on aspirate volume, patient comfort level, and evidence of tracheal tissue trauma. In the course of the eight-month trial, we have had the SIMEX cuff M devices on 10 patients. We have determined that optimal suction settings are -150 mmHg suction pressure/12 second suction duration/10-minute suction intervals. Secretion collection averaged 60 to 150 ml/day. Maceration of tissue surrounding the stoma has decreased significantly, as well as soiling of tracheostomy ties and surrounding clothing. Patients have tolerated these subglottic suction settings very well, with no reports of tracheol discomfort.

At the end of the eight month, 10 patient trial, two of the patients in the study developed VAC - non VAP related complications. This was probable resorption atelectasis due to mucus plugging of the airway. In both of these cases, the HME (heat and moisture exchanger) was discontinued and heated humidification initiated, along with deep tracheal suctioning. The patients recovered without incident.

The trial was in conjunction with the new VAE protocol instituted for all mechanically ventilated patients. There was a dramatic improvement in our VAE rates and significant enough to warrant further study. We have recently begun a 25 patient/15 control RCT to further study the potential of the SIMEX cuff M in decreasing VAE risk.

Current RCT Trial

We would like to report that three weeks into the RCT, the patients are tolerating the SIMEX cuff M well. Of the 25 patients on the device, we have not had a reported VAE to date.

Based on our initial clinical experience, we have already begun to discuss ways in which research and design efforts focused on current models of subglottic suction tracheostomy tubes (the patient interface) might further enhance the effectiveness and use of automated subglottic secretion drainage. Port size and location are of particular interest, as is the angle of the patient, because each variable effects the surface area for actual suction. We have many patients that sit up in wheelchairs and/or Geri chairs at greater than 60° angles. From our initial observations, the subglottic suction seems to be less effective at patient angles of greater than 50° . When the patient returns to a 40° or less angle, the subglottic suction is most effective. We will be investigating these variables further in our RCT.

References

- Ibrahim EH, Tracy L, Hill C, et al. The occurrence of ventilator-associated pneumonia in a community hospital; risk factors and clinical outcomes. Chest. 2001; 120:555-561.
- 2 Craven DE, Steger KA. Nosocomial pneumonia in mechanically ventilated adult patients: epidemiology and prevention in 1996. Semin Respir Infect. 1996; 11:32-53.
- 3 Rello J, Ollendorf DA, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest. 2002; 122:2115-2121.
- 4 Fagen JY, Chastre, et al. Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. The American Journal of Medicine. 1993; 94:281-288.
- 5 Cook D, Walter S, Cook R, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Annals of Internal Medicine. 1998; 129:433-440.
- 6 Valles J, Artigas A, Rello J, et al. Continuous aspiration of subglottic secretions in preventing ventilator-Associated

Pneumonia. Annals of Internal Medicine. 1995; 122:179-186.

- 7 Bo H, He L, Qu J. Influence of the subglottic secretion drainage on the morbidity of ventilator associated pneumonia in mechanically ventilated patients. Zhonghua Jie He Hu Xi Za Zhi. 2000; Aug23:8:472-474.
- 8 Kollef M, Skubas N, Sundt T. A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. Chest. 1999; Nov11 6:5:1339-1346.
- 9 Smulders K, van der Hoeven H, Weers-Pothoff I, Vandenbroucke-Grauls C. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. Chest. 2002; 121:3:858-862.
- 10 Damas P, Frippiat F, Ancion A, et al. Prevention of ventilatorassociated pneumonia and ventilator-associated conditions: A randomized controlled trial with subglottic secretion suctioning. Critical Care Medicine Journal, 2015; 43:1:22-30.
- 11 Juneja D, Javeri Y, Singh O, Nasa P, Pandey R, Uniyal B. Comparing influence of intermittent subglottic secretions drainage with/without close suction systems on the incidence of ventilator associated pneumonia. Indian Journal of Critical Care Medicine. 2011; 15:3:168-172.
- 12 Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent Subglottic Secretion Drainage and Ventilator-associated Pneumonia: A Multicenter Trial. Am J Resp Crit Care Med. 2010; 182:910-917.
- 13 Lorente L, Lecuona M, Jimenez A, Mora M, Sierra A. Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. Am J Resp Crit Care Med. 2007; 176:1079-1083.
- 14 Mahul P, Auboyer C, Jospe R, et al. Prevention of nosocomial pneumonia in intubated patients: Respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. Intensive Care Med. 1992; 18:1:20-25.
- 15 Ekstrom J, Khosravani N, Castagnola M, Messana I. Saliva and the Control of its Secretion. In: Ekberg O, ed. Dysphagia. 1st ed. Springer-Verlag Berlin Heidelberg: 2012:19-47.
- 16 Cozean J, Benefits of automated intermittent subglottic secretion drainage. Respiratory Therapy. 2015; 10:4:27-28.
- 17 AARC Clinical Practice Guidelines, Respiratory Care, 2010; 55:758-762.
- 18 http://www.livescience.com/32208-how-much-spit-does-aperson-produce.html Published October 15, 2012. Accessed December 8, 2015.
- 19 Kaye K, Marchaim D, Smialowicz C, Bentley L. Suction regulators: A potential vector for hospital-acquired pathogens. Infection Control and Hospital Epidemiology. 2010; 31:7:772-774.
- 20 Harvey C, Miller P, Lee J, et al. Potential muscosal injury related to continuous aspiration of subglottic secretion device. Anesthesiology 2007; 107:666-669.
- 21 Berra L, De Marchi L, Panigada M et al. Evaluation of continuous aspiration of subglottic secretion in an in vivo study. Crit Care Med 2004; 32:10:2071-2078.

Simple Solutions for Difficult Situations

Robert Kohler, EMT-P, Co-author Jeremy LaPlante

A short testimonial below was written by a user in the prehospital market. Robert Kohler EMT-P has used the VAR VORTRAN Automatic Resuscitator for several years, and has written an abstract on our device called "The Control of End tidal CO2", by Robert Kohler EMT-P, Stamford Emergency Medical Service.

Recently, Robert experienced a new incident using the VAR on a child who is inflicted with Epileptic seizures. Normally it is suggested that the VAR be used with a cuffed endotracheal tube but due to the size of the patient an un-cuffed tube was placed in the child. Robert explains the events that follows below;

I arrived on the scene at a doctor's office to find a 6 year old 25-kg girl in status epilepticus caricaturized by right arm/leg shaking and facial twitching during which the patient exhibited ataxic and ineffective respirations. The patient's doctor elected to intubate the patient, with a 5.0 uncuffed tube, who currently had an O2 saturation of 70%. Post intubation the patient began to seize again and it became apparent that the BVM was hampering what little respiratory effort that patient had left.

therapist can often concentrate and "sync", so to speak, with the patients ventilatory effort. However, in the field it is very different story.

To circumvent the battle I opted to use the Vortran Automatic Resuscitator (VAR). My concern was that the tube used was un-cuffed and we may not be able to create a seal under pressure. Thankfully I was wrong! I applied the vent and set the PIP initially to 15cm of water pressure and the vent worked flawlessly. I can only surmise that the conical nature of the pediatric away met the ET tube and created a seal. I eventually increased the PIP to 20cm of water pressure and although the patient continued to have sporadic seizures despite the medications administered she was able to comfortably exchange air, though still having ataxic respiration, because she could still exhale against the 20cm of PIP and during inhalation was assisted with 100 FiO2, and in addition, during periods of apnea was automatically ventilated at a rate of 22 breaths per minute. During our packaging and transport time of 20 min we maintained a Pulsox of 95% and an End-Tidal CO2 of 35mm/hg. Below is the trending summary from the Life Pak 15.

The BVM we all

commonly use in the field has one major drawback when ventilating a patient with an intrinsic respiratory effort. The patient does not have the ability to exhale while you are pushing air in. Consequently there is an ensuing struggle of air movement. Instinctively the action of the practitioner is to push harder to force air in and at the same time the patient try's harder to force air out. In the lab or operating room where they don't often have an emergent setting the



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year in a row that AARC members have selected Dräger for this prestigious recognition. The award was presented during the AARC 61th International Respiratory Convention in Tampa, Fla. Established in 1989, the AARC Zenith Award is considered the "people's choice" award of the respiratory care profession and highly prized by its recipients. Each year, AARC asks its membership, which comprises 48,000 respiratory therapists and other clinicians, to vote for those manufacturers, service organizations and supply companies that provide the respiratory care community with exemplary service.

AR and Central Sleep Apnea Linked: Researchers

Central sleep apnea and Cheyne Stokes respiration are linked to increased odds of atrial fibrillation, particularly in men aged 76 years and older, according to a prospective cohort study from University Hospitals Case Medical Center in Cleveland, Ohio, and colleagues. The researchers prospectively followed a population cohort of 843 older men without atrial fibrillation at baseline for a mean of 6.5 years. The men underwent assessments for their apnea-hypopnea index, presence of central or obstructive sleep apnea, presence of Cheyne Stokes respiration, and proportion of sleep time with greater than 90% oxygen saturation. In calculating the men's odds of developing incident atrial fibrillation, the authors adjusted for age, race, body mass index, cardiopulmonary disease, alcohol use, pacemaker, cholesterol, cardiac medications, and apnea type (obstructive or central). Men with central sleep apnea had 2.58 greater odds of atrial fibrillation than men without it (odds ratio [OR], 2.58; 95% confidence interval, 1.18 - 5.66), and men with central sleep apnea-Cheyne Stokes respiration had a similar increased risk (OR, 2.27; 95% CI, 1.13 - 4.56; P < .05 for both). Men with obstructive sleep apnea or hypoxemia, however, had no increased odds of atrial fibrillation. The greater risk for atrial fibrillation among older participants may represent a multiplicative effect from advanced age and sleepdisordered breathing, the authors suggest.

Length of Mechanical Ventilation Poses Risks

Critically ill patients who have been mechanically ventilated for more than seven days are at greatly increased risk for functional impairment and mortality at one year following discharge from the intensive care unit (ICU), according to a new study presented at the 2015 American Thoracic Society International Conference. "Prolonged mechanical ventilation has a significant impact on the long-term well-being of patients," said lead author Margaret Herridge. MD, MPH. of the University of Toronto. "In our study of nearly 400 ICU patients, we were able to identify a number of characteristics that predicted subsequent disability. Knowing these risk factors can help guide their rehabilitation needs." The study involved 391 patients who had undergone at least one week of mechanical ventilation. Median ventilation time was 16 days, mean length of stay in the ICU was 22 days, and mean length of stay in the hospital was 29 days. Assessment included the Functional Independence Measure (FIM), an indicator of disability level, along with measures of physical capacity, neuropsychological status, quality of life, healthcare utilization, and mortality. FIM score at seven days post post-ICU discharge was associated with patient age and length of stay in the ICU. The oldest patients with the longest ICU stays had the worst outcomes, with 40% of those patients aged 46-66 years with an ICU length of stay of 14 days or more dying within the first year of follow-up, 29% being readmitted to ICU, and most exhibiting severe impairments in daily activities, including bathing, dressing and climbing stairs. In contrast, patients younger than 42 years of age with an ICU length of stay of less than two weeks had the best functional outcomes. The rate of hospital readmission was high for all patients, ranging from 36% to 43% for different age and length of stay patient groups. FIM score, Charlson score (a measure of comorbidities), and age independently predicted mortality at one year. "A combination of FIM score at 7 days after ICU discharge, length of stay in the ICU, and patient age can be used to predict subsequent impairment in mechanically ventilated patients," said Dr. Herridge. "Earlier intervention based on these predictions may improve outcomes for these high-risk patients."

COPD Outcomes Show Improvement

For patients with moderate to severe chronic obstructive pulmonary disease (COPD), the dual bronchodilator combination of tiotropium plus olodaterol improves quality of life better than either therapy alone, according to an analysis of data from the Tiotropium+Olodaterol Fixed Dose Combination (FDC) Versus Tiotropium and Olodaterol in Chronic Obstructive Pulmonary Disease (COPD) (TONADO) studies. The global assessment rate was significantly better with the combination than with monotherapy. The secondary analysis of data from the phase 3 TONADO 1 and TONADO 2 studies was presented during a late-breaking session here at CHEST 2015: American College of Chest Physicians Meeting. The subanalysis involved 3100 patients with COPD: 1033 were randomly assigned to once-daily tiotropium 5 µg, 1038 to olodaterol 5 µg, and 1029 to a combination of both drugs for 52 weeks.

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Transpulmonary Pressure Measurement

Dr Jean-Michel Arnal, Dr Dominik Novotni

Introduction

In mechanical ventilation, basic monitoring combines airway pressure and flow. While the titration of ventilator settings based on measurement of airway pressure may be adequate for most mechanically ventilated patient, we know that this is an oversimplified surrogate for the pressure in the two components of the respiratory system, namely the lungs and the chest wall. It is now widely accepted that chest wall mechanics can be severely abnormal in critically ill patients.^{1,2,3} As a continuous effort to improve lung protection, the contribution of chest wall mechanics should not be ignored. Consequently, advanced monitoring in mechanical ventilation adds the measurement of esophageal pressure which is considered as a substitute for pleural pressure. Partitioning of lung and chest wall compliance is then possible and is very useful to assess lung recruitability, perform recruitment maneuvers, set PEEP and tidal volume. Transpulmonary pressure is airway pressure minus esophageal pressure measured during an end-inspiratory or end-expiratory occlusion, and represents the pressure to distend the lung parenchyma. Transpulmonary pressure may allow customization of ventilator settings in order to optimize lung recruitment and protective ventilation in mechanically ventilated patients.⁴

Contraindications

Use of esophageal catheter is contraindicated in patients with diseases such as esophageal ulcerations, tumors, diverticulitis, bleeding varices, recent esophageal or gastric surgery, sinusitis, epistaxis, or recent nasopharyngeal surgery.

Technique of placement Preparation

The adult esophageal balloon catheter kit contains an 86 cm closed-end catheter with a 9.5 cm balloon and a stylet together with a pressure extension tube and a 3-way stopcock. An additional extension line and a 3-5 mL syringe are needed. A topical anesthetic (eg lidocaine spray) is required in awake patients (figure 1).

Connect the extension line to the auxiliary port of the ventilator. Select the display with from top to bottom airway pressure, esophageal pressure, transpulmonary pressure, and flow. Check that esophageal pressure is zero on the waveform (figure 2).

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Figure 1. The adult esophageal balloon catheter kit.

Placement and measurement of esophageal pressure is easier and more accurate in patients in semi-recumbent position.

Placement

The catheter has depth marking to aid in positioning the balloon in the lower third of esophagus. The estimated depth in which to place catheter can be measured by the distance from nostril to



Figure 2. Display of pressures and flow on the ventilator.



Figure 3. Estimation of the depth to place catheter.



Figure 4. Insertion of the catheter.

ear tragus to xyphoid, or calculated as patient's height (in cm) x 0.288 in cm (figure 3).

Step 1

Select a nostril without obstruction and apply a suitable topical anesthetic if the patient is awake. Apply water soluble lubricant to the distal tip of the catheter.

Step 2

With the patient's head in neutral position or flexed slightly forward, slowly insert the catheter through the nostril and hypopharynx using a gentle advancing motion. If the catheter meets obstruction, do not force the catheter. Remove it and insert it through the other nostril. Gently insert the catheter to the stomach, which is around 15 cm deeper than the estimated depth (figure 4).

Step 3

Attach the extension tube to the Y connector of the stylet. Inflate the balloon with 3 ml of air using the 3-way stopcock, withdrawn 2 ml to leave 1 ml of air in the balloon. Turn the stopcock off to the syringe and open to the extension line. Check the esophageal pressure measurement on the ventilator. Esophageal pressure should increase during inspiration and should increase during a gentle manual compression of the abdominal left upper quadrant. If esophageal pressure waveform is similar to airway pressure with the same pressures measured during an end-inspiration occlusion, suspect a tracheal placement. Deflate the balloon and remove the catheter. Insert the catheter through the other nostril.

Step 4

Slowly pull out the catheter to the estimated depth. A qualitative change in the esophageal pressure waveform should be seen

with appearance of cardiac oscillations. In spontaneously breathing patients, esophageal pressure should be negative during inspiration. In passive patients, esophageal pressure is positive during insufflation (figure 5).



Figure 5. Placement of esophageal catheter in passive patient. Esophageal pressure increase during insufflation. Small waveforms are cardiac oscillations.

Step 5

When the balloon is in the proper position, disconnect the extension tube and remove the stylet. Connect the extension tube directly to the catheter and inflate the balloon again (see step 3). Secure the catheter with tape to prevent motion removal or displacement (figure 6 and 7). Never attempt to reinsert the stylet once removed.



Figure 6. Removal of the stylet and connection to the extension tube.



Figure 7. Secure the catheter with tape.

If esophageal pressure is measured continuously, repeat step 3 every 30 min. Upon completion of the pressure measurements, deflate the balloon prior to catheter removal.

Trouble shooting

Esophageal pressure is similar to airway pressure

Measure airway and esophageal pressures at the end inspiration and end expiration using end inspiration and end expiration occlusion, respectively. If they are similar, esophageal catheter is probably inserted in the trachea. Deflate the balloon and remove the catheter.

Pressure waveform is flat on top

There is probably not enough air in the balloon.

Pressure waveform is dampened

There is probably too much air in the balloon.

There is no pressure waveform

Check that the connections are adequate. The catheter may need to be advanced further into the esophagus or may be kinked on itself and needs to be withdrawn.

Verification of the correct position

Spontenously breathing patient: The validity of esophageal pressure measurement can be assessed using the dynamic occlusion test procedure. Patients make three to five inspiratory efforts while airways are occluded at the end of expiration. The correct position of the esophageal balloon is ascertained from the high correlation between swings in airway and esophageal pressure during this maximal effort. The acceptable range of delta Pes/ delta Paw during the dynamic occlusion test is from 0.8 to 1.2.⁴⁵ If the patient has no spontaneous ventilation (passive condition), the occlusion test is performed by applying manual compression on the chest during airway occlusion.

Correction of measured pressure

Some authors recommend correcting the measured esophageal pressure to take into account the ventral-to-dorsal pleural pressure gradient across the thorax and weight of the mediastinum, especially in supine position. The correction can be done by subtracting 5 cmH2O from measured value⁶ or by subtracting the esophageal pressure at the end of passive expiration measured after manually disconnecting the patient from the ventilator.⁷

How to interpret esophageal pressure

Airway pressure is the pressure of the whole respiratory system (lung and chest wall). Esophageal pressure is an assement of pleural pressure, ie the pressure to distend the chest wall. An increase in esophageal pressure means that chest wall compliance is decreased, as a result of intraabdominal hypertension, pleural effusion, massive ascites, thoracic trauma, edema of thoracic and abdominal tissues as a result of fluid rescuscitation.

1. Assessing lung recruitability using low flow pressurevolume curve

By using esophageal pressure measurement, low flow pressure- volume (PV) curve can be partitioned into chest wall PV curve and lung PV curve. Lung PV curve is probably more accurate than respiratory system PV curve to assess recruitability. There is probably a large potential for lung recruitability if lung PV curve shows a well defined lower inflection point and a large hysteresis (figure 8, 9-11, 12-14).^{8,9}



Figure 8. Setting of the pressure-volume curve using P/V Tool Pro.

2. Titrating recruitment maneuver

By using esophageal pressure measurement, the pressure to recruit the lung can be titrated. The goal is to reach a transpulmonary pressure around 25 cmH2O for the recruitment maneuver to fully recruit the lung and prevent excessive overdistension (figure 15 and 16-18).¹⁰

3. Setting PEEP

In ARDS patients, PEEP can be set in order to achieve a transpulmonary pressure of 0 to 10 cmH2O at end expiration using an end-expiration occlusion. The rationale is to prevent atelectrauma caused by repeated opening and closing of distal airways and alveoli. In a randomized controlled physiological study, setting PEEP according to transpulmonary pressure was associated with better oxygenation and respiratory system compliance than using the standard ARDS net PEEP-FiO2 table (figure 19-21).¹¹

4. Setting tidal volume and inspiratory pressures

Transpulmonary pressure at the end-inspiration is measured during an end-inspiration occlusion and assesses the stress applied to the lung. The recommendation is to set tidal volume or inspiratory pressure in order to keep transpulmonary pressure at end-inspiration below 25 cmH2O (figure 22).¹²

Other applications

In spontaneous breathing patients, respiratory muscle effort can be assessed by work of breathing or the esophageal pressure time product. In addition, esophageal pressure measurement is very useful to assess patient-ventilator synchrony in particular auto-triggering, inspiratory trigger delay, and ineffective inspiratory effort.

Limitations

An inappropriate volume to inflate the balloon and an inappropriate position of the catheter in the esophagus will lead to inaccurate measurements. In addition, there is a postural effect due mainly to the weight of mediastinum. It is recommended to measure esophageal pressure in semi recumbent position. Finally, because there is a physiological regional variation in pleural pressure, esophageal pressure estimates the middle pleural pressure.



Figure 9. Respiratory system PV curve using airway pressure in a patient with low potential of recruitability.



Figure 10. Chest wall PV curve using esophageal pressure in a patient with low potential of recruitability.



Figure 12. Respiratory system PV curve using airway pressure in a patient with high potential of recruitability.



Figure 13. Chest wall PV curve using esophageal pressure in a patient with high potential of recruitability.



Figure 14. Lung PV curve using transpulmonary pressure in early onset ARDS patient. Note the presence of a well defined lower inflection point and a large hysteresis, meaning that the potential of lung recruitability is probably high. Note also that when airway pressure was increased to 40 cmH2O, transpulmonary pressure was only around 15 cmH2O. This means that if a recruitment maneuver is performed, airway pressure should be set higher than 40 cmH2O.



Figure 11. Lung PV curve using transpulmonary pressure in early onset ARDS patient. Note the absence of low inflection point and a narrow hysteresis, meaning that the potential of lung recruitability is probably low. Note also that when airway pressure was increased to 40 cmH2O, transpulmonary pressure was around 25 cmH2O. It means that a recruitment maneuver would potentially harm the lung without benefit in terms of recruitment.



Figure 15. Settings of recruitment maneuver with the P/V Tool uses a fast pressure increase (ramp speed at 5 cmH2O/s), a pause at high pressure of 10 s, and a higher PEEP after the recruitment maneuver.



Figure 16. Airway pressure versus volume during a sustained inflation recruitment maneuver.



Figure 17. Esophageal pressure versus volume during a sustained inflation recruitment maneuver.



Figure 18. Sustained inflation recruitment maneuver performed with the P/V Tool in early onset ARDS patient (same patient as in figure 12-14). Airway pressure (16), esophageal pressure (17) and transpulmonary pressure (18) versus volume during the recruitment maneuver. Note that top airway pressure was set at 50 cmH2O in order to have transpulmonary pressure around 25 cmH2O. The duration of recruitment maneuver was 10 seconds. Note the increase in volume on airway and transpulmonary pressure curves (red arrows), which is an assessment of the volume recruited during the recruitment maneuver.

References

- 1 Talmor D, Sarge T, O'Donnell C, Ritz R, Malhotra, Lisbon A, Loring S. Esophageal and transpulmonary pressures in acute respiratory failure Crit Care Med 2006; 34:1389-1394
- 2 Gattinoni L, Chiumello D, Carlesso E, Valenza F. Benchtobedside review: Chest wall elastance in acute lung injury/ acute respiratory distress syndrome patients. Critical Care 2004, 8:350-355
- 3 Hess D, Bigatello L. The chest wall in acute lung injury/ acute respiratory distress syndrome. Curr Opin Crit Care 2008;14:94-102
- 4 Akoumianaki E, Maggiore S, Valenza F, Bellani G, Jubran A, et al. The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 2014;189:520-31
- 5 Baydur A, Cha EJ, Sassoon CS. Validation of esophageal balloon technique at different lung volumes and postures. J Appl Physiol 1987; 62:315-321
- 6 Loring SH, O'Donnell CR, Behazin N, Malhotra A, Sarge T, Ritz R, et al. Esophageal pressures in acute lung injury: do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? J Appl Physiol 2010;108:515-522
- 7 Guerin C, Richard JC. Comparison of 2 Correction Methods for Absolute Values of Esophageal Pressure in Subjects With Acute Hypoxemic Respiratory Failure, Mechanically Ventilated in the ICU. Respir Care 2012;57:2045-2051
- 8 Maggiore SM, Jonson B, Richard JC, Jaber S, Lemaire F, Brochard L. Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: Comparison with the lower inflection point, oxygenation, and compliance. Am J Respir Crit Care Med 2001;164:795-801
- 9 Demory D, Arnal JM, Wysocki M, Donati SY, Granier I, Corno G, Durand-Gasselin J. Recruitability of the lung estimated by the pressure volume curve hysteresis in ARDS patients. Intensive Care Med 2008; 34:2019-2025
- 10 Grasso S, Terragni P, Birocco A, Urbino R, Del Sorbo L, Filippini C, Mascia L, Pesenti A, Zangrillo A, Gattinoni L, Ranieri M. ECMO criteria for influenza A (H1N1)-associated







Figure 19. PEEP adjustment according to end-expiration transpulmonary pressure in an early onset ARDS patient. On each figure, airway, esophageal, and transpulmonary pressures are displayed from top to bottom. The cursor is positioned at the end-expiration occlusion. On the top figure, PEEP is 7 cmH2O. Transpulmonary pressure is negative at end-expiration with a high risk of atelectrauma. On the middle figure, PEEP is 9 cmH2O. Transpulmonary pressure is around 2 cmH2O at end-expiration which should prevent atelectrauma.

ARDS: role of transpulmonary pressure. Intensive Care Med $2012;\!38\!:\!395\!\cdot\!403$

- 11 Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring S. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;359:2095-2104
- 12 Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L. Lung stress and strain during echanical ventilation of the Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2008;178:346-55



Figure 20. Tidal volume adjustment according to end-inspiration transpulmonary pressure in an early onset ARDS patient (same patient as in figure 19-21). From top to bottom, airway, esophageal, and transpulmonary pressures are displayed. The cursor is positioned at the end-inspiration occlusion. Transpulmonary pressure is 7 cmH2O which is safe in terms of global stress applied to the lung.

Capnography: A Screening Tool for Sepsis?

Greg Spratt BS RRT CPFT

Background

The Surviving Sepsis Campaign (SSC), defines sepsis as "the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion."¹ Sepsis may present in a spectrum of severities ranging from systemic inflammatory response syndrome (SIRS) to septic shock.² (See Table 1)

Table 1. Sepsis²

Systemic Inflammatory Response Syndrome (SIRS) is a constellation of symptoms of systemic inflammation that may or may not be the result of infection. For example, patients with acute pancreatitis and major trauma, including burns, may have findings of SIRS. Manifestations include:

Temperature > 38° C or < 36° C

Heart rate > 90 beats/min

Respiratory rate > 20 breaths/min or P_aCO₂ < 32 mm Hg

WBC count > 12,000 cells/ μ L or < 4,000 cells/ μ L or > 10% immature forms

Sepsis is \geq 2 SIRS criteria with known or suspected infection.

Severe sepsis is sepsis with organ dysfunction. Cardiovascular failure is typically manifested by hypotension, respiratory failure by hypoxemia, renal failure by oliguria and/or azotemia, and hematologic failure by coagulopathy.

Septic shock is sepsis with refractory hypotension and impaired end organ perfusion despite adequate fluid resuscitation.

Every year, severe sepsis strikes more than a million Americans and hospitalizations for sepsis have more than doubled in the past decade. 3,4

The Agency for Healthcare Research and Quality (AHRQ) lists sepsis as the most expensive condition treated in U.S. hospitals, costing more than \$20 billion in 2011, more than acute myocardial infarction and acute cerebrovascular disease combined.⁵ Average direct cost of care by the hospital is estimated at \$25,000, but typical Medicare reimbursement for sepsis and sepsis with complications is \$7,100 and \$12,000 respectively so treating sepsis is commonly a losing proposition financially for hospitals. The direct cost of treating a sepsis patient is six-fold higher that treating a non-sepsis patient.⁴

In 2008, while only 2% of hospital patients were diagnosed with sepsis, sepsis was responsible for 17% of hospital deaths and septic shock has a 40-70% mortality rate.⁴ It has been estimated

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that 28-50% of patients developing sepsis die,⁶ more than deaths from prostate cancer, breast cancer and AIDS combined in the US.

Early Identification and Early Intervention

The SSC recommends screening for sepsis to improve outcomes stating, "We recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy." As 83% of cases with sepsis present to the emergency department (range 78-91% from bottom to top quartile),⁷ screening upon ED admission is critical and some have implemented screening even earlier during Emergency Medical Service (EMS) calls.⁸⁹ Noting that nearly 1 in 5 patients who develop sepsis do so after admission, familiarity with symptoms and screening is also vital in hospitalized patients not admitted with sepsis.

Early identification is key to allow for timely initiation of interventions shown to decrease mortality.¹⁰⁻¹¹ SSC recommends, "Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock as the goal of therapy.¹ Each hour of delay in providing administration of effective antibiotics is associated with an increase in mortality in those with septic shock.¹²⁻¹⁴ Overall, the preponderance of data supports giving antibiotics as soon as possible in patients with severe sepsis with or without septic shock.¹²⁻¹⁵

In early sepsis, increased capillary leakage and decreased vasomotor tone result in a decrease in venous return to the heart culminating in a decrease in cardiac output. Normal restoration in arterial vasomotor tone is impaired in sepsis because of a loss of vascular responsiveness. The end result is an imbalance between systemic oxygen delivery and oxygen demand, resulting in tissue hypoxia.²

As timeliness of identification and intervention is a key, screening tools have been developed and their use has been associated with decreased sepsis-related mortality. The first step in the 'SSC Bundle' is to measure the blood lactate level.¹ Lactic acid (normal value, < 2 mmol/L) is the byproduct of anaerobic metabolism secondary to suboptimal supply of oxygen to the tissues. Increased levels of lactic acid are associated with increased mortality in patients with septic shock.¹⁶ One prospective observational study estimated an 11% decrease in mortality for every 10% decrease in lactate clearance¹⁷ (lactate



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clearance is defined as a decrease of lactate to less than 2 mmol/L by 24h). $^{\rm 18}$

Capnography as a Sepsis Screening Tool

Drawing blood, analysis, and the return of results from lactate levels consume precious time when screening for sepsis, potentially delaying intervention. One study found a delay of up to 172 minutes from the time of ED triage for a whole blood lactate value to be obtained in patients with sepsis, well past the optimal 60-minute threshold recommended for starting antibiotics.¹⁹ Researchers have sought other screening methods that may be more efficient. As exhaled end-tidal carbon dioxide (etCO₂) concentration is inversely associated with lactate levels in febrile patients,²⁰ and has been used in other conditions as a marker for lactic acid/metabolic acidosis,²¹⁻²⁵ capnography has been considered, having additional advantages of being non-invasive, applicable for both intubated and non-intubated patients, available for use in both hospital and pre-hospital settings, and providing immediate results.

Hunter et al found a significant association between $etCO_2$ concentration and in-hospital mortality in emergency department patients with suspected sepsis across a range of disease severity.²⁶ In a prospective, observational study of 201 adult patients presenting with suspected infection and 2 or more SIRS criteria, lactate and $etCO_2$ were measured and analyzed along with patient outcomes. The area under the receiver operator characteristics curve (AUC) was 0.75 for lactate and mortality and 0.73 for $etCO_2$ and mortality. End-tidal CO_2 readings demonstrated an inverse relationship with serum lactate levels.

They conclude that $etCO_2$ may perform comparable to blood lactate levels as a predictor of mortality in patients with suspected sepsis across all sepsis severities, in both spontaneously breathing patients and those who required emergency intubation upon presentation to the ED. In addition, $etCO_2$ was also among 3 independent predictors of mortality when controlled for other potential predictors of mortality, demonstrating lower mean $etCO_2$ levels in non-surviving patients.

More recently, this group presented 3 papers at the 2015 Annual Meeting of the Society for Academic Emergency Medicine, the first being a pre-/post-intervention study on implementation of a pre-hospital (EMS) 'sepsis alert protocol' using etCO₂ on the ED management of 137 cases of sepsis (80% pre-alert group and 20% in the post-alert group).7 The pre-hospital sepsis alert protocol included an ED notification process prior to patient arrival. The mean lactate was 3.2 and etCO₂ was 30; the correlation between lactate and $etCO_2$ was 0.43 (p<0.001). In the pre-alert and post-alert groups, time to blood cultures decreased from 27 minutes to 14, time to antibiotics decreased from 56 minutes to 40, and time to fluids decreased from 34 minutes to 10. From pre- to post-alert, hospital length of stay decreased from 13 days to 9 and admission to the ICU decreased from 53% to 33% respectively. Moreover, mortality was cut in half from 14% prealert to 7% post.

A second paper was presented on the value of $etCO_2$ in prehospital (EMS) sepsis alert notification. Their findings suggest that $etCO_2$ is an objective measure of sepsis that can be obtained by EMS personnel to alert the hospital of a potential sepsis patient.⁹ The correlation between blood lactate and $etCO_2$ was -0.50 (p=0.008). The AUC for $etCO_2$ for predicting appropriate initiation of a sepsis alert was 0.97 compared to the lactate of AUC of 0.78. Using a cut-off level for $etCO_2$ of < 25 mmHg to predict potential sepsis alert patients yielded a sensitivity of 100% and a specificity of 95%.

In a third paper, the group examined the use of end-tidal carbon dioxide levels as criteria to activate a sepsis alert protocol for patients in a Level I trauma center emergency department.²⁷ All patients who met pre-established criteria for "sepsis alert" (SIRS + present source or suspicion of infection, and ED physician evaluation/judgment) were included. The correlation between lactate and $etCO_2$ was -0.45 (p=0.001). The AUC for $etCO_2$ for predicting sepsis was 0.87 compared to the lactic acid level which yielded an AUC of 0.68. Their conclusion was that these findings suggest that $etCO_2$ is a very useful clinical tool in the ED setting for determining the presence of sepsis and could be integrated into sepsis alert protocols to quickly deliver care to these patients.

Summary

Sepsis, severe sepsis, and septic shock are a common cause of hospital death with high mortality rates and high costs to the healthcare system. Rapid identification and intervention are key components to sepsis survival and improved clinical and economic outcomes. Evidence suggests that capnography may provide a comparable assessment tool to lactic acid levels, with advantages of providing immediate results, being non-invasive, and applicable in all environments including pre-hospital (EMS). Initial evidence suggests this method of screening for sepsis has the potential to improve mortality and clinical outcomes while reducing cost of care.

References

- 1 Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med 2013; 41(2):580-637
- 2 Merck Manual Professional Version Online. http://www. merckmanuals.com/professional/critical-care-medicine/ sepsis-and-septic-shock/sepsis-and-septic-shock Accessed 6-29-2015.
- 3 National Center for Health Statistics Data Brief No. 62 June 2011. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals.
- 4 Physician Executive Council: The Advisory Board Company 2013. 10 Imperatives to Reduce Sepsis Mortality. http:// www.advisory.com/research/physician-executive-council/ studies/2014/ten-imperatives-to-reduce-sepsis-mortality
- 5 Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project Statistical Brief No. 160 August 2013. http://hcup-us.ahrq.gov/reports/statbriefs/sb160.jsp
- 6 Wood KA, Angus DC. Pharmacoeconomic implications of new therapies in sepsis. PharmacoEconomics. 2004;22(14):895-906.
- 7 Advisory Board Company. 10 Imperatives to Reduce Sepsis Mortality. https://www.advisory.com/research/physicianexecutive-council/studies/2014/ten-imperatives-to-reducesepsis-mortality/formalize-identification
- 8 Stone A.M. Silvestri S. Hunter C. Cassidy D. Mangalat N. Ralls G.A. Papa L. The effect of an EMS sepsis alert protocol

on the ED management of patients with sepsis. Academic Emergency Medicine Conference 2015; 22(5 SUPPL. 1):S394.

- 9 Mangalat N, Papa L, Ralls G, Stone A, Silvestri S, Hunter C. The value of end tidal CO2 as a component of a prehospital sepsis alert notification. Academic Emergency Medicine Conference 2015; 22 (5 SUPPL. 1) (pp S241), 2015.
- 10 Levy MM, Dellinger RP, Townsend SR, et al; Surviving Sepsis Campaign: The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med 2010; 38:367– 374
- 11 Jones AE, Shapiro NI, Trzeciak S, et al; Emergency Medicine Shock Research Network (EMShockNet) investigators: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. JAMA 2010; 303:739–746
- 12 Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34:1589–1596
- 13 Ferrer R, Artigas A, Suarez D, et al; Edusepsis Study Group: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. Am J Respir Crit Care Med 2009; 180:861–866
- 14 Barie PS, Hydo LJ, Shou J, et al: Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. Surg Infect (Larchmt) 2005; 6:41–54
- Puskarich MA, Trzeciak S, Shapiro NI, et al; Emergency Medicine Shock Research Network (EMSHOCKNET): Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med 2011; 39:2066–2071
- 16 Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest 1991; 99(4):956–962
- 17 Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32(8):1637–1642
- 18 Abramson D1, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. J Trauma. 1993 Oct;35(4):584-8.
- 19 Goyal M, Pines JM, Drumheller BC. Point-of-care testing at triage decreases time to lactate level in septic patients. J Emerg Med 2010;38:578-81.
- 20 McGillicuddy DC, Tang A, Cataldo L. Evaluation of end-tidal carbon dioxide role in predicting elevated SOFA scores and lactic acidosis. Intern Emerg Med 2009;4:41-4.
- 21 Caputo ND, Fraser RM, Paliga A, Matarlo J, Kanter M, Hosford K, Madlinger R. Nasal cannula end-tidal CO2 correlates with serum lactate levels and odds of operative intervention in penetrating trauma patients: A prospective cohort study. J Trauma Acute Care Surg 2012;73(5):1202-7
- 22 Predictive Value of Capnography for Suspected Diabetic Ketoacidosis in the Emergency Department Soleimanpour H, Taghizadieh A, Niafar M, Rahmani F, Golzari SEJ, Esfanjani RM, Western J Emerg Med. 2013;14(6):590-594.
- 23 Fearon DM, Steel DW. End-tidal carbon dioxide predicts the presence and severity of acidosis in children with diabetes. Acad Emerg Med 2002;9:1373-8.
- 24 Gilhotra Y, Porter P. Predicting diabetic ketoacidosis in children by measuring end-tidal CO2 via non-invasive nasal capnography. J Pediatr Child Health 2007;43:677-80.

- 25 Nagler J, Wright RO, Krauss B. End-tidal carbon dioxide as a measure of acidosis among children with gastroenteritis. Pediatrics 2006;118:260-7.
- 26 Hunter CL, Silvestri S, Deanb M, Falk JL, Papa L. End-tidal carbon dioxide is associated with mortality and lactate in patients with suspected sepsis. American Journal of Emergency Medicine (2013) 31, 64–71
- 27 Hunter C. Silvestri S. Stone A.M. Ramirez L. Cassidy D. Mangalat N. Ralls G.A. Papa L. The use of end-tidal carbon dioxide levels as criteria to activate a sepsis alert protocol in the emergency department. Academic Emergency Medicine Conference 2015; 22 (5 SUPPL. 1) (pp S130), 2015.

Pulse Rate Performance of Two Pulse Oximeters in the NICU

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Background: Pulse oximeters display pulse rate (PR) and pulse oxygenation (SpO₂). These vital signs are important components of screening and diagnostic algorithms in newborns,^{1,2} making it necessary to establish pulse oximeter performance in the neonatal population. Inaccurate reporting of PR or SpO₂ values could lead to false alarms and inappropriate interventions.

Method: This study compared PR performance of the Nellcor N-600x pulse oximeter and the Masimo SET module of a Philips IntelliVue MX800 in a neonatal intensive care unit (NICU). Data were collected from 30 subjects during wakefulness and sleep. PR readings were compared to a heart rate (HR) reference obtained by ECG.

Results: The Nellcor N-600x pulse oximeter more accurately reported PR than did the Masimo SET module (RMSD 3.93 beats per minute (bpm) vs. 5.07 bpm, P < .001). Also, a significantly smaller proportion of PR measurements reported by the Nellcor monitor differed from the reference heart rate by more than 40 beats per minute (0.07% vs. 0.23%, P < .001). For three subjects, the Masimo SET module exhibited a clinically significant error (CSE), a PR that differed from the reference by at least 40 bpm for more than 30 seconds continuously. No CSEs occurred with the Nellcor N-600x monitor. SpO₂ readings reported by the two monitors were similar during periods when both instruments accurately reported PR. However, during periods when the Masimo SET module exhibited CSEs, the SpO₂ readings of the two pulse oximeters differed.

Conclusion: The Nellcor N-600x pulse oximeter more accurately reported PR compared to an ECG reference than did the Masimo SET module in this population of NICU patients. Only the Masimo instrument exhibited errors in PR that were large enough to potentially result in inappropriate intervention (CSEs).

Introduction

Pulse oximeters are commonly used to estimate SpO_2 in newborns, a recommended component of critical congenital heart disease (CCHD) screening in newborns.¹ Pulse oximeters also report pulse rate (PR). Heart rate is a factor in the American Heart Association's algorithm for neonatal resuscitation.² However, the methods recommended by the AHA to collect neonatal HR (intermittent auscultation of the praecordium and palpation of the umbilical cord) have been shown to be imprecise and inaccurate³ while pulse oximetry has been suggested to accurately report PR in infants in the delivery room.^{4,5} The accuracy of reported vital signs impacts clinician intervention. Inaccurate information can lead to unnecessary medical intervention due to false positive alarms. Therefore, it is essential to establish the accuracy of the data provided by pulse oximeters in a neonatal population. The present study compared the PR performance of two modern pulse oximeters relative to an ECG reference and assessed the SpO_2 performance of the instruments.

Method

The study was conducted at British Columbia Children's Hospital between February and June, 2013. After Institutional Review Board approval and receipt of informed parental consent, 30 neonatal patients in the intensive care unit were enrolled in the study. Twenty-nine of these subjects were included in the analysis. One subject was excluded after data loss due to a failure of the third-party data acquisition software. Subjects were closely monitored by caregivers and registered nurses at all times.

All sensors and monitors used in the study were cleared by the FDA and Health Canada. A Nellcor SpO_2 MAX-N sensor and a Masimo LNCS, LNCS Neo, or LNCS NeoPt sensor were applied to the wrist, or the foot if the wrist was unavailable, of each subject, and connected with the respective pulse oximeter monitors. All sensors were applied at post-ductal sites (ie left hand, feet). Sensors were covered with probe wraps to secure them against movement and to reduce ambient light and prevent optical crosstalk. ECG reference heart rate (HR) values were acquired using either a PHILIPS Intellivue MP70 or a MX800 monitor. Signals were recorded using a combination of proprietary data acquisition software and commercially available software (Rugloop, Demed Inc, Temse, Belgium).

After sensors were placed on each subject, electronic data were collected for approximately four hours. Data were collected for each subject during both wakefulness and sleep. Data were excluded if the ECG or oximeter reported zero or if no data were available, eg, due to sensor disconnect, sensor turning off, etc.

To analyze PR accuracy, measurements from each test instrument were extracted once per second and compared to simultaneous data from the ECG monitor. Standard measures of bias, precision (1 SD), and accuracy (RMSD, the root mean square of differences) were calculated as recommended by the pulse oximetry industry standard.⁶

Table 1. Patient Demographics and Baseline Characteristics.

Category	n (%)			
Male	18 (60)			
Race/ethnicity				
Asian	9 (30)			
African American	0 (0)			
Caucasian	20 (67)			
Hispanic	1 (3)			
	Median (standard deviation)			
Conceptional age, weeks	35.7 (13.6)			
Height, cm	44.0 (21.0)			
Weight, kg	2.3 (3.2)			

Additionally, the percentage of time that the PR reported by each monitor differed from the reference HR value by at least 40 beats per minute (bpm) was measured (E40). Forty bpm was chosen because an error of this size might result in an inappropriate or missed intervention when following published neonatal resuscitation guidelines.⁷ The Chi-square test was used to assess whether E40 differed significantly between monitors. A P-value less than 0.05 was considered significant.

Clinically significant errors (CSE) were defined as differences between PR and HR greater than 40 bpm and continuously sustained for more than 30 seconds. This interval of time was chosen because it is sufficiently long to trigger an inappropriate clinical intervention in response to a sustained erroneous PR value.5 Additionally, according to the ISO oximetry standard 80601-2-61, 30 seconds is the maximum time an oximeter is allowed to "hold" without indicating that it is holding.⁶

The Wilcoxon rank-sum test was used to determine the statistical significance of differences between devices. This non-parametric version of a paired samples t-test was chosen because the errors were not normally distributed. A P-value less than 0.05 was considered significant.

No convenience arterial blood gas sample was obtained during the study. Without a reference from co-oximetry, the accuracy of SpO₂ readings taken from the two pulse oximetry monitors were compared for agreement. The RMSD between the SpO₂ values from the two monitors was calculated during intervals of "good" agreement (< 5 bpm) between ECG-determined HR and pulse oximetry–determined PR, and during intervals where there was a CSE between the PR derived from either oximeter and the HR reference signal derived from the ECG.

Results

Data were collected from 29 subjects. Demographics and patient characteristics are summarized in Table 1. The majority of enrolled subjects (77%) were born prematurely. A majority of subjects were diagnosed with respiratory distress syndrome. A total of 114 hours of pulse oximetry data were collected with ECG HR reference values available for comparison. ECG HR values among the subjects ranged between 46 and 235 bpm. Transient bradycardia was observed in 7 subjects during the trial; medical interventions including stimulation and supplemental oxygen were provided for recovery.

Pulse rate

To assess the accuracy of the PR reported by each device, the RMSD between the pulse oximetry–derived PR and ECG-derived HR (ECG HR) was calculated. RMSD for the Nellcor N-600x pulse oximeter was significantly less than that for the Masimo SET module was (4.14 bpm vs. 10.48 bpm, P < .001) (Table 2). The Nellcor N-600x oximeter performance was within its device specifications of \pm 5 bpm under motion.

The percentage of time during which the absolute PR error was greater than 40 bpm (E40) for the Nellcor N-600x oximeter was 0.08%, compared to 0.89% for the Masimo SET module, across all subjects (Table 2). The difference between instruments was statistically significant (P < .001). Figure 1 shows pulse oximeter–reported PR vs. ECG HR for both the Nellcor N-600x oximeter and the Masimo SET module for all subjects.

One subject was identified as an outlier, with a PR RMSD outside of the range of $(3 \times SD + \text{mean PR RMSD})$. For this subject, the overall PR RMSD was 50 bpm for the Masimo SET module and 8 bpm for the Nellcor N-600x oximeter (Table 2). Data from the outlier subject is highlighted in Figure 1. The E40 results for this subject were 0.54% for the Nellcor N-600x oximeter and 22.46% for the Masimo SET module (Table 2). Figure 2 shows an interval of data from this subject during which the PR error for the Masimo SET module met the criteria of CSE.

Excluding the outlier subject, the PR RMSD for the Masimo SET module was greater than 5 bpm, not within specifications. E40, excluding the outlier subject, was still significantly smaller for the Nellcor N-600x oximeter compared to the Masimo SET module (0.07% vs. 0.23%, P < .001).

SpO₂

The Nellcor N-600x pulse oximeter reported SpO₂ values between 42-100%, and Masimo SET module reported SpO₂ values between 30-100%. The pooled SpO₂ difference for all collected data (Δ SpO₂ RMSD) was 1.66 %. During intervals when absolute PR error relative to ECG for both devices was less than 5 bpm, SpO₂ RMSD was 1.5%. During continuous intervals during which the Masimo SET module exhibited a CSE, Δ SpO₂ RMSD was significantly greater, 3.8% (P < .001). The increased disagreement between SpO₂ values during CSEs is also seen in Figure 2. No equivalent intervals of CSE were observed for the Nellcor N-600x pulse oximeter. The SpO₂ data are summarized in Table 3.

Discussion

Accurate data about neonatal vital signs are required to facilitate appropriate medical intervention, for example, as part of the pediatric resuscitation algorithm, or in CCHD screening. Therefore, it is important to characterize pulse oximeter performance in the NICU environment, particularly as it pertains to the usefulness of pulse oximetry–reported data to clinicians.

The PR reported by the Nellcor N-600x pulse oximeter was significantly closer to the reference HR value than that reported by the Masimo SET module, even after the data from an outlier subject was removed from the analysis (RMSD 3.93 bpm vs. 5.07 bpm, P < .001). The Nellcor N-600x pulse oximeter also had a significantly smaller proportion of PR measurements that differed from the reference HR by at least 40 bpm (0.07% vs. 0.23%, P < .001).

Table 2. Pulse Oximeter Performance in Reporting Pulse Rate.

	Nellcor N-600x monitor	Masimo SET module	Devices significantly different
All subjects RMSD (mean ± SD) (bpm)	4.14 (0.16 ± 4.14)	10.48 (-1.26 ± 10.41)	<i>P</i> < .001ª
Outlier subject RMSD (mean ± SD) (bpm)	8.32 (0.21 ± 8.32)	49.88 (-24.94 ± 43.19)	<i>P</i> < .001ª
All subjects, omitting outlier RMSD (mean \pm SD) (bpm)	3.93 (0.15 ± 3.93)	5.07 (-0.44 ± 5.05)	P < .001ª
All subjects E40	0.08%	0.89%	<i>P</i> < .001 ^b
Outlier subject E40	0.54%	22.46%	<i>P</i> < .001 ^b
All subjects, omitting outlier E40	0.07%	0.23%	<i>P</i> < .001 ^b

^a Wilcoxon rank-sum test

^b Chi-square test

In this analysis, data from 29 subjects was pooled. Extreme deviations in PR performance in individual subjects who present a unique set of challenging conditions may be missed when analyzing pooled data. Therefore, pulse oximeter performance was assessed during periods defined as clinically significant errors (CSEs); periods during which the absolute error in PR relative to HR was equal to or greater than 40 bpm for at least 30 seconds. No CSEs occurred with the Nellcor N-600x pulse oximeter. CSEs occurred with 3 subjects with the Masimo SET technology. For one of these 3 subjects, the PR reported by the Masimo monitor fell below 60 bpm for large intervals of time. Such a deviation from the correct HR value could result in inappropriate medical intervention.

These results are consistent with other observations in the literature. Kamlin et al5 also reported one outlier subject, monitored with the Masimo SET technology, for whom a clinically significant difference between reported PR and the ECG reference "may have led to interventions that were not indicated." Additionally, Du and Gorensky reported a case study using the Masimo SET technology in which a persistent PR error resulted in an inappropriate intervention.⁹

Due to limitations associated with collecting blood samples from neonates, co-oximetry reference data was not obtained in this study. Often, clinicians use agreement between pulse oximetry-reported PR and ECG-reported HR as a signal quality metric, and place greater confidence in SpO₂ readings when this signal quality is good.⁷ In this study, the agreement of the SpO₂ readings reported by the two oximeters was characterized during periods of good and poor agreement between PR and HR. The SpO₂ values reported by the two pulse oximeters were very similar during intervals where reported PRs were within 5 bpm of the reference HR. However, differences between reported SpO₂ values were close to 4 saturation points during intervals where the Masimo SET monitor exhibited a CSE, significantly greater than the difference in SpO₂ readings over the entire experiment. Assuming that PR agreement with HR can be used as a surrogate for confidence in SpO₂ readings, it is probable that SpO₂ readings from the Masimo instrument were responsible for the observed differences in SpO₂ readings during intervals when the Masimo instrument exhibited CSE. Further experiments with comparative SpO₂ values can investigate this possibility.

Conclusions

The Nellcor N-600x pulse oximeter more accurately reported PR compared to an ECG reference, as measured by RMSD, than the Masimo SET module in this population of NICU patients. Only the Masimo monitor exhibited errors in PR that were large enough to potentially result in inappropriate intervention (CSEs). During periods when the Masimo monitor exhibited CSE, the SpO_2 values reported by the two oximeters also differed. There is a high probability that the Masimo instrument is responsible for the observed poor agreement between reported SpO_2 values during periods when it exhibited CSE. However, further investigation is necessary to investigate this possibility.



Figure 1: Pooled data from 29 subjects (outlier plotted in red) showing PR vs. ECG HR for Nellcor N-600x oximeter (left) and Masimo SET module (right). The dashed lines in each graph indicate errors from ECG HR by \pm 40 bpm.

Figure 2. SpO₂ and pulse rate reported by two pulse oximeters for outlier subject, during a long period of disagreement between the Masimo SET module and ECG. When the Masimo SET module PR is different from the ECG HR, the Masimo SET module and Nellcor N-600x oximeter SpO₂ values also disagree.



Table 3. Pulse Oximeter Performance in Reporting SpO₂.

	ΔSpO ₂ RMSD (%, mean ± SD)	Compared to overall
Overall	1.66 (-0.61 ± 1.55)	$\Delta SpO_2 RMSD$
While absolute PR error is < 5 bpm	1.41 (-0.58 ± 1.29)	N.S.§
During periods of CSE for Nellcor N-600x	NA*	NA*
During periods of CSE for Masimo SET module	3.81 (1.12 ± 3.64)	<i>P</i> < .001§
Outlier during periods of CSE of Masimo SET module	5.16 (-3.57 ± 3.72)	<i>P</i> < .001

§Wilcoxon rank sum test

* No CSE was observed using Nellcor N-600x pulse oximeter during the trial

References

- 1 Knapp AA, Metterville DR, Kemper AR, Prosser L, Perrin JM. Evidence review: Critical congenital cyanotic heart disease. Health Resources and Services Administration, Maternal and Child Health Bureau. http://www.hrsa.gov/ advisorycommittees/mchbadvisory/heritabledisorders/ nominatecondition/reviews/cyanoticheart.pdf Published September 3, 2010. Accessed February 25, 2015.
- 2 Kattwinkel J, Perlman JM, Aziz K, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 122:S909-S919.
- 3 Kamlin CO, O'Donnell CP, Everest NJ, Davis PG, Morley CJ. Accuracy of clinical assessment of infant heart rate in the delivery room. Resuscitation 2006;71: 319-321.
- 4 Dawson JA, Saraswat A, Simionato L, et al. Comparison of heart rate and oxygen saturation measurements from Masimo and Nellcor pulse oximeters in newly born term infants. Acta Paediatr 2013;102:955-960.

- 5 Kamlin COF, Dawson JA, O'Donnell CPF, et al. Accuracy of pulse oximetry measurement of heart rate of newborn infants in the delivery room. J Pediatr 2008;152:756-760.
- 6 International Standards Organisation. Medical electrical equipment Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment. 2011. ISO 80601-2-61:2011.
- 7 Sahni R, Gupta A, Ohira-Kist K, Rosen TS. Motion resistant pulse oximetry in neonates. Arch Dis Child Fetal Neonatal Ed 2003;88:F505–F508.
- 8 Tobin RS, Polage JA, Batchelder PB. A Characterization of Motion Affecting Pulse Oximetry in 350 Patients. Anesth Analg 2002;94(1 Suppl):S54–61.
- 9 Du EH, Goresky GV. Disparate motion-resistant ${\rm SpO}_2$ and pulse rate parameters. Anesth Analg. 2011;112(Suppl):S-226

A Case Study: Use of Vibrating Mesh with a Valved Adapter in a Pediatric Patient with a Severe Asthma Exacerbation

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Introduction

Pediatric patients in respiratory distress due to an acute asthma exacerbation can quickly deteriorate requiring intubation and mechanical ventilation. Treating patients promptly and efficiently is key to preventing escalation of care. Bronchodilator therapy is an important part of the care plan. Ari, et al demonstrated superior inhaled mass % aerosol delivery via mouthpiece with a vibrating mesh (vm) with valved adapter (Aerogen Ultra) with no oxygen $34.99 \pm .3.17$ vs jet nebulizer (jn) via mouthpiece 7.66 ± 0.62 .¹ We theorized that use of high quality aerosol could prevent further deterioration of this patient.

Case Summary

A 10-year old patient with severe persistent asthma presented in the ER with respiratory distress demonstrated by intercostal retractions, inability to speak full sentences, breath sounds -I/E wheezes with markedly decreased aeration, clinical asthma score (CAS) 6 (> 5 severe) and oxygen saturation 90% without oxygen. He received two 5 mg albuterol treatments via vm with an open aerosol mask with little change. Patient refused bipap and high flow nasal cannula and intubation was imminent. He received another 5 mg albuterol treatment with a vm with valved adapter (Aerogen Ultra) via mouthpiece without oxygen. Within minutes his oxygen saturation increased to 98%, retractions subsided, breath sounds - increased aeration with inspiratory/expiratory wheezes, ability to speak full sentences and a repeat CAS of 2. The patient was transferred to PICU and received Q2 albuterol treatments via vm with valved adapter throughout the night where he continued to show improvement in CAS. The patient length of stay (LOS) from ER to discharge was 21 hours. He has gone 2 months with no readmissions on file.

Discussion

The selection of an efficient aerosol delivery device and modality of delivery (mouthpiece vs mask) are important choices in order to effectively treat the asthma patient in acute respiratory distress and prevent escalation of care.

Conclusions

This patient demonstrated a rapid clinical response to the application of a vm with valved adapter via mouthpiece. It was the consensus of the team caring for this patient that aerosol delivery provided by the device and modality played a vital role in preventing escalation of care. Further clinical studies are needed in order to support this hypothesis.

References

1 Ari A, Dornelas A, Sheard M, AlHamad B, Fink JB. Performance comparisons of jet and mesh nebulizers using different interfaces in simulated spontaneous breathing adults and children. J Aerosol Med Pulm Drug Deliv. 2014;28(0).

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References: 1. Hickin S, Mac Loughlin R, Sweeney L, Tatham A, Gidwani S. Comparison of mesh nebuliser versus jet nebuliser in simulated adults with chronic obstructive pulmonary disease. Poster at the College of Emergency Medicine Clinical Excellence Conference. 2014

Roflumilast Improves Corticosteroid Resistance COPD Bronchial Epithelial Cells Stimulated with Toll Like Receptor 3 Agonist

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is characterised by chronic pulmonary inflammation punctuated by periods of viral exacerbations. Recent evidence suggests that the combination of roflumilast with corticosteroids may improve the compromised anti-inflammatory properties of corticosteroids in COPD. We analyzed differential and combination anti-inflammatory effects of dexamethasone and roflumilast N-oxide in human bronchial epithelial cells (HBECs) stimulated with viral toll like receptor (TLR) agonists.

Methods: Lung tissue and HBECs were isolated from healthy (n = 15), smokers (n = 12) and smokers with COPD (15). TLR3 expression was measured in lung tissue and in HBECs. IL-8 secretion was measured in cell cultures after TLR3 stimulation with poly I:C 10 µg/mL.

Results: We found that TLR3 expression was increased by 1.95 fold (protein) and 2.5 fold (mRNA) in lung tissues from smokers with COPD and inversely correlated with lung function. The TLR3 agonist poly I:C 10 µg/mL increased the IL-8 release in HBECs that was poorly inhibited by dexamethasone in smokers (24.5%) and smokers with COPD (21.6%). In contrast, roflumilast showed similar inhibitory effects on IL-8 release in healthy (58.8%), smokers (56.6%) and smokers with COPD (50.5%). The combination of roflumilast N-oxide and dexamethasone showed additive inhibitory effects. Mechanistically, roflumilast N-oxide when combined with dexamethasone increased the expression of MKP1, and enhanced the inhibitory effects on phospho-p38, AP1 and NFkB activities which may explain the additive anti-inflammatory effects.

Conclusions: Altogether, our data provide in vitro evidence for a possible clinical utility to add roflumilast on top of inhaled corticosteroid in COPD.

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Background

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction, inflammation, and a progressive decline in lung function [1]. The primary cause of COPD is chronic exposure to cigarette smoke, which leads to airway inflammation and remodeling, thus increasing airflow limitation.

The current first-line maintenance treatment for COPD involves the use of bronchodilators, including longacting muscarinic antagonists (LAMAs) and long-acting beta agonists (LABAs), in combination with inhaled corticosteroids in those patients with severe COPD who are at risk of exacerbations. However, in contrast to other inflammatory diseases, corticosteroids are less effective in improving lung function and have little or no effect on controlling the underlying chronic inflammation in COPD patients [2]. The poor anti-inflammatory properties of corticosteroids in COPD have increased the development of other anti-inflammatory drugs. This is the case of roflumilast, the first phosphodiesterase-4(PDE4) inhibitor approved for COPD. It is indicated as a treatment to reduce the risk of COPD exacerbations associated with chronic bronchitis in patients with severe COPD and a history of exacerbations. In preclinical models, roflumilast and its active metabolite, roflumilast N-oxide, have been shown to inhibit a broad spectrum of inflammatory cytokines and reactive oxygen species (ROS) in different inflammatory and non-inflammatory cells relevant to COPD [3].

Exacerbations of COPD are the major cause of morbidity and mortality and are associated with accelerated decline in lung function and progression of the disease [4].

Respiratory RNA virus infections such as human rhinovirus (HRV), respiratory syncytial virus (RSV) and influenza virus are common causes of exacerbations of COPD [4]. In this regard, HRV-induced lung inflammation has been recently shown to be corticosteroid resistant [5,6]. Furthermore, neutrophilic inflammation in chronic cigarette smoking mice exacerbated with influenza virus infection was resistant to dexamethasone [7]. Similarly, the toll like receptor 3 (TLR3) agonist, poly I:C, induced a corticosteroid resistant neutrophil airway inflammation in mice [8]. Current data suggests that roflumilast has antiinflammatory effects on RSV-infected bronchial epithelial cells [9] and reverses corticosteroid resistance in neutrophils from COPD patients in vitro [10].

Viral exacerbations in patients with COPD are considered to be caused by inflammatory responses that overwhelm the protective anti-inflammatory defenses [4]. In fact, viral exacerbations increased neutrophil counts in the bronchial walls and in bronchoalveolar lavage fluid from COPD patients mainly through the release of neutrophil chemoattractant inflammatory cytokines IL-8 or LTB4 by infected airway epithelial cells [11-14].

The double-stranded (ds) and single-stranded (ss) RNA generated during RNA virus infection activates TLR3 and TLR7/8, respectively, which enhance inflammatory and antiviral responses as part of the host innate immune defense [15]. The expression of TLR3 has been detected in immune cells such as macrophages, natural killer cells, CD8+ T cells, and dendritic cells, and non-immune cells such as airway smooth muscle cells, airway epithelial cells, and endothelial cells [16-19]. The expression of TLR7/8 was first detected on dendritic cells and later in leukocytes, lymphocytes, endothelial and airway epithelial cells [20]. Despite the key role of viral exacerbations on COPD progression, the expression levels and distribution pattern of TLR3 and TLR7/8 in inflammatory cells and lung tissue of COPD patients are not sufficiently characterized and the information currently available is contradictory [17,19].

The purpose of the current study was to characterize the expression and distribution of TLR3, TLR7, and TLR8 in lung tissue from non-smokers, smokers and smokers with COPD and to analyze the differential effects of roflumilast N-oxide versus corticosteroids and their potential additive or synergistic antiinflammatory effect in bronchial epithelial cells stimulated with TLR3/7/8 agonists. Results from this study may be of potential value to understanding the clinical benefits of combining roflumilast and corticosteroids for COPD treatment [21].

Methods Patients

A total of 15 non-smoking controls, 12 current smokers without COPD, and 15 current smokers with COPD were included in the study. COPD patients were diagnosed according to the GOLD guidelines [22]. All lung tissues studied were taken from lung explants of nonsmoking subjects in the transplant program and from uninvolved lung tissue from smokers without COPD or with COPD during lobectomy/wedge resection for malignant lesions in the Thoracic Surgery and Respiratory Unit, University General Hospital Consortium, Valencia, Spain, between 2010 and 2014. Samples of distal lung, located as far as possible from the tumor, were chosen for the study. All pulmonary function tests were performed within 3 months before surgery or taken from the clinical history. Clinical data from all patients (see Table 1) were examined for possible co-morbidity. Inclusion criteria comprised either nonsmokers or current smokers with or without COPD who were free of symptoms of upper respiratory tract infection and were not receiving antibiotics perioperatively. After selection based on lung function, all lung tissue samples chosen for the study were checked histologically using the following exclusion criteria: (1) presence of tumor, (2) presence of post stenotic pneumonia, and (3) fibrosis of lung parenchyma. The study protocol was approved by the local research and independent ethics committee of the University General Hospital of Valencia. Informed written consent was obtained from each participant or their legal representative.

Isolation of primary bronchial epithelial cells and cell culture

Human bronchial epithelial cells (HBECs) from small bronchi were isolated as previously outlined [23]. Small pieces of human bronchi (0.5-1 mm internal diameter) were excised from microscopically normal lung areas, carefully dissected from lung parenchyma and plated on collagen-coated culture dishes (10 µg/cm² rat type I collagen; Sigma) in bronchial epithelial growth medium (BEGM), comprising bronchial epithelial basal medium (BEBM) supplemented with bovine pituitary extract (52 µg/ml, hydrocortisone 0.5 µg/ml), human recombinant epidermal growth factor ([EGF] 25 ng/ml), epinephrine (0.5 µg/ml), transferrin (10 µg/ml), insulin (5 µg/ml), retinoic acid (50 nM), triiodo-L-thyronine (6.5 ng/ml), gentamycin (40 µg/ ml), amphotericin B (50 ng/ml), and bovine serum albumin (1.5 µg/ml). Small bronchi were oriented with the epithelial layer in contact with the culture plate. After a period of $\sim 1-2$ weeks, bronchial epithelial cells were observed around the bronchi. After trypsinization (passage 1), cells were cultured accordingly for different experiments. All the experiments performed in this study with primary HBEC were done on monolayer cultures. The identity of the monolayer as bronchial epithelial cells was confirmed using morphological criteria and immunofluorescence for cytokeratin 5 (KRT5) as well as later use of in vitro differentiation in air-liquid interface as pseudostratified bronchial epithelium with basal cells, ciliated cells, columnar, and goblet cells (data not shown). Cell viability was assessed by vital trypan blue exclusion analysis using the Countness automated cell counter (Life Technologies, Madrid, Spain). Cell viability was >98% in all cell cultures.

The bronchial epithelial BEAS2B cell line was obtained from American Type Culture Collection and cultured in BEGM media with supplements (Lonza, Madrid, Spain) on collagen-coated culture dishes (10 μ gcm⁻²; rat type I collagen) at 37°C with 5% CO₂ in humidified air. The culture medium was replaced every 48 hours.

Immunohistochemistry

For immunohistochemical analysis of human pulmonary tissue from non-smokers, smokers, and smokers with COPD, tissues were fixed, embedded in paraffin, cut into sections (4-6 µm), and stained with haematoxylin, as reported previously [24]. The sections were incubated with rabbit anti-human TLR3 polyclonal antibody (diluted 1:250; Bioss, Woburn, USA), rabbit anti-human TLR7 polyclonal antibody (1:250; Novus Biologicals, Madrid, Spain), rabbit anti-human TLR8 polyclonal antibody (1:250; Novus Biologicals, Madrid, Spain) for 24 hours at 4°C. A secondary anti-rabbit antibody (1:100; Vector Laboratories, Burlingame, CA) with avidin-biotin complex/horseradish peroxidase (HRP) was used for immunohistochemistry. The non-immune IgG isotype control was used as negative control. All stained slides were scored by a pathologist under a Nikon Eclipse TE200 (Tokio, Japan) light microscope and representative photographs taken (10 slices per patient) as previously outlined [25]. Staining intensity was analyzed in alveolar macrophages and bronchial epithelium of small bronchi. Staining intensity for TLR3, TLR7, and TLR8 antibodies was scored on a scale of 0-3: 0, negative; 1, weak; 2, moderate; or 3, strong immunoreactivity. The percentage of cells positive for TLR3, TLR7 and TLR8 antibodies in alveolar macrophages and within bronchial epithelium was scored on a scale of 1-4as follows: 1, 0-25% cells positive; 2, 26-50% positive; 3, 51-75% positive; and 4, 76–100% positive. The score of the staining

Table 1 Clinical characteristics of patients

	Non-smokers (n = 15)	Smokers (n = 12)	Smokers with COPD (n = 15)
Sex (Female/Male)	7/8	3/9	3/12
Age (years)	60 [50-72]	60 [47–68]	55 [49–60]
Tobacco consumption, pack-year	0	40 [20–56]*	55 [34–83]*
FEV1, % predicted	92 [76–96]	87 [83–97]	73 [53–79] [‡]
FVC, % predicted	97 [72–107]	90 [86–99]	96 [84–114]
FEV1/FVC	78 [75–84]	80 [77–83]	61 [55–67] [‡]
PaO ₂ , mmHg	94 [89–99]	85 [81–90] [†]	80 [78–83] [‡]
PaCO ₂ mmHg	41 [34-47]	44 [37–48]	47 [42–54] [†]

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; Pack-yr = 1 year smoking 20 cigarettes-day; PaO₂: oxygen tension in arterial blood; PaCO₂: carbon dioxide tension in arterial blood; Data are the median [interquartile range]. * P < 0.05 compared with nonsmokers. $^{+}P < 0.05$ compared with nonsmokers and smokers without COPD. $\ddagger P < 0.05$ compared with nonsmokers and smokers without COPD.

intensity and the percentage of immunoreactive cells were then multiplied to obtain a composite score ranging from 0 to 12.

Western blot

Western blot analyses were performed to detect changes in TLR3, TLR7, and TLR8 expression in lung tissue from nonsmokers, smokers, and smokers with COPD. The Bio-Rad assay (Bio-Rad Laboratories Ltd., Herts, UK) was utilized to quantify the level of protein in each sample to ensure equal protein loading. Proteins were separated according to molecular weight by SDS-PAGE. Briefly, 15 µg of denatured protein and a molecular weight protein marker (Bio-Rad Kaleidoscope marker; Bio-Rad Laboratories) were loaded onto an acrylamide gel consisting of a 5% acrylamide stacking gel stacked on a 10% acrylamide resolving gel and electrophoresed at 100 V for 1 hour. Proteins were transferred to a polyvinylidene difluoride (PVDF) membrane using a wet blotting method. The membrane was blocked with 5% Marvel in PBS containing 0.1% Tween20 (PBS-T), probed with a rabbit anti-human TLR3 polyclonal antibody (1:1000; Bioss, Woburn, USA), rabbit anti-human TLR7 polyclonal antibody (1:1000; Novus Biologicals, Madrid, Spain), rabbit anti-human TLR8 polyclonal antibody (1:1000; Novus Biologicals, Madrid, Spain), and normalised to total mouse antihuman β -actin monoclonal antibody (1:1000; Sigma). Labeled proteins were detected using enhanced chemiluminescence methods and reagents (ECL plus; Amersham GE Healthcare, Buckinghamshire, UK). Densitometry of films was performed using the Image J 1.42q software (available at http://rsb.info. nih.gov/ij/, USA) and results are expressed as the ratio of the densitometry of the endogenous control β -actin.

Real Time RT-PCR

Total RNA was isolated from lung parenchyma, primary HBECs, and BEAS2B bronchial epithelial cells with the TriPure Isolation Reagent (Roche, Indianapolis, USA). The integrity of the extracted RNA was confirmed with the Bioanalyzer (Agilent, Palo Alto, CA, USA). Reverse transcription was performed in 300 ng of total RNA with TaqMan reverse transcription reagents kit (Applied Biosystems, Perkin-Elmer Corporation, CA, USA). cDNA was amplified with specific, pre-designed primer sets for MKP1, MIF, HDAC2, TLR3, TLR7, TLR8, and TRIF and the housekeeping gene GAPDH (Applied Biosystems) in a 7900HT Fast Real-Time PCR System (Applied Biosystems) using Universal Master Mix (Applied Biosystems). Relative quantification of each transcript was determined with the 2-^{ΔACt} method using GAPDH as endogenous control and normalized to the non-smoker or control groups.

Preparation of cigarette smoke extract solutions

Cigarette smoke extract (CSE) was prepared as previously outlined [26]. Briefly, the smoke of a research cigarette (2R4F; Tobacco Health Research, University of Kentucky, KY, USA) was generated by a respiratory pump (Apparatus Rodent Respirator 680; Harvard, Germany) through a puffing mechanism similar to the human smoking pattern (3 puffs/min; 1 puff volume of 35 ml; each puff duration lasting 2 seconds with 0.5 cm above the filter) and was bubbled into a flask containing 25 ml of prewarmed (37°C) Roswell Park Memorial Institute (RPMI)-1640 culture medium. The CSE solution was sterilized by filtration through a 0.22 µm cellulose acetate sterilizing system (Corning, USA). The resulting CSE solution was considered 100% CSE and was used within 30 minutes of preparation. CSE 10% approximately corresponds to the exposure associated with smokingoftwo packs per day[27]. The quality of the prepared CSE solution was assessed based on the absorbance at 320 nm, which is the specific light absorption wavelength of peroxynitrite. Stock solutions with an absorbance value of 3.0 \pm 0.1 were used. To test for cytotoxicity and apoptosis due to CSE, BEAS2B cells were treated with CSE concentrations of up to 5% for 24 hours. No significant differences in the lactate dehydrogenase supernatant level (lactate de-hydrogenase cytotoxicity assay; Cayman, Spain) or in the number of apoptotic cells (annexin V-FITC) were observed in comparison with the control group [25].

Cell stimulations and IL-8 assay

Primary HBECs from non-smoker, smoker, and smokers with COPD were adjusted to 500×10^3 cells per well in 6-well plates and incubated in BEGM culture medium at 37°C with 5% CO₂. Cells were then treated in the presence or absence of roflumilast N-oxide (0.1 nM-1 µM; Forest Research Institute, Jersey City, USA), dexamethasone (0.1 nM-1 µM; Sigma Aldrich, Madrid, Spain), or with a combination of fixed concentrations of dexamethasone at suboptimal concentrations (10 nM) and roflumilast N-oxide (1 nM, 10 nM, and 100 nM) for 1 hour. After drug incubations, HBECs were stimulated with the TLR3 agonist poly I:C at 10 µg/mL or with the TLR7/8 agonist CL097 (Invivogene, Toulouse, France) at 4 µg/ml final concentration, as previously outlined [28,29]. Cells were co-incubated with the drugs and the TLR agonists for 24 hours.

In additional experiments, BEAS2B cells were exposed to AIR or CSE 1% for 1 hour and then treated for 1 hour with roflumilast N-oxide (0.1 nM-1 μ M), dexamethasone (0.1 nM-1 μ M), or with a combination of fixed concentrations of

dexamethasone at suboptimal concentration (10 nM) and roflumilast N-oxide (1 nM, 10 nM, and 100 nM). Cells were then stimulated with poly I:C at 10 μ g/ mL or CL097 at 4 μ g/ml for 24 hours.

Roflumilast N-oxide and dexamethasone were dissolved in dimethyl sulfoxide (DMSO) at 10 mM stock concentration. Several dilutions of the stocks were performed with cell culture medium. The final concentrations of DMSO (0.1%) in the cell culture did not affect celular functions. Other chemicals (poly I:C or CL097) were dissolved in médium.

In other experiments Roflumilast N-oxide was added at 0, 1 nM, 10 nM or 1 μ M. 0 nM corresponds to vehicle (0.1% DMSO), 2 nM corresponds to the free plasma concentrations (unbound to plasma protein) after repeated, oral, once-daily dosing of roflumilast at the clinical dose of 500 μ g/day [30] and at 1 μ M roflumilast N-oxide completely and selectively inhibits PDE4 [31]. The half-maximum potency of roflumilast N-oxide to inhibit PDE4 amounts to 2 nM [31].

Supernatants were collected and centrifuged at 120 g for 5 minutes. IL-8 was measured in cell-free supernatant and cellular extracts were utilized to measure mRNA. IL-8 concentration was determined using a commercially available enzyme-linked immunosorbent assay kit for IL-8 (R&D Systems, Nottingham, UK).

NF-KB (p65) and AP1 nuclear transcription factor measure

BEAS2B cells were treated with or without CSE 1% for 1 hour and exposed to roflumilast N-oxide (10 nM, 1 μ M), dexamethasone (10 nM, 1 μ M) or the combination of roflumilast N-oxide 10 nM plus dexamethasone 10 nM for 1 hour and stimulated with poly I:C 10 μ g/mL at indicated times. Cells were then washed and centrifuged to extract the nuclear protein as previously described [10]. Measurement of nuclear NF- κ B (p65) transcription factor expression was performed using a commercially available NF- κ B (p65) transcription factor assay kit (Cayman Chemical, MI, USA) and with the ELISA AP1 Chemiluminescence Kit (Signosis, CA, USA).

Analysis of p38 phosphorylation

BEAS-2B were treated with or without CSE 1% for 1 hour and then exposed to roflumilast N-oxide (10 nM1 μ M), dexamethasone (10 nM-1 μ M), or a combination for 1 hour. Cells were then stimulated with poly I:C 10 10 μ g/ mL for 30 minutes. Total protein was extracted using a lysis buffer consisting of a complete inhibitor cocktail plus 1 mM ethylenediaminetetraacectic acid (Roche Diagnostics Ltd, West Sussex, UK) with 20 mM Tris base, 0.9% NaCl, 0.1% Triton X-100, 1 mM dithiothreitol and 1 μ g/ml pepstatin A. The Bio-Rad assay (Bio-Rad Laboratories Ltd., Herts, UK) was utilized for protein quantification to ensure equal protein loading. To quantify the phosphorylation of p38, Surveyor IC Immunoassay of p38 α phosphorylated at T180/Y182 in cell lysates was employed



Figure 1 Expression of TLR3 in lung tissues of non-smokers, smokers, and COPD patients. Total protein and mRNA was obtained from lung tissue of non-smokers (n = 15), smokers (n = 12), and COPD patients (n = 15). TLR3 protein and mRNA expression was determined by western blot (**A**) and real time PCR (**B**), respectively, in lung parenchyma. (**A**) Representative images of western blot for TLR3 and corresponding densitometry expressed as ratio of β -actin. (**B**) TLR3 mRNA expression expressed as the ratio to GAPDH. (**C**) Spearman " ρ " correlation of the protein expression of TLR3 in COPD patients and lung function, FEV₁% predicted. (**D**, **E**, **F**) Lung sections were immunostained for TLR3 and quantified by means of immunohistochemical score of TLR3 in alveolar macrophages (**D**) and bronchial epithelial cells (**E**). (**F**) Representative immunohistochemistry images are shown. The control IgG isotype signal was negative. Data are presented as individual values and mean ± standard deviation. Exact *P* values were obtained using Kruskal-Wallis and Dunn's post-hoc tests.



Figure 2 Expression of TLR7 in lung tissues of non-smokers, smokers, and COPD patients. Total protein and mRNA were obtained from lung tissues of non-smokers (n = 15), smokers (n = 12), and COPD patients (n = 15). TLR7 protein and mRNA expression were determined by western blot (**A**) and real time PCR (**B**) in lung parenchyma. (**A**) Representative images of western blot for TLR7 and corresponding densitometry expressed as ratio to β -actin. (**B**) TLR7 mRNA expression given as the ratio to GAPDH. (**C**, **D**, **E**) Lung sections were immunostained for TLR7 and quantified by means of immunohistochemical score of TLR7 in alveolar macrophages (**C**) and bronchial epithelial cells (**D**). (**E**) Representative immunohistochemistry images are shown. The control IgG isotype showed negative staining. Data are presented as individual values and mean ± standard deviation. Exact *P* values were obtained using Kruskal-Wallis and Dunn's post-hoc tests.

(R&D Systems Europe, Ltd). Results were expressed as pg of phosphor-p38/µgof total protein.

Analysis of results

Statistical analysis of results was carried out by parametric or non-parametric analysis as appropriate with P < 0.05 considered statistically significant. Non-parametric tests were used to compare results from the lung tissue of non-smoker, smoker, and smokers with COPD. In this case, data were displayed as mean \pm standard deviation. For comparisons between two groups, differences were analyzed using the Mann–Whitney U test. For comparisons between multiple groups, a nonparametric one-way analysis of variance (Kruskal-Wallis test) was performed and post hoc comparison were performed using the Dunn's post-hoc test, which generalizes the Bonferroni adjustment procedure. Correlations were analyzed using the Spearman (ρ) correlation analysis.

In vitro cell experiments were performed in HBECs from nonsmoker, smoker and smokers with COPD and in BEAS2B cells. Results were expressed as mean ± standard error of mean (SEM) of n experiments with the normal distribution for each data set confirmed by histogram analyses and Kolmogorov–Smirnov test. Parametric analyses were performed and two-group comparisons were analysed using the two-tailed Student's paired t-test for dependent samples or unpaired t-test for independent samples. Multiple comparisons were analysed by one-way or two-way analysis of variance followed by Bonferroni post hoc test.

Results

Expression and distribution of TLR3, TLR7 and TLR8 in lung tissue of non-smokers, smokers and smokers with COPD

TLR3 protein and mRNA expression was upregulated in lung parenchyma of smokers and smokers with COPD and inversely correlated with FEV₁% in COPD patients (Figure 1A, B, and C). TLR3 immunostaining was significantly elevated in alveolar macrophages and bronchial epithelial cells from smokers and smokers with COPD compared with non-smokers (Figure 1D, E, and F). TLR7 expression was detected in nearly all lung cellular structures, and was similar in lung tissue from non-smokers, smokers, and smokers with COPD (Figure 2). In contrast, TLR8 expression was significantly downregulated in lung parenchyma of smokers and smokers with COPD (Figure 3A and B). While TLR8 showed a marked expression in all lung structures of non-



Figure 3 Expression of TLR8 in lung tissues of non-smokers, smokers, and COPD patients. Total protein and mRNA were obtained from lung tissues of non-smokers (n = 15), smokers (n = 12), and COPD patients (n = 15). TLR8 protein and mRNA expression were determined by western blot (**A**) and real time PCR (**B**) in lung parenchyma. (**A**) Representative images of western blot for TLR8 and corresponding densitometry expressed as ratio to β -actin. (**B**) TLR8 mRNA expression given as the ratio to GAPDH. (**C**, **D**, **E**) Lung sections were immunostained for TLR8 and quantified by means of immunohistochemical score of TLR8 in alveolar macrophages (**C**) and bronchial epithelial cells (**D**). (**E**) Representative immunohistochemistry images are shown. The control IgG isotype showed negative staining. Data are presented as individual values and mean ± standard deviation. Exact *P* values were obtained using Kruskal-Wallis and Dunn's post-hoc tests.

smokers, the immunohistochemical staining of TLR8 showed a weak distribution in alveolar macrophages and bronchial epithelial cells from smokers and smokers with COPD (Figure 3C, D, and E).

Anti-inflammatory properties of dexamethasone and roflumilast N-oxide on primary human bronchial epithelial cells stimulated with TLR3 agonist

After 24 hours of stimulation with the TLR3 agonist poly I:C 10 µg/mL, the release of IL-8 was increased in HBECs from all patients showing higher amounts in cells from smokers and smokers with COPD. However, the TLR7/8 dual agonist CL097 did not increase IL-8 secretion (Figure 4A).

In HBECs from non-smoker patients, both roflumilast N-oxide and dexamethasone inhibited the poly I:Cinduced IL-8 secretion in a concentration-dependent manner with similar maximal percent inhibition ($58.8 \pm 1.4\%$ and $59.2 \pm 1.2\%$ respectively) and potency ($-\log IC_{50}$ 8.28 \pm 0.43 roflumilast vs 8.75 \pm 0.21 [M] dexamethasone; Figure 4B and Table 2). While roflumilast N-oxide inhibited IL-8 secretion in cells from smokers and smokers with COPD with similar maximal percent inhibition ($56.6 \pm 2.8\%$ and $50.5 \pm 1.5\%$, respectively)

and potency ($-\log IC_{50} 8.14 \pm 0.21$ and 8.28 ± 0.17 [M]), dexamethasone showed impaired maximal percent inhibition in both smokers and smokers with COPD ($24.5 \pm 7.9\%$ and $21.6 \pm 2.8\%$, respectively) and impaired potency in COPD patients ($-\log IC_{50} 7.84 \pm 1.7$ [M]; Figure 4C and D, Table 2).

In HBECs from COPD patients, the combination of sub-optimal concentrations of dexamethasone (10 nM) with different concentrations of roflumilast N-oxide (1 nM to 100 nM) additively increased the inhibitory effect of dexamethasone on IL-8 release (Figure 4D).

Further study of TLR3 revealed a higher expression of TLR3 (Figure 5A) and its adaptor TRIF (Figure 6) in HBECs from smokers and smokers with COPD compared with non-smokers. Interestingly, the TLR3 agonist poly I:C was able to increase significantly the expression of TLR3 (Figure 5B, C, and D) and TRIF (Figure 6B, C, and D) in HBECs from smokers with COPD and to a lesser extent in smokers and non-smoker subjects. Roflumilast N-oxide, reduced the increase of TLR3 and TRIF induced by poly I:C in all conditions. In contrast, dexamethasone only attenuated the increases of TLR3 and TRIF in non-smokers, but not in smokers or smokers with COPD (Figures 5 and 6).



Figure 4 Roflumilast N-oxide inhibited IL-8 release in human bronchial epithelial cells and demonstrated additive anti-inflammatory properties in corticosteroid resistance conditions. Human bronchial epithelial cells (HBECs) from non-smokers (n = 4), smokers (n = 4), and COPD patients (n = 5) were isolated from lung tissues. (**A**) HBECs from different patients were stimulated with TLR3 agonist poly I:C or the TLR7/8 dual agonist CL097 for 24 hours and IL-8 levels in the supernatants were measured by ELISA. (**B**, **C**, **D**) HBECs from different patients were incubated with roflumilast N-oxide (RNO) or dexamethasone (DEX) at different concentrations for 1 hour followed by the stimulation with poly I:C 10 µg/ml for 24 hours to measure IL-8 release. (**D**) In COPD patients, fixed concentrations of DEX 10 nM were combined with different RNO concentrations. Results are expressed as means ± SEM of n = 4-5 (4 non-smoker, 4 smokers, and 5 COPD patients) run in triplicate experiments. Two-way repeated measures analysis of variance (ANOVA) were performed. Post hoc Bonferroni test: *P < 0.05 compared with solvent controls. #P < 0.05 compared with monotherapy.

Cigarette smoke extract reduces corticosteroid responsiveness in BEAS2B bronchial epithelial cells stimulated with TLR3 agonist

In vitro simulation of smoke exposure was assessed to demonstrate similar behavior of HBECs from smokers and smokers with COPD and to study the underlying mechanistic pathways. In this regard, BEAS2B bronchial epithelial cells were incubated with or without cigarette smoke extract (CSE) 1% for 1 hour, followed by roflumilast N-oxide (0.1 nM-1 μ M) or dexamethasone (0.1–1 μ M) exposure for 1 hour and the stimulation with poly I:C 10 μ g/mL for additional 24 hours to measure IL-8 supernatant levels. CSE exposed cells showed higher IL-8 basal release as well as higher IL-8 amounts following poly I:C stimulation (Figure 7A). In other experiments, cells with or without exposure to CSE did not respond to TLR7/8 agonist CL097 (data not shown).

In absence of CSE pretreatment, both roflumilast N-oxide and dexamethasone concentration-dependently inhibited IL-8 secretion showing nearly identical maximal inhibitory percentage and potency (Figure 7B). In BEAS2B cells pretreated with CSE, roflumilast N-oxide inhibited IL-8 release with comparable maximal inhibitory percentage (44.9 ± 4.7%) and potency ($-\log IC_{50} 8.08 \pm 0.23$ [M]; Figure 7C and Table 2) compared with non-exposed cells. In contrast, inhibition of IL-8 by dexamethasone was impaired in the presence of CSE, reducing the maximal inhibitory percentage from 42.6 ± 2.9% to 27.9 ± 6.7% (Figure7B and C, Table2).

Combination of roflumilast N-oxide with dexamethasone shows additive anti-inflammatory effects: mechanistic implications

The combination of a fixed non-effective dexamethasone concentration of 10 nM with different concentrations of roflumilast N-oxide (1 nM–100 nM) in BEAS2B cells pretreated with CSE showed additive effects inhibiting the IL-8 release induced by TLR3 agonist (Figure 7C).

Poly I:C in presence or absence of CSE increased the expression of TLR3 and its adaptor TRIF in BEAS2B cells after 24 hours of stimulation (Figure 8A). Roflumilast N-oxide and dexamethasone effectively decreased the poly I:C-induced TLR3 expression in the presence or absence of CSE. However, in the presence of

CSE, only the combination of roflumilast N-oxide (10 nM) and dexamethasone (10 nM) inhibited the TRIF overexpression induced by poly I:C (Figure 8B). IL-8 release induced by poly I:C in BEAS2B was insensitive to corticosteroids (Figure 7C). As molecular modulators of corticosteroid efficacy, we found that HDAC2 gene expression was downregulatedby polyI:C andfurther decreased in presence of CSE (Figure 8C). Roflumilast N-oxide at 1 µM partially reversed HDAC2 to control levels, and the association of roflumilast N-oxide 10 nM and dexamethasone 10 nM showed additive effects, increasing HDAC2 expression (Figure 8C). The expression of MIF was not modified under any experimental condition (Figure 8D). The expression of MKP1 was not modified by poly I:C in the presence or absence of CSE and following roflumilast N-oxide or dexamethasone exposure. However, the combination of roflumilast N-oxide 10 nM and dexamethasone 10 nM synergistically increased MKP1 expression (Figure 8E).

In other experiments, we observed that TLR3 activation by poly I:C increased the phosphorylation of mitogen-activated protein kinase p38 as well as the nuclear activation of AP-1 and expression of NF- κ B (p65) that were enhanced in the presence of CSE (Figure 9A, B and C). Roflumilast N-oxide showed inhibitory effects on phosphorylation of p38 and nuclear activation of AP-1 and NF- κ B in the presence or absence of CSE. In contrast, dexamethasone showed a poor inhibitory effect (Figure 8A, B, and C). The combination of roflumilast N-oxide 10 nM and dexamethasone 10 nM synergistically inhibited p38, AP-1, and NF- κ B which may explain in part the additive anti-inflammatory effects of roflumilast N-oxide and dexamethasone in HBECs of COPD patients following TLR3 activation.

Discussion

The present study provides new evidence on the expression and distribution profile of the virus innate immune receptors TLR3, TLR7, and TLR8 in lung tissue of non-smokers, smokers and COPD patients as well as on the anti-inflammatory profile of roflumilast N-oxide and reduced corticosteroid responsiveness following the activation of TLR3 in HBECs from current smokers and COPD patients. Combination of roflimilast N-oxide and dexamethasone showed additive anti-inflammatory properties in HBEC from COPD patients. These results may provide in vitro rational for "adding on" a PDE4 inhibitor to the

Table 2 Anti-inflammator	y effects of	roflumilast	N-oxide and	dexamethasone	in human	bronchial	epithelial cells
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A)		HBEC; Non-smokers		HBEC; Smokers		HBEC; COPD	
Stimulus	Treatment	Maximal % inhibition	-logIC ₅₀	Maximal % inhibition	-logIC ₅₀	Maximal % inhibition	-logIC ₅₀
Poly (I:C) 10 μg/mL	RNO	58.8 ± 1.4	8.28 ± 0.43	56.6 ± 2.8	8.14 ± 0.21	50.5 ± 1.5	8.28 ± 0.17
	DEX	59.2 ± 1.2	8.75 ± 0.21	24.5 ± 7.9*	8.62 ± 0.31	21.6 ± 2.8*	7.84 ± 1.7* [#]
B)		BEAS2B		BEAS2B + CSE			
	Treatment	Maximal % inhibition	-logIC ₅₀	Maximal % inhibition		-logIC ₅₀	
Poly (I:C) 10 μg/mL	RNO	44.5 ± 1.5	8.07 ± 0.15	44.9 ± 4.7		8.08 ± 0.23	
	DEX	42.6 ± 2.9	8.06 ± 0.10	27.9 ± 6.7-		7.77 ± 0.28-L	

Inhibition of IL-8 release from (A) human primary bronchial epithelial cells (HBECs) from non-smokers (n = 4), smokers (n = 4) and chronic obstructive pulmonary disease patients (COPD; n = 5) or (B) BEA52B cells exposed with or without cigarette smoke extract (CSE 1%). (A) Cells were incubated with Roflumilast N-oxide (RNO; 0.1 nM- 1 μ M) or Dexamethasone (DEX; 0.1 nM- 1 μ M) for 1 hour and stimulated with Poly (I:C) 10 μ g/ml (TLR3 agonist) for 24 hours. (B) Cells were incubated with or without CSE 1% for 1 hour, followed by incubation with RNO or DEX for 1 hour and stimulated with Poly (I:C) 10 μ g/ml for 24 hours. Values are mean ± SEM of 3–5 independent experiments run in triplicate. IC₅₀ values for half-maximum inhibition were calculated by nonlinear regression analysis.*P < 0.05 vs RNO group; $\pm P < 0.05$ vs non-CSE treated group.

treatment regimen of patients with severe COPD taking inhaled corticosteroids who still suffer frequent exacerbations.

Although TLR3 and, to a lesser extent TLR7/8, have been studied as innate immune viral sensing receptors promoting inflammatory reactions and anti-viral responses in different cell types, their distribution and expression in different lung structures in COPD have been neglected. Among the few available studies, Todt, et al. [19] observed that active smoking, (independent of COPD stage) reduces both the percent of lung macrophages expressing TLR3 and poly I:C-induced CXCL10 production in vitro, without altering other endosomal or cytoplasmic receptors such as TLR7/8/9, RIG-I, MDA-5 or PKR, so that positive numbers of TLR3-macrophages directly correlated with lung function. In contrast, Koarai, et al. [17] observed an overexpression of TLR3 in alveolar macrophages of smokers and COPD patients that inversely correlated with lung function. The authors attributed this discrepancy to methodological differences in TLR3 determination, design, and endpoints of the experiments testing poly I:C-stimulated mediator production. Furthermore, a recent work performed by Kinose D, et al. [32] showed an association of the overexpression of TLR3 in sputum cells (mainly neutrophils) with the increase of COPD exacerbations which is in line with the results presented in this work.

To our knowledge, this is the first study which characterizes the main viral pattern recognition receptors TLR3, TLR7, and TLR8 in different lung structures of non-smokers, smokers, and COPD patients. TLR3 was overexpressed in lung parenchyma of current smokers with and without COPD as assessed by western blot, real time PCR, and immunohistochemistry analysis, and inversely correlated with lung function in alveolar macrophages, as previously reported by Koarai, et al. [17]. TLR3 was also overexpressed in different lung structures such as alveolar and bronchial epithelium, as well as in alveolar macrophages of current smokers and COPD patients. Consequently, the stimulation of HBECs from smokers and COPD patients with the TLR3 agonist poly I:C, increased the neutrophilic cytokine IL-8 almost two folds, supporting the hypothesis for which an elevated expression of TLR3 in lung tissue from virally exacerbated COPD patients could mediate inflammatory responses that overwhelm protective anti-inflammatory defenses, and thus plays a role in lung chronic inflammation and remodeling. In fact, a recent study performed in mice deficient in TLR3/7/9 receptor signaling did not exhibit cigarette smokeinduced airspace enlargement, which implicates TLR3 not only

in lung inflammation but also in lung remodeling [33]. TLR3 expression is enhanced by dsRNA viral exposure aside from the TLR3 stimulation by its agonist poly I:C and oxidative stress exposure [28,34]. In this work, the TLR3 agonist was able to induce TLR3 and TRIF expression, and cigarette smoke also potentiated TLR3 and TRIF overexpression in vitro. However, unlike in non-smokers and smokers, poly I:C increased the TLR3 expression in HBECs from COPD patients by almost 11fold, that together with the basal over expression of TRIF in HBECs from COPD patient suggest a priming HBECs phenotype which may explain their higher IL-8 release. As a limitation, we included only patients who were free of symptoms of upper respiratory bacterial or virus tract infection. However we cannot discard a chronic subclinical viral bronchial colonization. The presence of non-symptomatic lung viral colonization could stimulate or alter TLR3 expression representing a limitation of this study.

In contrast to TLR3, we did not detect differences of TLR7 expression and distribution in different lung structures, which is in agreement with the observations made in alveolar macrophages of non-smokers, smokers, and COPD patients [19]. However, the expression of TLR8 was decreased in lung parenchyma of smokers and COPD patients as well as in alveolar macrophages and bronchial epithelial cells. In contrast to TLR3, the role of TLR7 and TLR8 in COPD is not well understood. Based in our in vitro results, the stimulation of TLR7/8 in HBECs from different patients did not enhance IL-8 secretion. Similar results in airway epithelial cells have been reported previously [28,29] suggesting a less prominent role on airway inflammation for TLR7/8 when compared with TLR3.

The loss of corticosteroid responsiveness is a feature characteristic of severe asthma and COPD [35]. Furthermore, corticosteroids show impaired anti-inflammatory properties following airway viral infection as previously reported [5,6,8,36]. Recent evidence shows that HRV airway epithelial cell infection impaired dexamethasone-dependent inhibition of IL-8 release [6]. Additionally, in an animal asthma model infected with RSV, corticosteroids did not reduce lung inflammation [36]. The loss of corticosteroid responsiveness to lung virus-induced inflammation could be mediated by the activation of TLR3 as mice exposed to poly I:C demonstrated a corticosteroid resistant airway neutrophilia when treated with or without cigarette smoke [8].

In this work we observed that HBECs from current smokers and COPD patients stimulated with TLR3 agonist were insensitive to

the anti-inflammatory effects of dexamethasone. These results were also reproduced in vitro in BEAS2B cells pretreated with cigarette smoke and stimulated with poly I:C.

Oxidative stress induced by cigarette smoke or chronic inflammation is known to induce corticosteroid resistance. For example, we and others have shown that cigarette smoke may induce inflammation resistant to corticosteroids in different cell types relevant to COPD such as neutrophils [10], HBECs [37], or alveolar macrophages [35]. The increase of oxidative stress generated by cigarette smoke alters mechanistic pathways related with corticosteroid activity. It has been shown that cigarette smoke can phosphorylate mitogenactivated protein kinases such as p38, JUN or ERK1/2, thus promoting glucocorticoid receptor (GR) hyperphosphorylation and consequently the inhibition of GR nuclear translocation [38]. Similar results have been observed in corticosteroid resistant HRV infected airway epithelial cells [6]. Other cellular mechanisms that promote corticosteroid resistance include decreased corticosteroid-induced mitogen-activated protein kinase phosphatase 1(MKP1)geneexpression, NFκB over activation, or HDAC2 downregulation [38]. We have previously demonstrated that neutrophils from COPD patients are insensitive to corticosteroids and deficient in MKP1 and HDAC2 expression and activity. Furthermore, dexamethasone did not inhibit cigarette smoke-induced NF-KB in neutrophils

from COPD patients [10]. In a similar way, airway epithelial cells infected by HRV impaired dexamethasone-induced MKP1 gene expression, diminished binding of GR to glucocorticoid response element (GRE), and impaired GR nuclear translocation as well as NF- κ B over activation and GR ϵ hyperphosphorylation [6].

In this work, we observed that HBECs from smokers and smokers with COPD stimulated with poly I:C increased the TLR3 and TRIF expression which was not inhibited by dexamethasone. Additionally, the bronchial epithelial cells exposed to cigarette smoke and stimulated with TLR3 agonist induced HDAC2 downregulation and an increase in p38 phosphorylation and AP1 and NF- κ B nuclear expression that were poorly inhibited by dexamethasone.

PDE4 inhibitors have shown potent anti-inflammatory properties in several cell types implicated in COPD pathogenesis (with the exception of alveolar macrophages which show a low PDE4 expression [39,40]), and can decrease the cellular oxidative stress generated by cigarette smokeand RSV aswepreviouslyoutlined [3,9,23]. Additionally, the combination of the PDE4 roflumilast with corticosteroids has shown additive or synergistic properties on the activation of anti-inflammatory genes and the inhibition of proinflammatory cytokines [10,41,42]. In fact, roflumilast increased the GRE signal induced by corticosteroids in bronchial epithelial



Figure 5 TLR3 is overexpressed in primary bronchial epithelial cells from current smokers and COPD patients and downregulated by roflumilast N-oxide. (A) Human bronchial epithelial cells (HBECs) from non-smokers (n = 15), smokers (n = 12), and COPD patients (n = 15) were isolated from lung tissues. **(A)** mRNA expression of TLR3 in HBECs from different patients was determined by real time PCR as the ratio to GAPDH. **(B, C, D)** HBECs from different patients were incubated in the presence or absence of roflumilast N-oxide (RNO) or dexamethasone (DEX) for 1 hour and stimulated with TLR3 agonist poly I:C for 24 hours. Results are expressed as means ± SEM of n = 4-5 (4 non-smokers, 4 smokers, and 5 COPD patients) run in triplicate. Two-way repeated measures analysis of variance (ANOVA) were performed. Post hoc Bonferroni test: *P < 0.05compared with non-smoker group or with solvent controls. #P < 0.05 compared with poly I:C stimulus.



Figure 6 TRIF is overexpressed in primary bronchial epithelial cells from current smokers and COPD patients and downregulated by roflumilast N-oxide. (A) Human bronchial epithelial cells (HBECs) from non-smokers (n = 15), smokers (n = 12), and COPD patients (n = 15) were isolated from lung tissue. **(A)** mRNA expression of TRIF in HBECs from different patients was determined by real time PCR as the ratio of GAPDH. **(B, C, D)** HBECs from different patients were incubated in the presence or absence of roflumilast N-oxide (RNO) or dexamethasone (DEX) for 1 hour and stimulated with TLR3 agonist poly I:C for 24 hours to measure TRIF mRNA expression. Results are expressed as means ± SEM of n = 3 (3 non-smokers, 3 smokers, and 3 COPD patients) run in triplicate. Two-way repeated measures analysis of variance (ANOVA) were performed. Post hoc Bonferroni test: *P < 0.05 compared with non-smoker group or with solvent controls. #P < 0.05 compared with poly I:C stimulus.

cells and increased expression of the anti-inflammatory genes induced by GRE [41]. In neutrophils from COPD patients, roflumilast showed potent anti-inflammatory properties and the combination of roflumilast with suboptimal dexamethasone concentrations also increased the anti-inflammatory properties of dexamethasone. The exploration of the underlying mechanisms revealed that roflumilast enhanced the ability of dexamethasone to increase HDAC2 activity and MKP1 expression as well as to inhibit ERK1/2 phosphorylation and NF-κB nuclear expression. In a recent study, we explored the anti-inflammatory role of roflumilast on the dsRNA RSV infection and inflammation [9]. Roflumilast inhibited RSV infection, prevented the loss of cilia and the secretion of proinflamatory IL-13, IL-6, IL-8, and TNF α , and decreased formation of ROS. This suggests an antiinflammatory role of roflumilast in similar conditions to those observed in corticosteroid resistance. In the present work, in contrast to dexamethasone, we observed an inhibition of the TLR3 and TRIF expression by roflumilast N-oxide in HBECs from smokers and smokers with COPD. Furthermore, roflumilast N-oxide in combination with dexamethasone showed additive inhibition of IL-8 release in HBECs from smokers and smokers with COPD. This association synergistically increased MKP1 and HDAC2 expression in bronchial epithelial cells pretreated with

cigarette smoke and stimulated with poly I:C. Similar findings were also observed in neutrophils from COPD patients that were stimulated with cigarette smoke [10]. Furthermore, roflumilast N-oxide in combination with dexamethasone also showed additive inhibitory effects on p38 phosphorylation and AP1 and NF- κ B nuclear expression.

As previously reported, corticosteroid sensitivity was restored by inhibiting NF- κ B in infected HRV airway epithelial cells [6] which supports our findings on roflumilast N-oxide in cells stimulated with TLR3 agonist.

TLR3 agonist and CSE combination induced resistance to dexamethasone, however we do not tested whether the IL-8 increase in BEAS2B due to CSE alone is reversible by roflumilast, dexamethasone or their combination. In this regard, it has been shown previously that CSE reduced the increase of GRE nuclear binding induced by dexamethasone in bronchial epithelial cells, thus impairing its anti-inflammatory properties [43]. In contrast, we previously have observed anti-inflammatory properties of roflumilast in human bronchial epithelial cells stimulated with CSE (data not shown). Whether the combination of roflumilast and dexamethasone reverse corticosteroid resistance induced by CSE alone, remains to be explored, although the additive/synergic effects of roflumilast and







Figure 8 Roflumilast N-oxide regulation of TLR3 expression and molecular pathway implicated in corticosteroid efficacy. BEAS2B cells were pretreated with or without cigarette smoke extract (CSE) 1% for 1 hour followed by the incubation in the presence or absence of different concentrations of roflumilast N-oxide (RNO) or dexamethasone (DEX) for 1 hour. After drug incubation cells were stimulated with the TLR3 agonist poly I:C for 24 hours and total mRNA was extracted to quantify the expression of **(A)** TLR3, **(B)** TRIF, **(C)** HDAC2, **(D)** MIF, and **(E)** MKP1 genes by real time PCR. Each graph represents the mean \pm SEM of 3–4 independent experiments. One-way repeated measures analysis of variance (ANOVA) were performed. Post hoc Bonferroni test: **P* < 0.05 compared with control; #*P* < 0.05 compared with stimulus; $\pm P$ < 0.05 compared with monotherapy.

dexamethasone on GRE activation in absence of oxidative stress has been observed [41] suggesting similar results under oxidative stress conditions. Besides the utility of using BEAS2B cell line as a mechanistic model of corticosteroid resistance, we have to highlight that BEAS2B cells could respond differently to stimuli compared to primary cells, which represents an important limitation of this study.

Clinically there may be a scientific rationale for using roflumilast in combination with an inhaled corticosteroid. In a recent post hoc analysis of two phase III studies, roflumilast reduced exacerbation frequency in a subgroup of patients with severe COPD and chronic bronchitis who were taking an inhaled corticosteroid concomitantly [21].

Moreover, roflumilast is recommended for patients with severe diseasewho arealreadytakingaLABA/ inhaled corticosteroid combination. Although not tested in this work, the triple combination of LABA/inhaled corticosteroid/roflumilast has shown potent synergistic anti-inflammatory properties [41].



Figure 9 Roflumilast N-oxide shows additive or synergistic effects with dexamethasone in inhibiting p38, AP1 and NF- κ B induced by TLR3 stimulation. BEAS2B cells were pretreated with or without cigarette smoke extract (CSE) 1% for 1 hour followed by the incubation in the presence or absence of different concentrations of roflumilast N-oxide (RNO) or dexamethasone (DEX) for 1 hour. After drug incubation cells were stimulated with the TLR3 agonist poly I:C for 30 minutes (A), 45 minutes (B), or 1 hour (C), and total protein (A) or nuclear protein (B, C) was extracted to measure p38 phosphorylation, AP1 nuclear activation, or NF- κ B (p65) nuclear expression. Each graph represents the mean ± SEM of 3–4 independent experiments. One-way repeated measures analysis of variance (ANOVA) were performed. Post hoc Bonferroni test: **P* < 0.05 compared with control; #*P* < 0.05 compared with stimulus; \perp P < 0.05 compared with monotherapy.

Frequent exacerbations of COPD are associated with a high level of inflammation [44] that may be less sensitive to corticosteroids, thus the combination of these anti-inflammatory therapies may be more effective in reducing COPD exacerbations. Anyway, clinical translation of our findings are far from resolved.

Conclusions

The present work shows that TLR3 expression is up-regulated in lung tissue from smokers and smokers with COPD correlating inversely with lung function, while TLR8 is down-regulated and TLR7 remains unaffected. TLR3 over-expression triggered IL-8 release in human bronchial epithelial cells from smokers and smokers with COPD patients as well as in cells exposed to CSE, that was insensitive to corticosteroids but not to roflumilast N-oxide suggesting a prominent role of cigarette smoke on corticosteroid insensitivity. Combination of roflumilast N-oxide with dexamethasone showed additive antiinflammatory effects that provide in vitro evidence for a possible clinical utility to add roflumilast on top of inhaled corticosteroid in severe COPD.

References

- Sethi S, Mahler DA, Marcus P, Owen CA, Yawn B, Rennard S. Inflammation in COPD: implications for management. Am J Med. 2012;125(12):1162–70.
- 2 Roche N, Marthan R, Berger P, Chambellan A, Chanez P, Aguilaniu B, et al. Beyond corticosteroids: future prospects in the management of inflammation in COPD. Eur Respir Rev. 2011;20(121):175–82.
- 3 Hatzelmann A, Morcillo EJ, Lungarella G, Adnot S, Sanjar S, Beume R, et al. The preclinical pharmacology of roflumilast–a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2010;23(4):235–56.
- 4 Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet. 2007;370(9589):786–96.
- 5 Farr BM, Gwaltney Jr JM, Hendley JO, Hayden FG, Naclerio RM, McBride T, et al. A randomized controlled trial of glucocorticoid prophylaxis against experimental rhinovirus infection. J Infect Dis. 1990;162(5):1173–7.
- 6 Papi A, Contoli M, Adcock IM, Bellettato C, Padovani A, Casolari P, et al. Rhinovirus infection causes steroid resistance in airway epithelium through nuclear factor kappaB and c-Jun N-terminal kinase activation. J Allergy Clin

Immunol. 2013;132(5):1075-85. e1076.

- 7 Bauer CM, Zavitz CC, Botelho FM, Lambert KN, Brown EG, Mossman KL, et al. Treating viral exacerbations of chronic obstructive pulmonary disease: insights from a mouse model of cigarette smoke and H1N1 influenza infection. PLoS One. 2010;5(10):e13251.
- 8 Kimura G, Ueda K, Eto S, Watanabe Y, Masuko T, Kusama T, et al. Toll-like receptor 3 stimulation causes corticosteroid-refractory airway neutrophilia and hyperresponsiveness in mice. Chest. 2013;144(1):99–105.
- 9 Mata M, Martinez I, Melero JA, Tenor H, Cortijo J. Roflumilast inhibits respiratory syncytial virus infection in human differentiated bronchial epithelial cells. PLoS One. 2013;8(7):e69670.
- 10 Milara J, Lluch J, Almudever P, Freire J, Xiaozhong Q, Cortijo J. Roflumilast N-oxide reverses corticosteroid resistance in neutrophils from patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2014;134(2):314–22.
- 11 Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. Am J Respir Crit Care Med. 2000;162(6):2226–31.
- 12 Jafri HS, Chavez-Bueno S, Mejias A, Gomez AM, Rios AM, Nassi SS, et al. Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction, and chronic inflammatory infiltrates associated with longterm airway hyperresponsiveness in mice. J Infect Dis. 2004;189(10):1856–65.
- 13 McNamara PS, Flanagan BF, Hart CA, Smyth RL. Production of chemokines in the lungs of infants with severe respiratory syncytial virus bronchiolitis. J Infect Dis. 2005;191(8):1225– 32.
- 14 Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. Thorax. 2006;61(3):250–8.
- 15 Guillot L, Le Goffic R, Bloch S, Escriou N, Akira S, Chignard M, et al. Involvement of toll-like receptor 3 in the immune response of lung epithelial cells to double-stranded RNA and influenza A virus. J Biol Chem. 2005;280(7):5571–80.
- 16 Freeman CM, Martinez FJ, Han MK, Washko Jr GR, McCubbrey AL, Chensue SW, et al. Lung CD8⁺ T cells in COPD have increased expression of bacterial TLRs. Respir Res. 2013;14:13.

- 17 Koarai A, Yanagisawa S, Sugiura H, Ichikawa T, Akamatsu K, Hirano T, et al. Cigarette smoke augments the expression and responses of toll-like receptor 3 in human macrophages. Respirology. 2012;17(6):1018–25.
- 18 Sukkar MB, Xie S, Khorasani NM, Kon OM, Stanbridge R, Issa R, et al. Toll-like receptor 2, 3, and 4 expression and function in human airway smooth muscle. J Allergy Clin Immunol. 2006;118(3):641–8.
- 19 Todt JC, Freeman CM, Brown JP, Sonstein J, Ames TM, McCubbrey AL, et al. Smoking decreases the response of human lung macrophages to double-stranded RNA by reducing TLR3 expression. Respir Res. 2013;14:33.
- 20 Diebold SS. Recognition of viral single-stranded RNA by Tolllike receptors. Adv Drug Deliv Rev. 2008;60(7):813–23.
- 21 Rennard SI, Calverley PM, Goehring UM, Bredenbroker D, Martinez FJ. Reduction of exacerbations by the PDE4 inhibitor roflumilast–the importance of defining different subsets of patients with COPD. Respir Res. 2011;12:18.
- 22 Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532–55.
- 23 Milara J, Armengot M, Banuls P, Tenor H, Beume R, Artigues E, et al. Roflumilast N-oxide, a PDE4 inhibitor, improves cilia motility and ciliated human bronchial epithelial cells compromised by cigarette smoke in vitro. Br J Pharmacol. 2012;166(8):2243–62.
- 24 Ortiz JL, Milara J, Juan G, Montesinos JL, Mata M, Ramon M, et al. Direct effect of cigarette smoke on human pulmonary artery tension. Pulm Pharmacol Ther. 2010;23(3):222–8.
- 25 Milara J, Peiro T, Serrano A, Cortijo J. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke. Thorax. 2013;68(5):410–20.
- 26 Milara J, Ortiz JL, Juan G, Guijarro R, Almudever P, Martorell M, et al. Cigarette smoke exposure up-regulates endothelin receptor B in human pulmonary artery endothelial cells: molecular and functional consequences. Br J Pharmacol. 2010;161(7):1599–615.
- 27 Su Y, Han W, Giraldo C, De Li Y, Block ER. Effect of cigarette smoke extract on nitric oxide synthase in pulmonary artery endothelial cells. Am J Respir Cell Mol Biol. 1998;19(5):819– 25.
- 28 Koarai A, Sugiura H, Yanagisawa S, Ichikawa T, Minakata Y, Matsunaga K, et al. Oxidative stress enhances toll-like receptor 3 response to double-stranded RNA in airway epithelial cells. Am J Respir Cell Mol Biol. 2010;42(6):651–60.
- 29 Ohkuni T, Kojima T, Ogasawara N, Masaki T, Fuchimoto J, Kamekura R, et al. Poly(I:C) reduces expression of JAM-A and induces secretion of IL-8 and TNF-alpha via distinct NFkappaB pathways in human nasal epithelial cells. Toxicol Appl Pharmacol. 2011;250(1):29–38.
- 30 Bethke TD, Bohmer GM, Hermann R, Hauns B, Fux R, Morike K, et al. Dose-proportional intraindividual singleand repeated-dose pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor. J Clin Pharmacol. 2007;47(1):26–36.
- 31 Hatzelmann A, Schudt C. Anti-inflammatory and immunomodulatory potential of the novel PDE4 inhibitor roflumilast in vitro. J Pharmacol Exp Ther. 2001;297(1):267– 79.
- 32 Kinose D, Ogawa E, Kudo M, Marumo S, Kiyokawa H, Hoshino Y, et al. Association of COPD exacerbation frequency with gene expression of pattern recognition

receptors in inflammatory cells in induced sputum. Clin Respir J. 2014. doi:10.1111/crj.12171.

- 33 Wortham BW, Eppert BL, Flury JL, Morgado Garcia S, Borchers MT. TLR and NKG2D signaling pathways mediate CS-induced pulmonary pathologies. PLoS One. 2013;8(10):e78735.
- 34 Groskreutz DJ, Monick MM, Powers LS, Yarovinsky TO, Look DC, Hunninghake GW. Respiratory syncytial virus induces TLR3 protein and protein kinase R, leading to increased double-stranded RNA responsiveness in airway epithelial cells. J Immunol. 2006;176(3):1733–40.
- 35 Barnes PJ. Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2013;131(3):636–45.
- 36 Chi XY, Jiang SJ, Wang J, Wang JP. Effect of glucocorticoid in mice of asthma induced by ovalbumin sensitisation and RSV infection. Asian Pac J Allergy Immunol. 2011;29(2):176–80.
- 37 Heijink I, van Oosterhout A, Kliphuis N, Jonker M, Hoffmann R, Telenga E, et al. Oxidant-induced corticosteroid unresponsiveness in human bronchial epithelial cells. Thorax. 2014;69(1):5–13.
- 38 Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol. 2010;120(2–3):76–85.
- 39 Gantner F, Kupferschmidt R, Schudt C, Wendel A, Hatzelmann A. In vitro differentiation of human monocytes to macrophages: change of PDE profile and its relationship to suppression of tumour necrosis factor-alpha release by PDE inhibitors. Br J Pharmacol. 1997;121(2):221–31.
- 40 Tenor H, Hatzelmann A, Kupferschmidt R, Stanciu L, Djukanovic R, Schudt C, et al. Cyclic nucleotide phosphodiesterase isoenzyme activities in human alveolar macrophages. Clin Exp Allergy. 1995;25(7):625–33.
- 41 Moodley T, Wilson SM, Joshi T, Rider CF, Sharma P, Yan D, et al. Phosphodiesterase 4 inhibitors augment the ability of formoterol to enhance glucocorticoid-dependent gene transcription in human airway epithelial cells: a novel mechanism for the clinical efficacy of roflumilast in severe chronic obstructive pulmonary disease. Mol Pharmacol. 2013;83(4):894–906.
- 42 Tannheimer SL, Sorensen EA, Haran AC, Mansfield CN, Wright CD, Salmon M. Additive anti-inflammatory effects of beta 2 adrenoceptor agonists or glucocorticosteroid with roflumilast in human peripheral blood mononuclear cells. Pulm Pharmacol Ther. 2012;25(2):178–84.
- 43 Rider CF, King EM, Holden NS, Giembycz MA, Newton R. Inflammatory stimuli inhibit glucocorticoid-dependent transactivation in human pulmonary epithelial cells: rescue by long-acting beta2-adrenoceptor agonists. J Pharmacol Exp Ther. 2011;338(3):860–9.
- 44 Perera WR, Hurst JR, Wilkinson TM, Sapsford RJ, Mullerova H, Donaldson GC, et al. Inflammatory changes, recovery and recurrence at COPD exacerbation. Eur Respir J. 2007;29(3):527–34.

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