Volume 10 Number 2 Spring 2015

Respiratory Therapy™

The Journal of Pulmonary Technique

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- **Total support**
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The SmartVest® SQL® is designed to help patients incorporate HFCWO therapy into their daily routines. The smaller, quieter, lighter air pulse generator — truly portable at just 17 lbs. — features Soft Start and a programmable ramp option to acclimate users to therapy more quickly and provide a more comfortable treatment experience. The SmartVest is available in eight sizes and fits like a piece of clothing, with Velcro-like closures for a customized fit.

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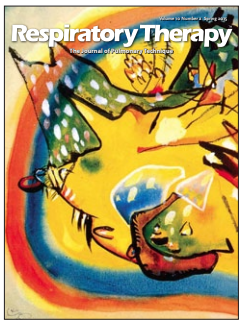

Respiratory Therapy™
The Journal of Pulmonary Technique

Vol. 10 No. 2
Spring 2015

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DEPARTMENTS

ARTICLES

The Utilization of a Resource Algorithm to Enhance Departmental Communications

Diane Horoski Senior System Analyst, Kenneth Miller MEd, RRT-NPS, AE-C Angela Lutz, RRT-NPS

Fluctuating workloads, changing patient acuity, and staffing patterns require precise and proper communication. It is unrealistic to expect departmental leadership to be in-house twenty-four hours a day to address questions or alter workload assignments. Historically, staff was obligated to make front-line decisions, often without proper guidance and/or global insight. Clinical management of difficult patients would then be limited to in-house staff's clinical experiences. Often the proper resource was not contacted to assist in the problem resolution. Advanced technological interventions were delayed until departmental leadership was in-house. Equipment issues were often pushed aside until leadership was available. All of these things often led to staff frustration and confusion.

To combat these issues, our department developed an on-call resource algorithm (Figure 1). Our algorithm addresses administrative, technological, and clinical management issues in order for the in-house staff to promptly contact the appropriate on-call leader. All staff were provided education and process information on the utilization of the algorithm. Staff feedback was encouraged and questions were answered.

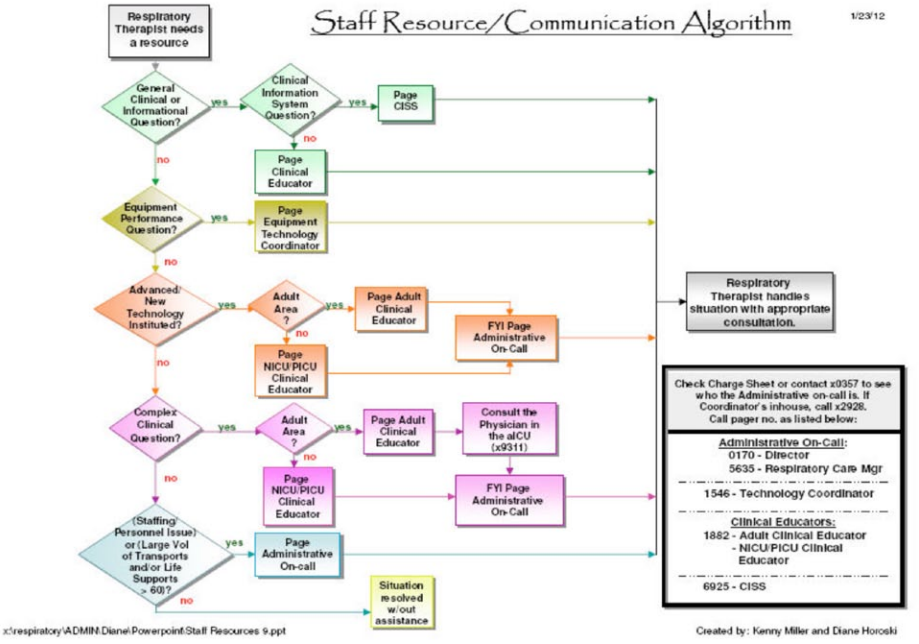

Figure 1

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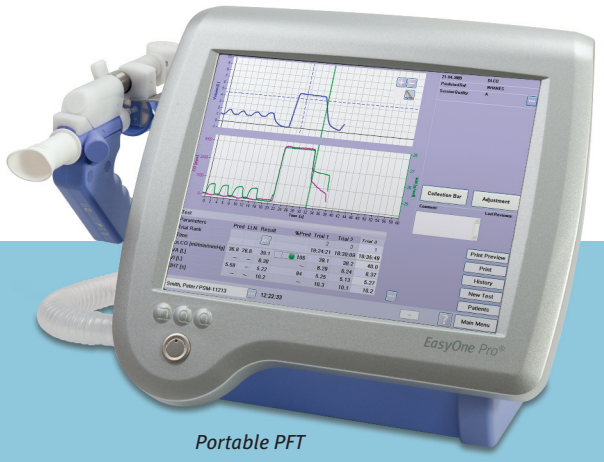

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Editorial Advisory Board

The New Sound of Airway Clearance Therapy

A Paradigm Shift in Respiratory Care

Can you hear it? It's the new sound of the **Vibralung® Acoustical Percussor**, and it's starting a revolution in Airway Clearance Therapy (ACT). The Vibralung Acoustical Percussor applies vibratory sound waves over a wide range of frequencies (5 to 1,200 Hz) to vibrate the column of gas in the tracheo-bronchial tract. As a result, mucus is loosened and separated throughout the airways to promote safe, effective and gentle ACT like no other alternative.

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The Vibralung Acoustical Percussor is a gentler form of ACT than oscillatory PEP devices, or those that make contact with the external chest wall. It may be especially useful for airway clearance therapy when other means like vests and hand-held chest percussors cannot be used. It's the ideal choice whenever airway clearance is the goal and patient comfort is preferred.

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When Your Care Is Critical

One-Year Review of High Flow Oxygen Delivery System Outcomes

Susan Carvin, RRT-ACCS, Kenneth Miller, MEd, RRT-ACCS, AC-E, Diane Horoski, Senior Analyst, Robert Leshko, BS, RRT, Rita Pechulis, MD

Introduction: Improving gas exchange and decreasing work of breathing are clinical end-points when managing patients with respiratory failure. Often the interventions are to provide high flow oxygen via a mask or more aggressive form of clinical management like non-invasive or mechanical ventilation. A High Flow Oxygen (HFO) delivery system provides an alternate or a bridge between high flow oxygen administration and forms of ventilation. High Flow Oxygen can be provided via a nasal cannula or via a tracheal adapter. By providing flow rates up to fifty liters a minute, high molecular humidity and a precise oxygen delivery, it may reduce the need for Non-invasive Ventilation (NIV) and intubation in selected patient populations.

Methods: We examined the number of patients who were placed on HFO over a twelve-month time frame in our medical-surgical ICU. All patients placed on HFO either had a SpO2<88% or had an increased work of breathing (noted by a respiratory rate>30 or the use of accessory muscles). Reasons for HFO flow utilization, duration of use, number of times placed on HFO and therapy outcomes were assessed.

Results: Two hundred patients, 120 males and 80 females, were placed on HFO from January 1, 2013 to December 31, 2013. Patient ages ranged from twenty-one to ninety years old. One Hundred and thirty-three patients (67%) were placed on HFO for the improved of oxygenation and 67 patients (31%) were placed for increased work of breathing or for humidification enhancement. Outcomes are seen in Table 1.

Conclusion: The utilization of High Flow Oxygen allowed our clinician team to improve oxygenation and decrease work of breathing without the need for the institution of non-invasive or invasive mechanical ventilation in over fifty percent of patients who were placed on it and ICU length of stay was reduced in this group. High Flow Oxygen delivery system provides another weapon in the arsenal of oxygen therapy in improving gas exchange and reducing work of breathing. It may reduce the need for more aggressive forms of therapy; reduce the need for intubation and duration of ICU stay. Larger clinical studies need to be conducted to determine its full impact on patient outcomes.

Table 1

	Males	Females	Oxygen	NIV	MV	Expired
HFO	120	80	105 (52.5%)	50 (25%)	40 (20%)	5 (2.5%)
ICU LOS			7.5 days	11.4 days	18.5 days	

The authors are with Lehigh Valley Health Network, Allentown, Penna.

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

The Development of a Respiratory Care PICU, NICU Internship

Angela Lutz, RRT-NPS, Kenneth Miller, Med, RRT-ACCS, NPS, Chris Fenstermaker, MS, RRT-NPS

Introduction: Providing optimal respiratory care in the Pediatric or Neonatal ICU requires clinical and technological expertise. Historically, educational curriculum has been sparse or limited in these areas. Often experienced adult therapist are promoted or coerced into working in these patient populations. To address this dearth of qualified PICU/NICU therapist our department developed a PICU/NICU internship for either new graduates or seasoned therapists who wished to expand their skill level.

Methods: All candidates into the program had completed a generic departmental orientation, had achieved the NBRC RRT credential, had a pre-assessment skills inventory, and had agreed to a program contract. The program curriculum included the following: a twenty-four-week didactic and clinical orientation, attendance to various educational programs, clinical stimulations and access to salient educational materials. The interns were assigned to clinical preceptors for their clinical orientation and were provided didactic education by clinical experts. Textbook and journal reviews were also provided for enhanced education. During the program a score of 80% or greater had to be maintained to continue and progress in the program. Regularly scheduled preceptor evaluations were reviewed and discussed to address any issues and fine-tune learning. Upon completion on the program, the interns were required to pass the NBRC Neonatal-Pediatric Specialty Exam (RRT-NPS) within a nine-month time frame.

Results: In the past year we have had three interns complete the internship program. All three are currently working either in the NICU or PICU clinical arena and have achieved the RRT-NPS status. In the upcoming year five interns are enrolled in the program.

Conclusion: The NICU/PICU internship has provided an educational process to transition new graduates or seasonal therapist into the NICU/PICU patient population. The program has provided a systematic and sequential approach to the clinical and didactic education salient to the NICU/PICU patient population.

Kenneth Miller is the Clinical Educator, Dean of Wellness, Respiratory Care Services, Lehigh Valley Health Network Allentown, PA.

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News

■ Spring 2015

Improving COPD Outcomes with Aclidinium

New research is highlighting the benefits of aclidinium bromide to boost exercise endurance, exertional dyspnea and physical activity in patients with moderate-to-severe COPD. A study out of the Insaf Respiratory Research Institute, Wiesbaden, Germany, says that following 3 weeks of taking aclidinium 400 mcg twice daily significantly reduced the intensity of exertional dyspnea and improved cycling exercise endurance compared with placebo. Researchers administered a randomized, double blind, crossover study from November 2011 to June 2012 at 14 locations in Germany, Spain and the United Kingdom. Eligible participants were aged 40 years or older and had moderate-to-severe COPD, along with being current or former cigarette smokers. Participants with a history of asthma or any other respiratory or cardiovascular condition were excluded from the study. One hundred and twelve participants were randomly assigned aclidinium 400 mcg twice daily or placebo that was administered with a dry powder inhaler (Genuair, AstraZeneca; Tudorza Pressair, Almirall) during a 3-week period. Participants were tested at baseline and after the treatment to determine changes in exercise endurance time and lung volume. After 3 weeks of therapy, the change — 58.5 seconds — from baseline in endurance time was greater with aclidinium compared with placebo (95% CI, 9-108).

Safety for Vent Patients

As ventilator patients have become more mobile, both in Long Term Care centers and at home, the issue of increased safety has become an issue. One of the areas that is most important when it comes to providing a safe environment for the vent patient is ensuring a secure vent circuit. Unfortunately when it comes to securing a vent circuit we typically think about keeping it securely fastened to the patient's tracheostomy tube. Now that the vent patient is gaining more mobility and moving around more freely we should also keep in mind that the vent circuit itself will always need to be stabilized, or secured, in order to avoid serious injury or even death. It is apparent that without something securing the vent circuit to the patient, it could easily fall away from the wheelchair mobile patient and becoming ensnared in the wheel of the chair. If this were to occur the obvious result would be significant damage to the circuit, which could result in serious injury or even death for the ventilator patient. 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).

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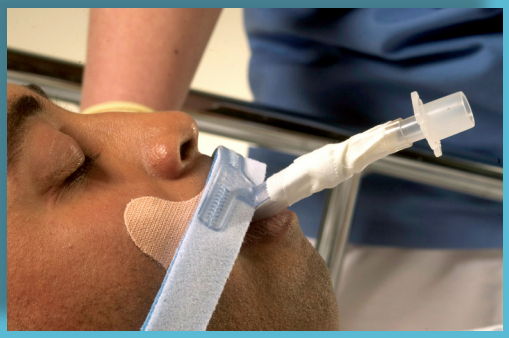

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The 701VCS is a belt made of a soft cotton laminate that fits comfortably around a patient's waist. It comes with a strap that is permanently fastened on one end to the belt while the other end of the strap is fitted with a small piece of Velcro hook. The vent circuit is secured to the belt by laying the circuit onto the belt and then placing the strap over the circuit and attaching the Velcro hook end of the strap to the belt. The second product is the 701VCS/NG. It uses the same soft laminate belt but instead of a single strap to secure just the vent circuit it incorporates a second shorter strap that is also permanently attached to the belt. The second strap is used to secure a nasal gastric (or oral gastric) tube to the belt thereby keeping it from falling away from the patient. The 701VCS and the 701VCS/NG can be used on vent patients who are confined to beds.

Company Wins Again

The company Drager has announced that it received the esteemed Zenith Award from the American Association for Respiratory Care (AARC) for delivering outstanding products and services to the respiratory care profession. The award was presented during the AARC 60th International Respiratory Convention in Las Vegas on Dec. 9, 2014. 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 52,000 respiratory therapists and other clinicians, to vote for those manufacturers, service organizations and supply companies that provide the respiratory care community with exemplary service. For the sixth straight year in a row, AARC members selected Dräger for this prestigious recognition. Dräger's Respiratory Care devices span the spectrum of critical care, neonatal care, acute care, noninvasive therapy and emergency/transport ventilation.

Electronic Nebulizer Approved

The eRapid Nebulizer System (eRapid) from PARI has been approved as the first electronic nebulizer by the Food and Drug Administration to deliver Genentech›s Pulmozyme for cystic fibrosis treatment. A huge improvement for cystic fibrosis patients, eRapid is able to reduce average treatment times with Pulmozyme from 6-8 minutes down to 2-3 minutes. Both adult and pediatric patients showed a strong preference for eRapid over conventional nebulizers in a clinical study. "We have been pleased with eRapid's fast treatment times in the lab and are excited that patients now have access to a much faster Pulmozyme therapy. As the first electronic nebulizer to deliver Pulmozyme, eRapid is a true breakthrough for cystic fibrosis patients who take the therapy daily, often for years," said Lisa Cambridge, director of Medical Science and Pharmaceutical Alliances at PARI Respiratory Equipment, Inc.

Users Given Options

ResMed and Brightree announced recently that ResMed›s AirView patient management system will directly integrate with Brightree›s leading home medical equipment (HME) billing and business management software solution. The companies say that directly integrating with ResMed›s comprehensive AirView patient management system gives Brightree users added capabilities within the software environment and workflows they rely on every day. The AirView-Brightree integration is the latest connectivity achievement in ResMed and Brightree›s longstanding relationship, and is one of multiple enhancements planned for this year. Past advances have included Brightree integration with ResMed›s U-Sleep premium sleep compliance solution, as well as a data exchange agreement allowing HMEs to order ResMed equipment directly from the Brightree platform.

Trade Commission Decides

The International Trade Commission (ITC) issued its final decision in the case brought by ResMed (RMD) against BMC Medical and 3B Medical. In a notice issued today, the ITC ruled in favor of 3B/BMC and found that ResMed's patent on its humidifier was invalid. 3B Medical Vice President, Alex Lucio, called the decision a "monumental win," adding that "ResMed chose a very expensive high-profile battle, when this dispute could have easily been resolved with direct discussions between the parties." The ITC's decision is the latest in a lengthy 18-month battle that has spanned across the globe and spawned litigation not only in the U.S., but also Germany and China, calling into

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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

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PM167

question the validity of many other ResMed patents. The ITC decision also sides in ResMed's favor on some of the mask patents covering products that 3B/BMC discontinued earlier this year but found that ResMed failed to meet the domestic industry requirement as to another of its mask patents.

Tech Teams Up

Welch Allyn, a leading medical diagnostic device company that delivers pragmatic innovation at the point of care, today announced it has partnered with Nonin Medical, a leader in designing and manufacturing noninvasive medical monitoring solutions, to provide its clinically-proven PureSAT SpO2 technology. The partnership allows Welch Allyn to offer technologies from three leading manufacturers as part of its next generation vital signs device that allows customizable vital signs capture, interval monitoring and wireless transfer of patient data to the electronic medical record (EMR). Nonin Medical›s clinically-proven PureSAT pulse oximetry technology delivers fast and reliable readings by utilizing intelligent pulse-by-pulse filtering to provide precise oximetry measurements—even in the presence of motion, low perfusion or other challenging conditions. PureSAT signal processing pre-filters the pulse signals to remove undesirable signals and advanced algorithms then separate the pulse signals from artifact and interference.

New CEO Appointed

The Executive Board of Linde AG has appointed Kristen Hoefer Chief Executive Officer (CEO) of Lincare Inc., Clearwater, Florida, a subsidiary of The Linde Group, effective 1 March 2015. Hoefer succeeds John Byrnes, who has been CEO of Lincare since 1997 and is retiring from the company on the expiry of his contract at the end of February. "We're delighted that we've been able to attract the calibre of Kristen Hoefer, a proven healthcare executive with international experience. I am confident that she will continue to apply and develop the successful approach we've adopted to date in our strategically important healthcare business," said Dr Wolfgang Buchele, Chief Executive Officer of Linde AG. Hoefer holds degrees in bioengineering and business. She has held a number of management positions of increasing responsibility across many businesses of the global diversified health care company Abbott Laboratories, where she has spent more than twenty years. In her most recent role, she was responsible for the company's pharmaceutical business in Western Europe. Lincare's work in respiratory homecare involves the treatment of patients with chronic respiratory diseases in settings other than hospitals. Respiratory therapies offered by Lincare include oxygen therapy and inhalation therapy.

Viva Vivo Deal

CareFusion, a leading global medical technology company, announced it has signed an exclusive US distribution agreement with Breas Medical for their Vivo line of ventilation equipment. Under the terms of the agreement, CareFusion will be the exclusive US distributor for the Vivo by Breas line of life support and bi-level ventilators from Breas Medical, including the Vivo 50, Vivo 40 and Vivo 30. The Vivo product line is designed for home mechanical ventilation and complements CareFusion's other ventilator products such as the AVEA, VELA, 3100A and 3100B HFOV, Infant Flow SiPAP, ReVel and LTV Series ventilators. The combination of CareFusion and Breas Medical

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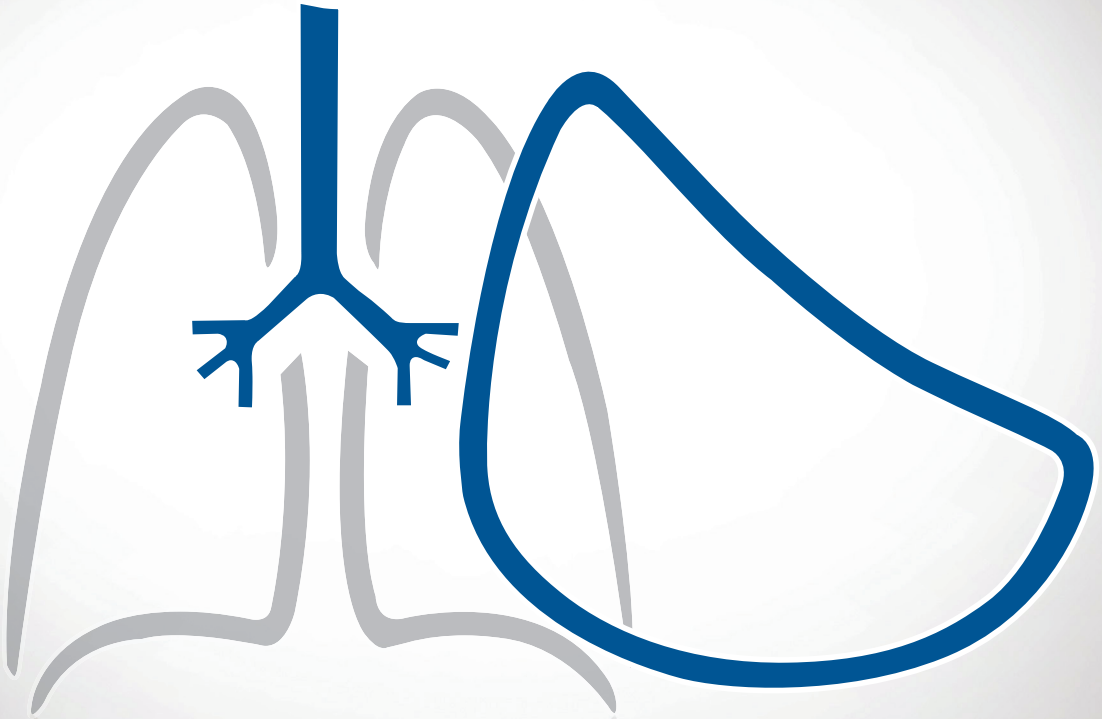

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EXECUTIVE PREVIEW OF THE FOCUS CONVENTION

Electromed

Booth #402

What products will you be presenting at Focus?
Electromed will present the SmartVest Airway Clearance System at the 2015 FOCUS Spring Conference. The SmartVest System uses high frequency chest wall oscillation (HFCWO), a proven clinical therapy prescribed for people with airway clearance needs. Clinical research shows HFCWO to be highly effective at clearing airways of excess mucus and helping reduce infections and hospitalizations that can result when impaired airway clearance is inadequately treated. The SmartVest System consists of an inflatable garment connected to a programmable air pulse generator. During therapy, the SmartVest garment delivers a rapidly repeating pulse of air, alternately squeezing and releasing the upper body. Each squeeze simulates a "mini cough," which acts to loosen, thin and propel mucus toward major airways, where it can be more readily coughed up or suctioned away.

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

Why should Focus participants visit your display?
Participants will learn firsthand what makes the SmartVest System a preferred choice for HFCWO therapy through hands-on demonstration of the innovative SmartVest SQL System.

In today's healthcare environment, there is a comprehensive focus to reduce hospital readmission penalties associated with the Affordable Care Act. Solutions like the SmartVest System help patients with impaired airway clearance improve bronchial drainage, reducing the likelihood of future lung infections and other health risks and complications. Electromed is the only HFCWO device company to earn Home Care Accreditation from The Joint Commission, a symbol of quality and commitment to meeting performance standards for in-home patient therapy and service. We look forward to seeing you in Orlando.

B&B Medical

Booth #1008

What products will you be presenting at Focus?
B&B Medical Technologies manufacturers clinically proven endotracheal tube holders, tracheostomy anti-disconnect devices and nebulizers for adult, pediatric and infant patients as well as our new Bubble CPAP valve, the B&B Bubbler.

What new products or upcoming developments will you be highlighting?
The B&B Bubbler, water seal CPAP valve. StabilTube Plus, endotracheal tube holder with skin-friendly hydrocolloid adhesive.

Why should Focus participants visit your display?
In addition to our popular endotracheal tube holders, tracheostomy anti-disconnect devices and continuous nebulizer, B&B will be featuring our newest product, the B&B Bubbler water seal CPAP valve. We will also be giving away lung-shaped stress balls while supplies last.

Dale Medical

Booth #404

What products will you be presenting at Focus?
Tracheostomy and endotracheal tube holders.

Discuss educational/training materials you'll be offering at the convention.
Perspectives publication, availability of Dale reps for in-services, online in-service videos on the use of products for early mobility initiatives.

What speakers or papers will your company be featuring?
Information from Perspectives publication will be included.

Why should Focus participants visit your display?
See the holders, learn how they are applied, the features and benefits of the devices, plus continuing education credits via Perspectives publication.

MGC Diagnostics

Booth #504

What products will you be presenting at the Focus?
MGC Diagnostics will feature recent product developments and technology advancements including the Platinum Elite body plethysmograph and Ultima Series cardiopulmonary diagnostics systems with RTD real-time diffusion MultiGas technology; together with our BreezeSuite cardiopulmonary diagnostic software incorporating the latest HIPAA – HITECH Security Safeguards protecting patient identifiable health information.

What new products or upcoming developments will you be highlighting?
MGC Diagnostics will be highlighting the newly released Ultima Series that combines gas exchange and pulmonary function testing into one integrated system, giving the user the latest in technology and software.

Discuss educational/training materials you'll be distributing or promoting.
MGC Diagnostics continues to provide educational opportunities with our annual Cardiorespiratory Diagnostics Seminar held in Las Vegas, NV in October. Participants will advance their knowledge of diagnostic techniques, performance standards,

quality assurance procedures, and clinical applications. The program format includes lectures, hands-on demonstrations and small group discussions – all conducted by a faculty of experts.

Why should FOCUS participants visit your display?
Managing the MGC Diagnostics exhibit will be our Best-in-Class clinical, sales and support staff available to answer not only product questions, but provide expert consultation for clinical application and cardiorespiratory business needs. MGC Diagnostics delivers diagnostic solutions for detection, classification and management of cardiorespiratory patients worldwide. Our enduring experience and single-minded focus give us unmatched insight into the real needs of our customers.

AARC

Booth #TBD

What products will you be presenting at FOCUS?
The No-Bite V (suction catheter introducer) – A Safer and More Comfortable way to suction your fragile patients: End-of-Life, Cancer, Elderly, etc. Best Practice Solution when nasal suctioning is contraindicated. Every RT, RRT, RCP is familiar with nasopharyngeal or nasotracheal suctioning and the many problems associated with inserting a suction catheter up a patient's nose. To name a few: bleeding, pain and trauma, coiling of suction catheter, MRSA colonization's in nares, and the list goes on… So basically with the No-Bite V, you can avoid all these problems by avoiding the nose altogether! It makes suctioning easy for not only the caregiver but also the patient.

Are there any new products you wish to emphasize?
The No-Bite V is newer but we already have a growing number of Top Hospital References! 2014 has been a huge year for the No-Bite V. Just this 2014, The No-Bite V has passed Value Analysis Process and purchased by: NYU, Cleveland Clinic, Kaiser Permanente, Nationwide Children's, Rush University, University of Arizona, United States VA Med Centers and many more hospices, home cares, and nursing homes. It is now becoming popular worldwide as well, distributing to hospitals in Japan, S. Korea, Saudi Arabia, UAE, Qatar and Kuwait. The RT community has been very instrumental in adding the No-Bite V to their toolbox.

Discuss educational/training materials you'll be offering.
At our booth we will be offering No-Bite V in-servicing on mannequin heads, everybody is welcome to participate and practice techniques in a return demonstration. Also, for those people who cannot attend the conference, we always offer a free online No-Bite V training with an opportunity to earn 0.5 CERP credits on our website www.NJRMedical.com. Once you finish the online course, you can print out your certificate.

What speakers or papers will you be featuring?
We will have the inventor of the No-Bite V at our booth and assisting the in-servicing. Also we will have case studies documenting the success of the No-Bite V in both the ICU environment as well as the Hospice and Palliative Care setting.

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

SPOTLIGHT ON OXIMETRY

Covidien

Describe the oximetry products your company offers.
Covidien offers Nellcor monitors, sensors and alarm management systems, designed to enhance clinician efficiency and effectiveness.

Recently, Covidien became the first company to receive FDA clearance for a motion-tolerant bedside pulse oximeter portfolio that is also compliant with ISO 80601-2-61 (International Organization for Standardization) standards for pulse oximetry.

The Nellcor Bedside Respiratory Patient Monitoring System incorporates the latest Nellcor digital signal processing technology for accurate, reliable readings even during low perfusion and other forms of signal interference, providing clinicians with access to the most critical information regarding their patients' respiratory status. With continuous SpO2 and pulse rate monitoring capabilities, plus trending data and SatSeconds alarm management, the technology offers clinicians the ability to detect respiratory complications earlier and intervene sooner.

SatSeconds alarm management technology, built into the Nellcor N-600x Bedside Pulse Oximetry Monitor offers a safe, practical way to reduce clinically insignificant alarms. The SatSeconds alarm management function analyzes desaturation events by multiplying the duration (seconds) by the number of percentage points the patient exceeds the alarm limit. Clinicians can set SatSeconds alarm management technology limit to 10, 25, 50 or 100. Once the limit is set, only events that equal or surpass the set limit cause the alarm to sound.

The LoSat expanded accuracy feature of Nellcor SpO2 adhesive sensors with OxiMax technology assures clinicians of the industry's widest accuracy range (60% to 100% SpO2) when used with the Nellcor N-600x bedside pulse oximetry monitor. 1 This allows improved patient assessment at challenging lower saturation levels. The low saturation feature in Nellcor adhesive sensors offers clinicians the ability to monitor patients accurately and non-invasively in lower SpO2 ranges.

Covidien also offers the Nellcor N-65 Portable Pulse Oximetry Monitor, an economical, easy-to-use handheld device, as well as the Nellcor N-85 Portable Pulse Oximetry Monitor with Microstream technology, a convenient, handheld device that accurately provides both SpO2 and etCO2 values.

Tell us about your company's R&D pertinent to oximetry.
Covidien is proud of the funds it allocates to research and development activities that have made it a market leader in innovation of medical products, including pulse oximetry. Our commitment to innovation in pulse oximetry monitoring is evident with the expansion of our R&D center in Boulder, Colorado. Nellcor brand R&D efforts are well supported, and Covidien currently has numerous research and development projects in process.

The Covidien commitment to R&D efforts is evident in meeting technology recommendations for CCHD screenings with pulse
Continued on page 46…

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview from Mercury Medical is Western Regional Manager Franklin Gerardo Pecoraro, CCPT, CPFT, AS, BS.

Respiratory Therapy: Can you describe the LiteSaver?
Franklin Gerardo Pecoraro: The LightSaver from Mercury is a disposable color-coded manometer with a red timing light attached to the side of the manometer. The LiteSaver is designed to fit on all of Mercury Medical's adult and small adult self-inflating resuscitators.

RT: What are the key specifications of the LiteSaver?
FGP: Timing Light:

- The red timing light blinks every 6 seconds which enables 10 breaths a minute
- The LiteSaver battery has a shelf life of 1 year.
- Once activated, the light will blink continuously for 1.5 hours (the light will stay on and not blink after this timeframe).

Disposable Color-Coded Manometer:

- Full scale of 0 to 60 cm H_2O.
- The manometers accuracy between 0-15 cm H_2O equals ±3 cm H_2O.
- The manometers accuracy between 15-60 cm H_2O equals ±5 cm H_2O.

RT: Why is a pressure manometer important during manual resuscitation?
FGP: Manometers are used for measuring Peak Inspiratory Pressures or PIP as well as Positive-End Expiratory Pressure (PEEP). Attaching a manometer to a self-inflating resuscitator will provide the clinician with a means to deliver consistent and controlled inspiratory pressures, reducing the chance of lung injury such as Barotrauma. A lower PIP can also reduce the incidence of gastric distention that is a common problem during manual ventilation.

RT: Why is a timing light important during manual resuscitation?
FGP: The timing light is used for maintaining the correct respiratory rate during manual ventilations. If the clinician squeezes the bag each time the red light flashes, then the ventilation rate will be 10 breaths per minute as recommended by the AHA. When ventilation rates exceed AHA recommendations, the lungs can become hyperinflated, blood can be inhibited from returning to the heart and breaths become stacked, not allowing the patient to completely exhale.

RT: What is the recommended PIP during Manual Resuscitation?
FGP: It is recommended that the PIP pressure should not exceed 20 cm H_2O. Studies have shown that when PIP is not monitored during manual resuscitation, the pressures can easily exceed 18-20 cm H_2O that exceeds the lower Esophageal Sphincter Pressure (LESP) allowing air to enter the stomach, possibly resulting in gastric distention.

RT: What is the recommended Respiratory Rate during Manual Resuscitation?
FGP: The AHA recommends ventilation rates of 10 breaths per minute or every 6 seconds and, if possible, during the upstroke of chest compressions.

RT: This sounds like a device that would be used more often in a pre-acute care versus the acute care.
FGP: Not necessarily. Any time a patient is being manually ventilated, managing ventilation rates, volumes and pressures is extremely important, regardless of the setting.

RT: Can the LiteSaver be used with other self-inflating resuscitators other than those offered through Mercury Medical?
FGP: Yes. The LiteSaver can be purchased attached to a right-oriented or left-oriented Tee Piece which can connect to the patient port of any adult or small adult self-inflating resuscitator.

Input on questions was provided by Chris Campbell, Managing Editor for the Journal, Respiratory Therapy. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

ONLY ONE

How a New Idea Can Enhance a Product's Capabilities . . . and Improve Patient Outcomes.

LiteSaver

a disposable, color-coded manometer with integrated timing light

Any time a patient is being manually ventilated, managing ventilation rates, volumes and pressure is extremely important.

Having a manometer with timing light integrated with a BVM (CPR bag) is critical for validating delivered pressures and helps clinicians in delivering proper ventilation rates.

- Variety of BVM configurations
- No additional components necessary
- Easy-to-Use Timing Light with Pull Tab for activation
- Light blinks every 6 seconds
- Assists in Reduced Risk of Aspiration
- Assists in Reduced Stacking of Breat

The LiteSaver Manometer assists clinicians in delivering safer, slower ventilation resulting in sufficient expiration time avoiding breath stacking.

Visit the Mercury Medical Booth #415
at the 2015 Focus Spring Conference
Disney Coronado Resort, Orlando, Florida

Patent # US 5,557,049 B1, # US 8,522,618 B1, Other Patents Pen

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In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in this interview from Hometown Oxygen Charlotte, LLC is Herman Randall, RRT.

Respiratory Therapy: Please tell us a little about your overall business model and your patient population.
Herman Randall: Hometown Oxygen Charlotte, LLC is a full service Respiratory services provider servicing neonatal to adult clients.

RT: How long have you been providing ventilator management as part of your service?
HR: Hometown Oxygen has been providing ventilator management to patients since 2009.

RT: What ventilators have you historically utilized?
HR: I have personally over the last 30 years utilized ventilators from: Pulmonetics, Respironics, Newport, and Aequitron.

RT: What Astral features led you to try it?
HR: The internal battery, the touch screen, the ability to use any type circuit, the waveforms and the weight.

RT: What are the primary modes and circuit types you are using with Astral?
HR: The modes we are most often using are: P(A)CV, P-SIMV and PS.

RT: Now that you've been using Astral, what do you see as the key differentiators from other ventilators you've used?
HR: Ease of use for the clinician, other healthcare workers and family, as well as the internal battery life.

RT: What specific objective or subjective improvements have you seen in your patients using Astral?
HR: It is easier for the client to transport their child, because they no longer need an external battery. The parents have to carry suction machines, oxygen, pulse oximeters, and other related baby items so one less item is a big deal to them. It has been easier to transition the client from the hospital ventilator to the Astral.

RT: What has been the feedback from your patients, families and caregivers related to ease of use, comfort and portability?
HR: The parents and other healthcare providers have stated it was easy for them to understand the Astral ventilator.

Input on questions was provided by Denise Hartsell, RRT, RPSGT, Clinical Product Manager at ResMed Inc. If you would like to participate in this feature, as a company or healthcare provider, please contact Christopher Hiscox or Steve Goldstien at s.gold4@verizon.net.

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The Interthoracic Connection

Rebecca Wills, MA, BA, CRT-NPS
Contributing clinical experts are Suzanne Seberg MS, CCC-SLP and Sarah Economides, PT, DPT, PCS

Introduction

In the age of healthcare reform licensed therapists, clinicians and other healthcare providers must work together to achieve our patients' goals and maximize outcomes. This article will highlight the shared roles of Respiratory Therapists, Physical Therapists and Speech Language Pathologists working with the muscles used for trunk and posture control, respiration and breath support. An emphasis on this interthoracic connection results in positive effects on airway protection, cough strength, swallow and phonation.

Review of Respiratory System

Respiration is a complex neurological process originating in the respiratory center of the brain, specifically at the pons and medulla oblongata. A signal is sent to the diaphragm, the primary breathing muscle, to contract. With contraction, the diaphragm moves downward creating negative pressure in the thoracic cavity, drawing air into the lungs through the nose and mouth.

Exhalation is typically passive. As the diaphragm relaxes it moves upward, gently moving the air from the lungs and out through the nose and mouth.

Although the diaphragm is responsible for approximately 2/3 of our tidal volume[1] it does not work alone. The intercostals are responsible for chest expansion which allows the lungs to fill, and stabilization of the ribcage. When additional tidal volume is required, accessory muscles also contribute. Accessory muscles may be activated to increase tidal volume or to compensate for a weak diaphragm. These accessory muscles include scalene, trapezius, pectoralis major, sternocleidomastoid and the abdominals. Accessory muscles may also be recruited to assist in exhalation in times of respiratory distress, diaphragm paresis and to assist in upward movement of the diaphragm.

Posture and Trunk Control

Many of the same muscles used for respiration are also used for trunk control and posture, including the diaphragm, intercostals and abdominals. The central nervous system coordinates these multipurpose muscles.

Numerous daily tasks require trunk control, such as breathing, coughing, eating, talking, walking and bowel and bladder emptying. Sitting upright requires trunk support and is a result of anterior pelvic tilt, shoulder abduction and protracted shoulders. This upright posture encourages upper chest breathing and use of accessory muscles of respiration. This posture is necessary for adequate respiration, secretion clearance and breath support for speaking.

Slouched posture is a result of a posterior pelvic tilt and shoulder adduction/protraction. A chronically slumped posture can cause a multitude of postural-related deficiencies including:

- Restricted breathing mechanics
- Compromised swallowing mechanics which increases the risk of aspiration
- Mechanically compromised recruitment of accessory muscles necessary for increased lung volumes
- Impaired diaphragm mechanical advantage

Position supports to encourage upright sitting posture include:

- Longitudinal towel rolls for increased ribcage expansion and posture support
- Iron cross position results in stretching of the pectoral and bicep muscles, increased chest excursion and lung volume expansion (LVE).
- Abdominal binder (ensure that the binder is properly positioned to avoid restriction of the rib cage)

The Body's Closed System

The human body is designed as a perfectly closed system. The trunk has the thoracic and abdominal cavities and is completely separated by the diaphragm. The trunk is sealed at the top by the vocal folds and at the bottom by the pelvic floor muscles. Due to this closed system, we are able to generate and maintain interthoracic pressure (also known as the Valsalva maneuver) which is necessary for trunk power, posture control, balance, lifting, bowel and bladder control, coughing, gastromotility and to regulate abdominal pressure. These functions are impaired or absent when there is a breach in this closed system. A breach may exist due to weakened trunk or pelvic floor muscles, compromised vocal folds or the presence of an endotracheal or tracheostomy tube.[2]

Impact of a Tracheostomy Tube

When the closed system is breached due to placement of a tracheostomy tube, the impact is considerable. A tracheostomy tube is inserted below the level of the vocal cords, which changes the airflow and bypasses the entire upper airway. Lack of airflow results in loss of sensation in the oropharynx, decreases the senses of smell and taste and eliminates the

The author is the Pulmonary Program Manager at Madonna Rehabilitation Hospital in Lincoln, NE.

natural ability to humidify our inhaled air. Without airflow through the vocal folds, there is little to no opportunity for phonation. An open tracheostomy tube creates a constant leak in our closed system and prevents glottis closure. Adequate subglottic pressure is necessary to achieve vocal loudness, sustained sounds and varied voice frequency. Subglottic pressure is measured in cmH2O and can be measured using a cuffolator or NIF (negative inspiratory force) manometer. Conversational speech requires subglottic pressures between 5-10 cmH2O and a normal swallow approximately 7-10 cmH2O.[3]

Airway Patency and Secretion Clearance

A successful cough requires both inspiratory and expiratory muscle strength. Simply put, one needs to take in a big breath and blow out forcefully to cough effectively. Inspiratory muscle strength may be easily determined using an Incentive Spirometer to measure inspiratory capacity (IC). Peak expiratory cough force (PECF) is one way to measure expiratory strength. The standard-of-care for persons with asthma includes the use of a Peak Flow Meter to measure peak expiratory flow (PEF). A Peak Flow Meter may also be used to measure PECF as an indicator of expiratory muscle strength. An average adult PECF is approximately 300/lpm and a productive cough requires greater than 170/lpm.[4] PECF is also used as an indicator for readiness for trach decannulation.

Various pulmonary function tests (PFT) may be performed to assess respiratory muscle strength, such as maximum inspiratory pressure (MIP) or negative inspiratory force (NIF) and maximum expiratory pressure (MEP); however, "cough peak flow (CPF) is an acceptable alternative to measuring maximal expiratory flow (MEP) in assessing expiratory muscle weakness in these patients especially as performing the MEP can be quite cumbersome."[5]

Expiratory muscle strength training (EMST) has been shown to "increase expiratory muscle strength, improve cough function, positively affect speech characteristics and promote swallow performance in clinical populations."[5] There are numerous inspiratory and expiratory training devices available that can be incorporated into any discipline's care plan to maximize the strength training effect.

The breech in the closed system due to tracheostomy tube placement has a significant impact on airway patency and secretion clearance. Without the requisite subglottic pressure, a patient with an open trach is unlikely to generate enough internal pressure to produce an effective cough, relying instead on oral and tracheal suctioning. This results in an increased risk of atelectasis, infection, pneumonia and returns to an acute care setting with a prolonged length of stay (LOS).

An individual with an open tracheostomy tube is unable to perform, and therefore benefit from, the described maneuvers to measure inspiratory and expiratory muscle strength or the respiratory muscle trainers.

Restoring a Closed System

The ability to restore a closed system for a tracheostimized patient will typically create the necessary subglottic pressure to generate and maintain the desired internal pressure. Once the closed system is restored, many if not all, of the functions lost due to trach tube placement will return.

One mechanism for recreating a closed system is with the use of a Passy Muir Valve (PMV). Invented by a patient named David Muir, the Passy-Muir Tracheostomy & Ventilator Swallowing and Speaking Valve is a simple medical device used by tracheostomy and ventilator patients. When placed on the hub of the tracheostomy tube or in-line with the ventilator circuit, the PMV redirects exhaled air flow through the vocal folds, mouth and nose enabling voice and improved communication. Years of evidence-based research has shown that the PMV offers patients numerous clinical benefits beyond communication, including: improved swallowing, secretion management, oxygenation, smell and taste and infection prevention and overall quality of life. Early introduction and use of the PMV has also been shown to facilitate ventilator and trach tube weaning and pediatric speech/language development.

Ventilator patient with PMV using an expiratory muscle trainer.

To summarize thus far, there is an interthoracic connection of posture and trunk control to respiration and breath support for speech; and although the body's closed system can be impacted by a trach tube, the placement of a one way speaking valve can restore positive airway pressure.

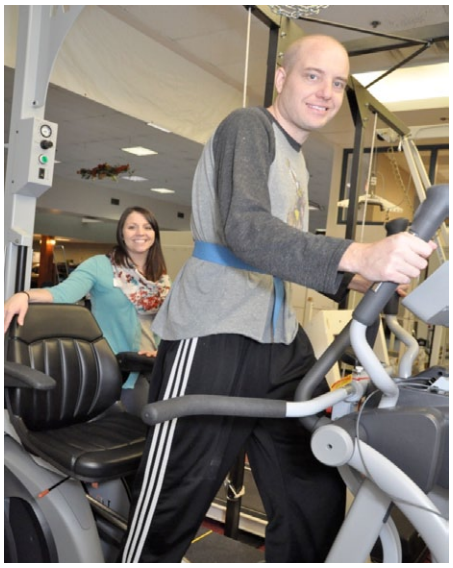
For persons needing a tracheostomy tube for an extended length of time, clinicians focus on enhancing quality of life through rehabilitation and use of the PMV, which can facilitate patient participation.

Tracheostomy Tube Patients and Rehabilitation

The most common goals for persons in rehabilitation are to maximize their independence and return to their life roles. The following case example will demonstrate the benefits associated with the application of the principles outlined in this article.

Case example: Scott C., a 35-year-old husband and father of two young children

- Scott was diagnosed with Guillain Barre Syndrome and spent two weeks at an acute care hospital.
- When he transferred to Madonna Rehabilitation Hospital's long term acute care hospital (MLTCH), Scott was on a mechanical ventilator, unable to communicate and paralyzed from the neck down.
- Within 24 hours of admission, Scott was co-evaluated by his Speech Language Pathologist and Respiratory Therapist for assessment to initiate the PMV.
- Within 12 days of his admission Scott was completely weaned from the ventilator.
- Six days later his tracheostomy tube was removed.
- Additional goals for Scott included: independence with



Already weaned from the ventilator and trach tube, Scott continues to make progress through inpatient rehabilitation.

transfers and activities of daily living (ADL), increase activity tolerance, increase wheel chair sitting time to four hours for participation in community outings, improve his speech and be able to direct his own cares.

- After four weeks on MLTCH, Scott transferred to Madonna's inpatient Acute Rehab Hospital for another two weeks, with three hours of therapy each day.
- Scott met all of his inpatient goals and was discharged to Madonna's Outpatient program for four weeks of additional Rehabilitation.

Almost four months after the acute onset of his symptoms, Scott went home to his family. He returned to work and resumed his home roles. He even ran a 5K race to raise awareness of Guillain Barre.

Scott was able to meet his goals through the incorporation of interdisciplinary interventions and a collaborative, team approach to rehabilitative care. Specifically:

Introducing the PMV early. The benefits of the PMV for Scott were both physiologic and psychosocial. He was able to communicate his needs to his caregivers, speak with family and friends over the phone and avoid the isolation and depression that often affect those on mechanical ventilation.

Restoring Scott's closed system with the PMV reduced the frequency of invasive tracheal suctioning. He was able to increase his oral intake without increasing aspiration risks. The posture and trunk control therapy contributed to his lung volume expansion and postural muscle strength, allowing Scott to tolerate an upright position during these activities.

Application of the PMV also facilitated his ability to increase his activity tolerance and ambulation due to improved posture and trunk control.

The PMV allowed his therapists to introduce expiratory muscle strength training (EMST), increasing expiratory strength for breath support for phonation. Additional benefits of EMST include improved secretion management and airway clearance, greater vocal intensity, improved speech intelligibility and increased words per minute. Once Scott was able to use a cap on his trach, inspiratory trainers were introduced.

These interventions contributed to the timeliness of weaning Scott from the ventilator and trach decannulation.

Summary

Understanding the interthoracic connection and utilizing a multidisciplinary team method of treatment for all patients, especially for those with tracheostomy tubes, will contribute to reaching patients' goals and maintaining life time management of their health.

Rebecca Wills is the Pulmonary Program Manager at Madonna Rehabilitation Hospital in Lincoln, Nebraska and a part time Clinical Consultant with Passy Muir, Inc. Rebecca can be reached at rwills@madonna.org or 402-413-3187.

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Biphasic Cuirass Ventilation for Pulmonary Compromise Due to Neuro-Muscular Illness or Injury

Gary Mefford, RRT, Denise Fernandez, CRT

The history of ventilation via cuirass interfaces for individuals dealing with the pulmonary sequelae of illnesses that result from depression of or elimination of the communication between the brain and the skeletal muscles has a very long history. There are multiple benefits that have been able to be realized for individuals with this type of illness via this treatment. Interestingly, this type of non-invasive support had almost faded into medical history in the US and had essentially become non-existent until relatively recently. There is now a modern version of cuirass ventilator that provides better support and additional advantages over any of the previous versions. This device is the brainchild of the late Dr Zamir Hayek and is available for patients requiring support of respiratory function in the hospital, at home or essentially any care venue. This device is the Hayek RTX Biphasic Cuirass Ventilator. The type of support provided by the RTX is unique in that it is biphasic rather than previous cuirass ventilators that functioned with only negative pressure. Support provided with Biphasic Cuirass Ventilation (BCV) ventilates using negative pressure in the cuirass or shell against the chest wall and abdomen to create inspiration in the same natural fashion as the old negative pressure vents, but rather than exhalation being passive, with BCV exhalation is an active phase where exhalation is assisted with positive pressure in the cuirass. This advancement provides greater ability to produce adequate tidal volumes. Within the realm of treatment provided by the RTX is included a very comfortable, but effective means of cuirass applied high frequency chest wall oscillation for secretion mobilization and an assisted cough via the cuirass as well. In this article the basic common pulmonary deficits caused by the spectrum of illnesses referred to as neuromuscular (NM) illnesses will be discussed and how this modern generation of non-invasive support of ventilation via the extra-thoracic interface known as a BCV can help treat these pulmonary deficits. Also discussed will be how BCV offers an alternative and advantageous means for many patients with respiratory compromise due to NM illness to have an improved overall maintenance of health and quality of life. Finally we will include interview responses from a patient, patients' caregivers and two clinicians who have had experience using BCV in this population.

To begin with for the purposes of this discussion we will provide a definition of this very general and broad descriptor we will call pulmonary compromise due to Neuro-Muscular Illness or injury. We will then take a basic general look at some of the causes, the symptoms and how these symptoms can be very effectively mitigated by treatment with BCV. Also discussed will be what the clinical prognosis and expectations will be for these patients as it relates to treatment with BCV. Finally our Q&A's with experts in use of the device.

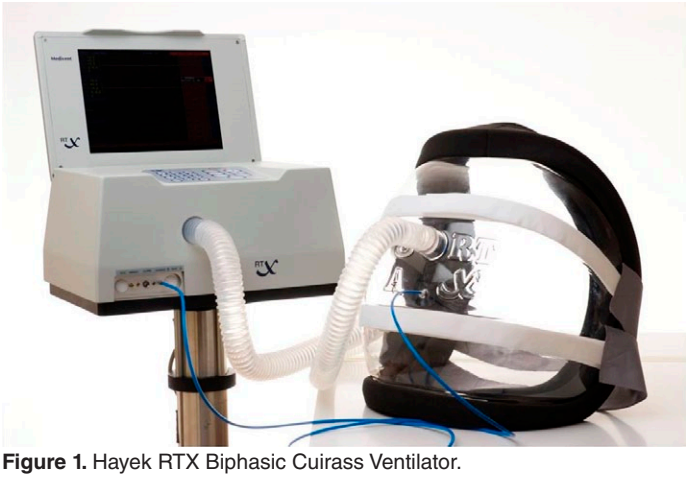


Figure 1. Hayek RTX Biphasic Cuirass Ventilator.

Definition

Pulmonary Compromise Due to Neuro-Muscular Illness or Injury: Pulmonary system deficits resulting from disease process marked by decreased skeletal muscle function. This may result from decreased production of or lack of transport of signals from the brain to skeletal muscle due to either failure of the nervous system to send or carry the signal or failure of the signals to cross the neuromuscular junction or failure of the muscles to respond to the sent signal.

This grouping encompasses a spectrum from progressive to stable and static illnesses that may be mild with slight to no initial pulmonary symptoms and rare pulmonary compromise to advanced and severe with complete disassociation between the brain and the muscles resulting in some or complete degree of pulmonary muscle paralysis with significant, frequent and severe pulmonary involvement. For the purpose of treatment with Biphasic Cuirass Ventilation including Secretion Clearance and Assisted Cough with the Hayek line of pulmonary support tools (BCV) this grouping also includes spinal cord injuries and other nervous system injuries that result in loss of pulmonary muscle function primarily injuries to the cervical spine particularly at the higher levels and injuries to the nerves servicing the pulmonary muscles particularly the diaphragm.

The authors are with United Hayek Medical Devices.

Diagnoses that fall into this category are numerous and more commonly include illnesses such as Amyotrophic Lateral Sclerosis (ALS), Muscular Dystrophy, Guillain-Barré Syndrome, Spinal Muscle Atrophy (SMA) and Poliomyelitis. The specific diagnosis is determined by multiple factors. These include in part medical history, symptoms on presentation, progression of the illness, hereditary factors, lab tests, electromyographic testing and multiple other sources of clinical information based on the presentation of the illness may go into determining accurate diagnosis.

Some of these diagnosis offer hope of resolution with time and treatment, most are either progressive in nature with little chance of reversal or settle at a static level beyond which they do not progress or reverse. Pulmonary compromise resulting from each illness and injury is unique to the particular diagnosis.

Causes: Cause of neuromuscular dissociative injury and illness can be by a myriad of sources including a wide range of hereditary, acquired or unknown sources of onset. They result from failure of the neurologic and muscular systems and their interfaces anywhere along the chain of communication from the brain to the muscle with failure to send, transport, receive or process neural stimulus resulting in degrees of weakness up to complete paralysis.

Symptoms: The pulmonary compromise often caused by the pulmonary muscle weakness or paralysis that is the result of these various sources of NM illness have a relative commonality that can benefit from treatment with BCV. These common elements of pulmonary compromise may include hypoventilation, reoccurring atelectasis, high susceptibility to and potential for frequent pneumonias, retained pulmonary secretions, weak cough with low or nonexistent cough flows, loss of chest wall mobility, and multiple subsequent additional problems that result from these listed if they are not or cannot be adequately addressed.

Treatment with BCV

(Addressed by pulmonary symptoms)

Hypoventilation: BCV provides a means of non-invasive pulmonary support of ventilation that will bring alveolar minute ventilation back up to levels that can be adjusted to meet the patient's body's needs for CO2 clearance thus providing a tool for management of hypoventilation that allows the patient to speak, eat and drink while receiving support as long as those functions remain preserved. This provides an alternative to other pulmonary support devices that might require a facial interface (pressure mask), which can be injurious or uncomfortable or an invasive interface for ventilation such as a tracheostomy, which provides an additional source of entry of infectious organisms into the respiratory tract and that comes with a large group of side effects related to having a foreign object inserted into the trachea bypassing or blocking normal pulmonary system functions. Many patients have a strong preference for this type of support that avoids the artificial airway or mask, but rather utilizes a cuirass or chest shell as the interface between the patient and the ventilator as a treatment for hypoventilation.

Recurrent atelectasis, retained pulmonary secretions due to weak cough with low or nonexistent cough flows with high susceptibility to pneumonia: Impaired function of pulmonary muscles, being primarily bed bound, and respirations at low tidal volumes are all risk factors for atelectasis or alveolar derecruitment. These are also symptoms in many cases of neuromuscular illnesses. Since retained secretions and subsequent potential mucous plugging of airways can result, atelectasis is also likely to develop due to blockage of air entry into effected lung regions. This combination of lack of ability to breathe deeply, cough effectively, alveolar collapse, and secretion retention can greatly increase the likelihood of development of pneumonia. This primary pulmonary infection can and often does lead to greater compromise with systemic infective and inflammatory processes that are for these patients a primary source of fatality. Utilizing BCV to support ventilation provides a means of keeping atelectasis at bay and maintaining full lung volumes. This is achieved by virtue of the fact that for equal tidal volume exchange compared to positive pressure types of support the lung inflation is provided very evenly to both healthy and sick lung units. The more even and complete inflation is due to the more natural pull of gas into the lungs from across the chest and from below the diaphragm, thus distributing the inspired gas volume more evenly throughout the lungs. This is unlike inflation with positive pressure which typically inflates the more compliant healthy lung units quite readily even to the point of over inflation and potential damage, particularly in the face of lung volume loss with atelectasis, while not expanding those alveoli that have collapsed and are less compliant. As a treatment tool to provide airway clearance and assistance of cough, BCV is able to provide an intense yet comfortable high frequency chest wall oscillation that breaks up and thins pulmonary secretions while also providing facilitation of transport of the secretions from the distal lung regions up to the trachea.

The effect of this portion of the treatment cycle is assisting the natural mucocilliary escalator system and results in a highly effective secretion mobilization strategy. Following the oscillation phase of the Secretion Clearance mode treatment cycle the RTX switches to the part of the mode that provides a comfortable but strong negative pull on the chest wall and diaphragm creating a full deep breath. This is followed by a short strong positive phase that causes high exhaled flows and assists expectoration of the secretions that were thinned and brought to the large airways. The rate and duration of the cycles are tailored specifically to the patient's needs and best effect.

This secretion clearance treatment mode is unique among all ventilators and is part of the way that BCV can reverse and prevent atelectasis, decrease the incidence of pneumonias dramatically and minimize hospitalizations due to pulmonary issues for patients with respiratory compromise of any source including neuro-muscular.

This is all very comfortable versus other devices that shake while they squeeze to provide chest wall oscillation or require mask pressure to inflate and deflate the lungs to extract secretions for airway clearance and works using the same interface to provide non-invasive support of ventilation.

Decreased Chest Wall Mobility or Loss of Chest Wall Range of Motion: One of the possibly lesser considered, but very important changes to the pulmonary system that can occur over time for individuals with neuromuscular illness is a restrictive

effect caused by decreased range of motion of the bony and cartilaginous structures that comprise the thorax. As a single tidal volume is utilized with positive pressure or a pressure applied that does not offer the lungs and chest wall a regular opportunity to fully expand, the articulations of the thorax that allow the ribs to expand and allow full inflation become stiff and ultimately rigid. This ability to fully expand the thorax is known as chest wall mobility or chest wall range of motion is a very important part of the pulmonary reserves and greatly contributes to airway clearance ability and keeping lungs free of atelectasis and secretion stasis. With routine use of BCV for support and/or secretion clearance with assistance of cough regular full lung expansion is achieved and chest wall range of motion is maintained and over time increased resulting in a greater level of health and wellness for patients with neuromuscular related pulmonary compromise.

Expectations/Prognosis

Because of the broad range of causes and sources, prognosis for each of the different diagnoses that make up this group of illnesses each have a range of their own unique long term prognosis. With some, if the most acute phase is survived, and adequate support is provided for affected systems then some individuals will experience full recovery from their neuromuscular compromise. Guillain-Barré Syndrome or Botulinum Toxicity patients often experience full recovery from their paralysis. Other neuromuscular illnesses are progressive and irreversible with few to no cases of recovery of function having been previously recorded. Research offers great hope with many brilliant scientists working very hard to generate new treatments or even cures.

Regardless of the prognosis the commonality of these illnesses effect on the pulmonary system and the elements required for treatment means that the expectation should be that as long as the patient wishes to seek their greatest level of health these ongoing issues need to be addressed and addressed as aggressively as possible. The fullest possible spectrum of treatment options should always be part of the patient's education on their illness and all of these options should be made available to patients when making decisions regarding their treatment. If the person who is prone to or experiencing pulmonary compromise resulting from a neuromuscular illness or injury is seeking a comfortable means of non-invasive pulmonary support, airway clearance with assistance of cough and an excellent way to maintain chest wall mobility while providing a means to keep their self out of the hospital or shorten their stay if inpatient then Biphasic Cuirass Ventilation with its built in Secretion Clearance and Assist Cough modes must and should always be considered.

Denise Fernandez CRT is Lead Clinical Educator for Hayek Medical and has developed a unique and close relationship with many of the patient and clinician users of BCV. She presented questions to several individuals who have had significant experience using BCV. She developed two sets of questions one for clinicians and another for patients or their caregivers to answer. These questions and their responses follow:

Dr Frank Austan DH Sc., LRCP (RRT) is Director, Respiratory Care/Pulmonary Services Philadelphia VA Medical Center. Dr Austan recently presented a poster at the 2014 AARC Congress "A Case Study: Use of Biphasic Cuirass Ventilation Upon Diagnosis of Amyotrophic Lateral Sclerosis" and had a corresponding abstract published in the October issue of Respiratory Care Journal. It is cited with the references for this article. Dr Austan is a leader in the VA health system, but he also provides care at the bedside as a Respiratory Therapist. He fielded both sets of questions based on his role as clinician and patient advocate offering answers from his observation of their perspective and his as care provider.

Clinician Interview Dr Frank Austan

DF: What originally attracted you and your team to BCV as a therapy for your patients?
Dr Austan: The potential of BCV to provide:

a. greater comfort by supporting the normal "Thoracic Pump" breathing
b. Increasing the length of time in avoiding the application of BIPAP (positive breathing ventilation) that often requires wearing a full face BIPAP mask that prevents verbal communication as well as increasing the risk of facial tissue breakdown and,
c. Postponing (Increasing the length of time until the inevitable decision re. the need for a tracheostomy tube is required and mechanical ventilation

DF: What observations have you made as to how this has benefitted the patients that you have used it with?
Dr Austan:

a. BCV delayed the inevitable need for a tracheostomy and conventional mechanical ventilation.
b. Less respiratory therapy equipment is required; CPT Percussor; Coughalator etc.

DF: Do you find patients generally have fewer hospitalizations when they utilize BCV at home?
Dr Austan: BCV has the potential to reduce hospitalizations by providing the following therapies:

a. Deep Breathing Exercise
b. Airway Clearance via cough assist and oscillatory therapy (CPT)
c. Preventing a decrease in functional residual capacity (FRC) during the hours of sleep
d. Supports the "Thoracic Pump Mechanism" as a mechanical diaphragm that supports ventilation

DF: When BCV is used for acute pulmonary exacerbations what have been your observations as to how length of stay is affected?
Dr Austan: No experience with acute exacerbation.

DF: Do you find the patients adapt well to this type of support and can it be a good long term option for the right patients?
Dr Austan: Considering the terminal nature of ALS and associated eventual respiratory failure, the early introduction of BCV assists in establishing a segue that "bridges" improvement in the patient's compliance and tolerance of the device.

DF: What are some of the challenges you have encountered to providing your NM patients with BCV?
Dr Austan: Non familiarity of BCV by the pulmonary/respiratory care establishment of the fact that a "State of the Art" non-invasive negative pressure ventilation system now available in the medical market place.

DF: What have you found presents the greatest challenge to patients using BCV?
Dr Austan: Last minute care planning and application when

a state of exacerbation ensues. Patients require a period of "training" gradual acclimation to BCV.

DF: Has it been an advantage for your patients that recruitment, support and airway clearance are all provided in one device with the Hayek and how so?
Dr Austan: BCV provided multiple therapeutic modalities ie Cough assist; Deep breathing exercise via negative pressure assist; Vibrational Chest Physical Therapy.

DF: There are twelve sizes of cuirass, what might you offer as to the best way to provide accurate fitment for each individual patient?
Dr Austan: Chest measurement.

DF: What are some tips you might offer to other clinicians who are beginning to explore use of BCV for their NM populations?
Dr Austan:

a. BCV is driven by the respiratory therapist ("Champions" for BCV)/physician.
b. Develop rapport with the physician staff in the setting where BCV will be of benefit to the their patient's ie ALS Clinic.

DF: What do you envision as to how you might further develop BCV with your NM population in the future?
Dr Austan: I envision BCV following algorithm for ALS cases: Diagnosis > BCV > BCV and BIPAP in combination > BIPAP > Tracheostomy > Mechanical Ventilation.

DF: Any additional comments you would like to make?
Dr Austan: An "old" technology (Iron Lung; Chest Cuirass) that has been significantly innovated eliminating the need to purchase separate pieces of therapy equipment such as: Mechanical Chest Percussor, CPAP machine, Coughalator, Non-invasive negative pressure ventilation.

Dr Amanda Dove is a Pediatric Pulmonologist who sees patients in and around the San Antonio Texas area. She has been prescribing BCV for NM patients referred to her practice for several years.

Clinician Interview Dr Amanda Dove

DF: What originally attracted you and your team to BCV as a therapy for your patients?
Dr Dove: The potential to provide via BCV a more normal assistance with respirations and simulation of normal breathing cycle. We felt that by being able to support patients with a more normal thoracic Pump/Bellows assistance of breathing we would see increasing length of time before our patients would be getting trached and being put on a ventilator, which is what we have seen.

DF: What observations have you made as to how this has benefitted the patients that you have used it with?
Dr Dove: I have seen an increase in cardiac output and renal perfusion decreasing the amount of Lasix being given to patients. The increase in cardiac output has helped them and we have observed decrease in the sound of wet lungs.

DF: Do you find patients generally have fewer hospitalizations when they utilize BCV at home?
Dr Dove: Yes, when well supported, fewer events of atelectasis and subsequent pneumonia due to poor airway clearance.

DF: When BCV is used for acute pulmonary exacerbations what have been your observations as to how length of stay is affected?
Dr Dove: LOS similar to patients without BCV due to length of antibiotic therapy.

DF: Do you find the patients adapt well to this type of support and can it be a good long term option for the right patients?
Dr Dove: The patients do adapt well, often without the ability to lie on stomach. They prefer to utilize rather than BiPAP as face is free and they are able to talk. Enhanced cardiac output as noted. Better urine output.

DF: What are some of the challenges you have encountered to providing your NM patients with BCV?
Dr Dove: Lack of easy availability in hospital, has to be brought in; poor support from hospital, not readily available to reach inpatients, and family. Also admitting is difficult because hospital staff can't support care without the system being on site when needed, they rely on patients and their family to bring in their systems.

DF: What have you found presents the greatest challenge to patients using BCV?
Dr Dove: Lack of portability; patients cannot use current model in vehicle while traveling. Poor planning for smooth transition of these patients into hospital, using BCV inpatient and off of BCV, advancing to conventional vent with acute illness if needed and back to BCV when ready. It is difficult to listen to breath sounds while in use, but it can be quite easily removed and placed back on. Use post surgery is a challenge still with certain procedures and it must be removed to obtain EKG or adjust leads.

DF: Has it been an advantage for your patients that recruitment, support and airway clearance are all provided in one device with the Hayek and how so?
Dr Dove: Yes, allow us to see discontinued need for other devices.

DF: There are twelve sizes of cuirass, what might you offer as to the best way to provide accurate fitment for each individual patient?
Dr Dove: Tape measure, and trial fitting with different sizes for best result.

DF: What are some tips you might offer to other clinicians who are beginning to explore use of BCV for their NM populations?
Dr Dove: Involve well trained and BCV versed Respiratory Therapists to assist with enlightening physicians new to the therapy and patient education.

DF: What do you envision as to how you might further develop BCV with your NM population in the future?
Dr Dove: I am actively working to develop better hospital support. Will continue relationship with Hayek Representative and seek greater agreement with algorithm proposed for SMA, MD patients.

DF: Any additional comments you would like to make?
Dr Dove: The increase in cardiac output is a real positive with using this for ventilation.

Patient/Caregiver Interview Dr Frank Austan

DF: How has using BCV changed your respiratory treatment

regimen?
Dr Austan:

a. Improves ability to cough (Patient)
b. Improved ability to breathe deeper (Patient)
c. Treatment of shortness of breath due to respiratory failure (Provider)

DF: What have your patients said that they feel when using BCV?
Dr Austan: Able to breathe easier; feel less short of breath (Patient).

DF: Is it difficult to talk while using BCV?
Dr Austan: The voice intensity improved with a "deep breath" (Patient), increase in VT (Provider).

DF: Would you say that the cuirass is comfortable to wear?
Dr Austan: Initially a little uncomfortable but able to adapt and became comfortable with greater use (Patient).

DF: Can you eat while being ventilated with BCV?
Dr Austan: Comfortable (Patient); Swallowing was not affected (Provider).

DF: How long can you wear the Cuirass?
Dr Austan: Initial startup was to use as deep breathing exercises. As cough became weaker, added cough assist. Use during the hours of sleep to assist in resting the respiratory muscles; as breathing became more difficult was on for longer periods of time during the day (Patient & Provider).

DF: What are some of the benefits that you have experienced by using BCV (clinical outcomes)?
Dr Austan: Improved exhalation of carbon dioxide by improving alveolar ventilation (Provider), and improved the patients cough (Patient & Provider).

DF: Is it hard to use the cuirass and the Hayek system?
Dr Austan: Was not difficult to apply by the nursing staff in an extended rehab facility; patients often weak and unable to apply BCV on their own (Provider).

DF: What benefits has BCV brought to your patients' quality of life?
Dr Austan: Improves quality of life by not impeding speech, eating, or drinking. Provides effective treatment for shortness of breath secondary to hypoventilation. It delayed the inevitable application of BIPAP Ventilation; tracheostomy, and tracheal suctioning.

DF: What is the one thing you would say is the main benefit of using BCV and why?
Dr Austan: Assists in supporting normal "Thoracic Pump" breathing. It treats hypercarbia as measured by end-tidal CO2 Monitoring.

DF: What considerations would you offer to other individuals needing the benefits provided by BCV?
Dr Austan: The clinician must have a complete understanding of BCV technology and its use as therapy in order to effectively introduce BCV to the physician as well as ability to present it in a positive light embracing BCV which in turn helps with patient attitude towards the treatment.

DF: Any additional comments you would like to make?
Dr Austan: In long term care of the patient with gradual inevitable respiratory failure due to wasting respiratory muscles, patient experience improved quality of life using non-invasive BCV as compared to patients receiving non-invasive Bi-Level Positive Pressure Breathing (BIPAP) .

Jamie Quist has been using BCV at home almost since it began to be offered in the US. He may well have the most experience with BCV of anyone in the country.

DF: How has using BCV changed your respiratory treatment regimen?
Mr Quist: Using BCV has greatly impacted my treatment regimen, specifically its excellent cough assist mode. Prior to BCV I used an airway clearance vest that, while effective, did not help bring mucus up after loosening it. The problem with airway clearance vests is that once mucus is loose the wearer has to contend with both getting the mucus up as well as the squeezing pressures of the vest. This can cause a lot of stress to the patient, both physically and mentally. The beauty of BCV and the cough assist mode is that the negative pressure pulls your chest and diaphragm out, making it easy and less stressful to cough mucus up Add the varying vibration frequencies and cough mode into the mix and BCV becomes my go to tool for daily breathing treatments.

DF: How do would you say that you feel when using BCV?
Mr Quist: In terms of how I feel when wearing the BCV I would say I'm extremely relaxed. The reason why BCV is so much more comfortable than any positive airway device is that the BCV's mechanics work the same the way the body is physiologically designed to breathe. Often wearers of CPAP and BiPAP machines complain of feeling suffocated and claustrophobic while wearing masks and that's because air is being shoved into the lungs rather than going in passively. Since all the BCV machine is doing is pulling the diaphragm and rib cage out and open, air goes into the lungs passively and efficiently.

DF: Is it difficult to talk while using BCV?
Mr Quist: Talking on the machine is extremely simple. Again, since air goes into the lungs the same way it would in a person not wearing the machine the patient doesn't have to struggle to speak.

DF: Would you say that the cuirass is comfortable to wear?
Mr Quist: The cuirass is comfortable to wear. Padding can always be customized with various foams and the mechanics of the machine are quite relaxing once you get used to the rhythm.

DF: Can you eat while being ventilated with BCV?
Mr Quist: Eating on the BCV can be done, but it's important to be careful when doing so. Always eat sitting up and make sure you're not trying to swallow when air is going into your lungs. It's also crucial to not over eat since that can cause reflux or stomach discomfort.

DF: How long can you wear the Cuirass?
Mr Quist: As long as the wearer's skin isn't getting too dry and having pressure sores form from an improper cuirass fitting, the it can be worn as much as they want. When I'm feeling good I'll come off during the day and then go back on for bed. I have worn it for extremely long periods when sick and was fine.

DF: What are some of the benefits that you have experienced by using BCV (clinical outcomes)?

Mr Quist: The best outcome I've had from using the BCV was being able to come off my trach. I had a tracheostomy for 6 years and towards the end of that time my lungs were having a lot of problems from the positive airway pressures. I was continually getting pneumothoraces all over my lungs and was stuck in the hospital for an accumulative period of about 3 months. Once I was able to switch over to the BCV machine I no longer had to worry about the pneumothoraces and thankfully haven't had any since.

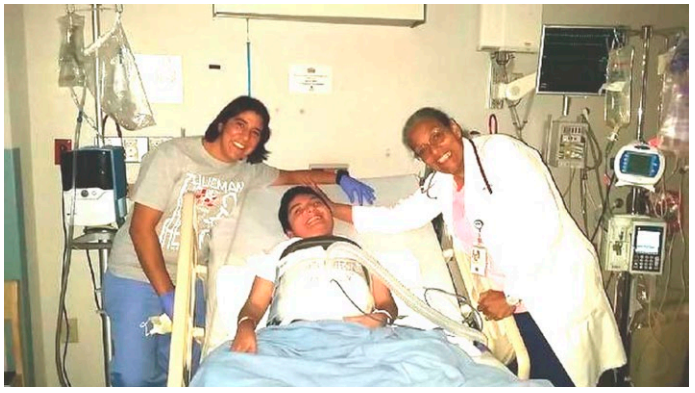
DF: Is it hard to use the cuirass and the Hayek system?
Mr Quist: The cuirass and Hayek system are both extremely easy to use. Once the patient's settings are determined there's not much they need to do. Navigating between modes is easy and intuitive.

DF: What benefits has BCV brought to your quality of life?
Mr Quist: BCV has given me a lot of my freedom back. I'm able to shower now and go out more. My lungs also don't produce as much mucus as they did with the trach, which is very relieving.

DF: What is the one thing you would say is the main benefit of using BCV and why?
Mr Quist: The main benefit to the device is the obvious one, breathing. People with compromised lungs know the harsh reality of what it's like to not be able to breathe and it's something that is truly terrifying. BCV allows me to keep breathing and in turn helps me fulfill my goals in life.

DF: What considerations would you offer to other individuals needing the benefits provided by BCV?
Mr Quist: Anyone looking for airway assistance should definitely try BCV. Give it some time, make sure you get proper settings and a proper fit and you'll be happy with the device.

DF: Any additional comments you would like to make?
Mr Quist: I just want to take the opportunity to thank United Hayek in their continued support and dedication to their customers as well as to bettering respiratory aid in general. They're doing some great work that will continue to benefit many people from all over.



L-R: Denise Fernandez, Marco Gayton, Dr Amanda Dove.

Marco A. Gaytan, Jr. is an adolescent patient who is followed by Dr Amanda Dove and to whom Denise Fernandez introduced BCV nearly three years ago.

DF: How has using BCV changed your respiratory treatment regimen?
Mr Gaytan: I have a better quality of life and am certain it has extended my life since I have had fewer hospitalizations. I use the respiratory treatments with the cuirass. I feel that utilizing the Cuirass has cleared my secretions a lot better than any other CPT out there that I have used. I feel the medicine with the cuirass takes a better effect.

DF: How do would you say that you feel when using BCV?
Mr Gaytan: Using BCV, has changed my life and my family's life since I am able to communicate and able to breathe better. I never thought at first by looking at it that it would be such an awesome piece of respiratory equipment.

DF: Is it difficult to talk while using BCV?
Mr Gaytan: Not at all. I felt my voice projected and it gave me the strength to talk louder.

DF: Would you say that the cuirass is comfortable to wear?
Mr Gaytan: The cuirass is very comfortable. I even rest my phone and tv remote on my cuirass. I am able to talk to my family and I do not get sores as I did by wearing a mask on my face.

DF: Can you eat while being ventilated with BCV?
Mr Gaytan: I can eat while be ventilated and able to play my games and play with my brothers and sisters. Talking all the time.

DF: How long can you wear the Cuirass?
Mr Gaytan: I wear the cuirass at night and for my respiratory treatment regimens. The longest I wore the cuirass was for 21 days straight with an hour break during the day.

DF: What are some of the benefits that you have experienced by using BCV (clinical outcomes)?
Mr Gaytan: I had less hospitalizations and has helped me avoid getting trached.

DF: Is it hard to use the cuirass and the Hayek system?
Mr Gaytan: It is not at all hard to use and very easy to work with. The representatives are there to help the families and are available at all times like Denise Fernandez.

DF: What benefits has BCV brought to your quality of life?
Mr Gaytan: My life was improved and I received the strength to need ventilation less during the day. I do not get short winded during the day and my facial scars healed.

DF: What is the one thing you would say is the main benefit of using BCV and why?
Mr Gaytan: It helps me get better rest at night while sleeping, I know this because the next day I am able to be more active. I feel energized the next day. I have the energy to get out of bed.

DF: What considerations would you offer to other individuals needing the benefits provided by BCV?
Mr Gaytan: I remember the first time I tried the cuirass. I was scared because of the cuirass on my chest. I told my mom that I would not like it. Denise Fernandez spoke to me and placed it on herself for a while and showed me that it did not hurt at all. She asked me to sleep with it for the night and she would spend the night with me to make sure I got a good rest with it. When I woke up in the morning she looked at me and asked how I felt. I told her I felt like I could run and that I had a dream of running. I was wearing oxygen for 3 days before I got the cuirass and when I placed the cuirass on I did not

need my oxygen any more. Denise told me that my heart rate went down, my respirations, blood pressure all went down, my saturations went up and she told me how my cardiac output may have increased as well. I wanted to go home with this. Denise said she would work with Dr Dove to get it prescribed for me. My hospitalizations decreased, because I was going to the hospital at least once a month. I love my cuirass.

DF: Any additional comments you would like to make?
Mr Gaytan: Thank you to Denise Fernandez for introducing BCV to my family. You are awesome.

To learn more about how to obtain BCV for your patients, yourself or your loved one visit www.hayekmedical.com, call 855 2 GETBCV, or email gary.mefford@hayekmedical.com.

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Waste Not, Want Not, Part 2: Understanding Aerosol Delivery System Efficiency

Michael McPeck, RRT FAARC

In the part 1 of this article (Dec 2014-Jan 2015)1 I wrote that there are a number of compound efficiencies that, when summed, can improve the overall efficiency of aerosol drug delivery, or the System Efficiency as its been named in Figure 1. So the next logical question is, what part do these different components play, in terms of overall System Efficiency, and how do we manage or control them? The goal of this paper is to conceptualize the various components of aerosol delivery and, specifically, overall System Efficiency, so we can better appreciate how these systems function and how they can be improved.

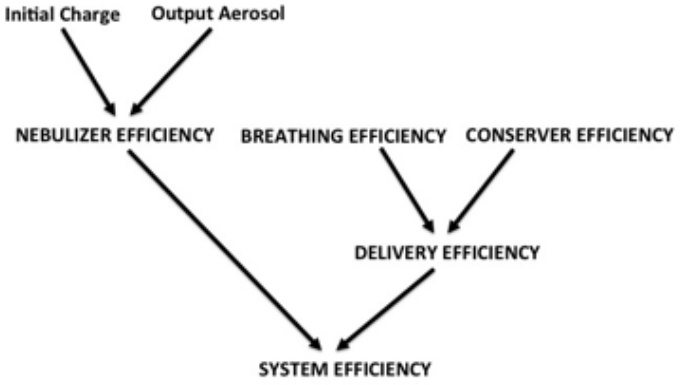

Figure 1

Let's look first at Nebulizer Efficiency. It has two components: Initial Charge and Output Aerosol. Initial Charge, in the context of drug delivery, is essentially the amount, or mass, of drug placed into the nebulizer for the treatment. A large drug mass placed into the nebulizer will render a greater Nebulizer Efficiency than a small drug mass, all other things being equal. While it is tempting to think that we can improve Nebulizer Efficiency by adding more drug mass to the nebulizer, the plain fact is that most of our nebulizer solutions, being unit doses, limit the amount of drug mass available per unit dose. If we add multiple unit doses, the Initial Charge volume may become so great that nebulization time must be prolonged in order to actually achieve delivery of the added drug mass. So adding drug mass, while theoretically feasible, is rarely practical.

There are two exceptions to this, however. One pertains to the use of levalbuterol, which is available in three concentrations: 0.31 mg/3 mL, 0.63 mg/3 mL, and 1.25 mg/3 mL. In the case of levalbuterol, the 3 concentrations, where one dosage form is double the base dosage form, and the other is quadruple the base dosage form, allow considerable latitude in altering Nebulizer Efficiency based upon Initial Charge.

An even more extreme example is 0.5% albuterol. "Concentrated" 0.5% albuterol contains 2.5 mg of albuterol in 0.5 mL of total volume for a concentration of 5 mg/mL (0.5%). Compared to "standard" albuterol, at a concentration of 2.5 mg per 3 mL (0.083%), "concentrated" albuterol is >6 times more concentrated, although it contains the same mass. Therefore, using a more concentrated solution is one way to increase Nebulizer Efficiency in any nebulizer and has been used for breath-actuated nebulizers to compensate for the inherent inefficiency caused by long delivery times in the breath-actuated mode. However, adding concentrated inhalation solution to any nebulizer would result in improved Nebulizer Efficiency. But, as stated above, there are only two inhalation solutions available in different concentrations, so the actual options and opportunities for increasing Nebulizer Efficiency by this method are limited.

The second component of Nebulizer Efficiency is Output Aerosol. At first blush it seems logical to assume that the greater the output of a nebulizer, in mL/min, the greater the drug mass that will be emitted in that output, and therefore the greater the Nebulizer Efficiency. And while that is true, increasing nebulizer output appreciably is fairly difficult to accomplish. The vast majority of pneumatic jet nebulizers are engineered, by virtue of their jet orifice diameter, to operate most efficiently at 8 L/min of input flowrate. Lesser flowrates diminish output while greater flows theoretically increase output. However, higher flowrates eventually run up against the maximum flowrate than can be expressed through a critical orifice. When this occurs, it does not matter how much driving pressure is available: flow is limited by the diameter of the jet orifice, and additional output will not be achieved.

Stepping through the figure, it can be seen that Nebulizer Efficiency has a direct bearing on overall System Efficiency. But, for reasons that have been discussed, increasing the efficiency of inexpensive, plastic, disposable small volume nebulizers is neither practical nor possible. Electronic vibrating mesh nebulizers are, by design, exceptionally efficient because they have minimal Retained Charge and extremely high Output Aerosol. But such efficiency comes with a premium price tag that is not universally appropriate for all clinical applications, especially when less expensive options are available.

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Stepping further through the figure, it is also apparent that the other component that influences overall System Efficiency is Delivery Efficiency. This refers to the delivery system itself, not the aerosol generator component or nebulizer. If a given device had an exceptionally high Nebulizer Efficiency, but an ineffective delivery method, resulting in a low Delivery Efficiency, it is obvious how System Efficiency would suffer. Delivery Efficiency itself is the product of two other compound efficiencies: Breathing Efficiency and Conserver Efficiency.

Breathing Efficiency is a function of the patient's breathing pattern and whatever coaching we, as respiratory therapists, are able to provide in an appropriate manner. Breathing Efficiency is complex, inasmuch as it consists of multiple interrelated components. We usually think of these components with respect to the intricacies of mechanical ventilation; namely, breathing rate, tidal volume, minute volume, respiratory cycle time, inspiratory time and I : E ratio. It is obvious that aerosol delivery occurs only during the inspiratory phase, and both the depth and the timing of the inspiratory phase can markedly influence aerosol delivery and, hence, Delivery Efficiency. We know that rapid, shallow breathing patterns are less conducive to aerosol delivery than slow, deep breathing patterns. However, we are not always able to control or modify the breathing pattern in spontaneously breathing patients even when we observe and identify low Breathing Efficiency.

So far, we have seen that SVNs are limited with respect to a relatively fixed Output Aerosol and what can be accomplished through modifying the Initial Charge. Consequently, there is not a great deal of improvement that can be accomplished in the realm of Nebulizer Efficiency. Similarly, we see the links between Breathing Efficiency, Delivery Efficiency and overall System Efficiency and realize that when we cannot control or improve Breathing Efficiency, the negative effect is carried through to the overall system.

That leaves the final component in this scheme, namely, "Conserver Efficiency." But what is Conserver Efficiency, and why is it so important?

Simply put, Conserver Efficiency is practically the only component in this scheme that can be managed in such a way as to increase overall System Efficiency. Conserver Efficiency compensates for poor or diminished Breathing Efficiency and even poor Nebulizer Efficiency. Essentially, Conserver Efficiency allows a greater percentage of the nebulizer's output to be inhaled by the patient rather than wasted or vented to the room during the exhalation phase of a continuously-operating nebulizer system.

To construct an aerosol delivery device that maximizes Conserver Efficiency, it is necessary to incorporate a one-way valve that allows aerosol generated during the patient's exhalation phase to be held, or conserved, in a flexible reservoir of suitable size that can expand and contract as necessary to either hold aerosol during exhalation, or deliver it to the airway during inspiration. A reservoir approaching or exceeding a typical adult tidal volume (eg, 500 mL) would be sufficient for both children and adults. Typical "tee" nebulizers usually have a short, 6-inch section of 22-mm diameter corrugated aerosol tubing attached to function as a reservoir but these are essentially useless because they are open systems that allow aerosol to escape to the room, and they are of such small internal volume as to be meaningless as a reservoir. Likewise vented, or breath-enhanced, nebulizers tend to have slightly larger internal diameters than typical "acorn-type" nebulizers, ostensibly to function as a reservoir. But again, the internal volume is so small as to be essentially meaningless as a functional reservoir.

In summary, on a conceptual basis that considers the fundamental components of overall aerosol System Efficiency, improving aerosol drug delivery of plastic disposable SVNs is essentially impossible without the use of a valved conserver or reservoir incorporated into the system in such a manner as to hold aerosol generated during exhalation and deliver it to the patient, along with instantaneous nebulizer output, on the subsequent inhalation.

In part 3 of this series, in a subsequent issue, we will finalize this discussion by exploring how to incorporate a physical reservoir, or conserver, into an aerosol delivery system. The point of doing so will not be to improve the nebulizer output because, as we have already examined, that cannot be accomplished to any great degree. Rather, we will explore how the incorporation of a reservoir allows a greater percentage of the nebulizer output to actually be delivered to the airway opening, thereby increasing Delivery Efficiency and, ultimately, System Efficiency. Similarly, we will explore how the use of a reservoir eliminates room air entrainment that dilutes inspired aerosol mass, and compensates for changes in breathing pattern and I:E ratio to render enhanced, as well as consistent, aerosol delivery under different conditions. Then finally, we will examine a simplified new concept called Fraction of Inhalable Aerosol, for evaluating the potential System Efficiency of different designs of pneumatic jet small volume nebulizer.

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Spirometric Data Quality as Assessed by Repeatability in COPD Exacerbations

AJ Harrison, G Sowman, H Kaur-Nagra PhD, D Price, M Brown, P Ford MD

Introduction

Spirometry is one of the few clinical measurements that requires maximum patient effort in order to achieve acceptable and repeatable results. Obtaining valid Spirometry data from chronic obstructive pulmonary disease (COPD) patients who present to the clinic with an exacerbation can be challenging.

Pharmaceutical trials are reliant on accurate data to meet endpoints. We will demonstrate that by using standardised equipment and Over-Reading[2] we can maintain excellent data quality in this challenging patient population. The patient factor is significant when low values are expected for COPD patients struggling with an exacerbation. Having well-trained clinical staff who can coach these patients correctly can have a significant impact on the quality of Spirometry. The accuracy and quality of Spirometry is also particularly important in clinical trials where Spirometry data are used as primary endpoints.

A total of 93 moderate to very severe COPD patients performed 672 Spirometry sessions. Out of those sessions, 96% met the ATS/ERS FVC repeatability criteria[1] and 99% met the FEV repeatability criteria[1]. The ATS/ERS 2005 criteria are widely used in clinical trials as a benchmark for the quality of Spirometry.

Methods

In an international multicentre trial, 93 COPD patients (Gold II-IV) aged 43-80 years old and presenting with a COPD exacerbation were randomised into a clinical trial. Spirometry was performed at both the initial visit and subsequent sessions over a 6 month follow-up period. The Spirometry was conducted by well-trained technicians in 8 centres in 3 European countries. In total, 672 Spirometry sessions were performed. An average patient therefore performed 7 Spirometry sessions. At all sites, the Spirometry was performed using the Vitalograph Spirometry System (including Vitalograph Pneumotrac™ (Fleisch) spirometer run on Spirotrac software customised for the trial) with Over-Reading.

Training

Before the trial commenced all technicians were trained in the correct use of the equipment and trial specific procedures. In addition, all technicians were required to demonstrate their ability to perform acceptable and repeatable Spirometry sessions prior to gaining trial accreditation. Throughout the trial each centre was monitored for spirometric quality to ensure that site re-training was undertaken if required.

Over-Reading

After primary review by the technician, the sessions were transmitted to a central database at Vitalograph and QA reviewed ("Over-Read") by one of three expert Over-Readers within 1-2 business days of receipt. All of the Over-Readers reviewed each session according to the trial-specific acceptability criteria (based on the ATS/ERS Guidelines).[1]

As per the ATS/ERS standards,[1] the protocol allowed up to eight manoeuvres per session which needed to meet the FVC and FEV acceptability criteria. The repeatability for both FEV and FVC was calculated as the difference between the two highest acceptable readings of a session.

Results

A total of 672 (100%) spirometric sessions were recorded at 8 sites in 3 European countries by 93 patients (Country A: 41 patients, Country B: 30, Country C: 22) presenting with a COPD exacerbation. The repeatability for both FEV and FVC was calculated as the difference between the two highest acceptable readings (Figure 1).

The mean figures for each country's repeatability (Figure 1) are within the ATS/ERS recommendation of 150ml. The overall mean repeatability was 69 for FVC and 40 for FEV. Country C had both the lowest FVC and FEV mean repeatability (but also the fewest patients).

The distribution of the repeatability as a percentage for all sessions were graded (Table 1).

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Figure 1: Mean Repeatability in ml (all sessions)

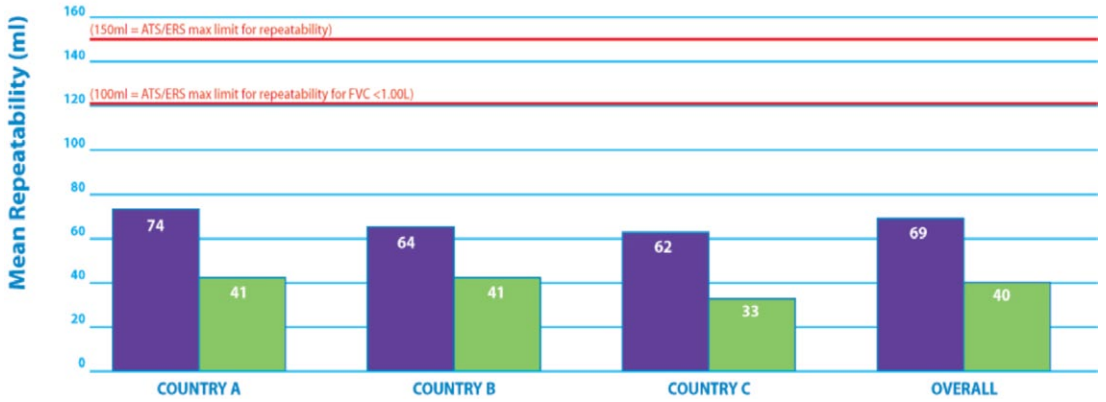

Table 1. % of total sessions within repeatability grade by country.

Repeatability (ml)		Country A (%)	Country B (%)	Country C (%)	Overall (%)
FVC	<50ml	45.5	70.6	53.4	48.5
	<100ml	78.2.5	93.9	84.5	79.3
	<150ml	94.4	99.7	96.6	96.0
	>150ml	5.6	0.3	2	4.0
FEV1	<50ml	73.8	50.9	71	72.9
	<100ml	93.1	79.5	96.6	93.8
	<150ml	98.1	97.6	100.0	99.0
	>150ml	1.9	2.4	0.0	1.0

Overall 4% of FVC manoeuvres were outside the ATS/ERS repeatability limit and just 1% for FEV.

Conclusion

With standardised equipment, well-trained technicians and QA review by independent Over-Readers, patients presenting to clinic with COPD exacerbations can produce reliable and repeatable data in clinical trials.

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Ebola: Considerations Regarding Transport, Contaminated Equipment, and New PPE Requirements

Timothy France, BS, RRT, Justin Tse, BS, RRT-NPS

Ebola was first discovered in 1976 when simultaneous outbreaks occurred, one along the Ebola River in the Democratic Republic of the Congo and the other in Nzara, Sudan. The virus is transmitted by direct contact with blood or body fluids of an infected host through mucous membranes, open wounds or contaminated needles. At present, Ebola is not known to spread through air, water or food.[1] Ebola on dry surfaces can survive for hours, and can survive for several days in bodily fluids. Other key facts[2] regarding Ebola are listed below:

- Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever, is a severe, often fatal illness in humans.
- The virus is transmitted to people from wild animals, and spreads in the human population through human-to-human transmission.
- The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks.
- The first EVD outbreaks occurred in remote villages in Central Africa, near tropical rainforests, but the most recent outbreak in West Africa has involved major urban as well as rural areas.
- Community engagement is key to successfully controlling outbreaks. Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, good laboratory service, safe burials and social mobilization.
- Early supportive care with rehydration and symptomatic treatment improves survival. There is, as yet, no licensed treatment proven to neutralize the virus, however, a range of blood, immunological and drug therapies are under development.
- There are currently no licensed Ebola vaccines, but two potential candidates are undergoing evaluation.

When considering the decision to transport a patient with Ebola to another facility, or within your own facility, there are several factors that need to be addressed. The CDC has listed some key points below for air transport but these can also be used for ground transport or transport within the hospital itself.

- Transport must be coordinated with public health and civil aviation authorities or local law enforcement at the origin and destination.
- Infection control policies and procedures should be established before transport, and implemented during all phases of patient transport.
- A portable isolation unit is recommended to contain infected materials and minimize contamination of the aircraft/ambulance.
- Personnel providing care during transport should be trained in clinical management, infection control, and correct use of personal protective equipment (PPE).
- PPE should be used by all in the patient care area, and anyone who may have contact with the infected patients or their body fluids; infection control guidelines should be followed, and procedures that could increase the risk of exposure to the patient's body fluids should be avoided.[3]

Whether the patient is already at the facility for treatment, or is being transported to another facility for treatment, equipment precautions at both the receiving and transferring facilities need to be addressed. The CDC recommendations for medical equipment being used with Ebola patients are that disposable equipment should be used whenever possible. Once used, disposable equipment is considered biohazard material and must be disposed of according to federal regulations. The Department of Transportation (DOT) considers Ebola infected material a Category A infectious material and it is subject to Hazardous Materials Regulations that govern transporting hazardous materials. Ebola infected material that has had the virus deactivated does not fall under these regulations and therefore is not considered hazardous material. Proper methods for deactivation of the Ebola virus are approved onsite autoclave or incineration. Reusable equipment must be decontaminated per manufacture's recommendations using an approved disinfectant. Hospitals should reach out to the manufacturer of the non-disposable equipment for specific instructions regarding the reprocessing of their equipment.[4]

The donning of Personal Protective Equipment (PPE) goes beyond the usual hand washing and gowning and gloving for standard or contact isolation. There cannot be one millimeter of skin exposed while caring for an Ebola patient. Recommendations from the CDC are that all individuals have numerous training sessions regarding PPE use and that there is a dedicated individual onsite at all times to supervise the use of PPE use.[5]

The University of Nebraska Medical Center, one of only a few medical centers in the United States with a biocontainment patient care unit, has a nice handout that demonstrates the donning and doffing of PPE while treating an Ebola patient.[6]

Cleaning and disinfecting contaminated equipment properly and

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employing the proper use of PPE are important processes that can help keep this disease from spreading.

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Filtering Ventilator Expiratory Flow

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Since the early days of positive pressure ventilation, ventilators have evolved from devices that were created from parts that could be obtained at a plumbing store, to sophisticated, innovative "life support systems." With the introduction of transducers to measure flow, the need for expiratory filtering became apparent with certain transducers placed in the expiratory side of the ventilator. There seems to be two reasons for filtering expiratory flow. One is to diminish the transmission of humidity and or patient derived biological products from causing accuracy issues with the particular type of flow sensor used by the ventilator, as well as protecting the internal components on some machines. The other reason is a position taken by some manufacturers that the use of an expiratory filter is protecting the caregiver from infection derived from the patient.

This article will briefly review the historical development of ventilator flow measurement, the CDC guidelines for infectious airborne and droplet diseases and whether current filters are needed or even protect against those diseases.

The most popular ventilators used in American hospitals today employ either a hot wire anemometer (PB 7200/840/980, Drager Evita XL/V500/VN500, GE Carestation) or a differential pressure pneumotach (Hamilton G5/C2/C3/C1/T1/MR1/Galileo, Drager Oxylog 3000, Newport HT70). Some ventilators can use either device depending on the patient population and the mode of ventilation (Carefusion Avea). A less commonly used flow sensor is the ultrasonic flow sensor employed in the Maquet Servo I, which is also capable of using a monitoring pneumotach flow sensor.

The development of variable flow, and subsequent measurement of flow was a great move forward in the management and comfort of the ventilated patient. Flow graphics analysis allows the clinician to better optimize patient settings. The type of flow sensor used dictates whether a ventilator will have issues with measurement accuracy when faced with humidity or patient secretions. This is most common with heated wire or heated wire mesh anemometer flow sensors because the heated wire anemometer gets quite hot, such that secretions and nebulized medications can literally bake onto the wires inhibiting flow measurement. Humidity condensing into water droplets creates an evaporative cooling affect further impacting measurement performance. In order to minimize inaccuracies, ventilators using this type of technology (PB7200/840/980, Drager Evita XL/V500, GE Carestation, Carefusion Avea non-neo mode) place their flow sensors as far away from the patient interface as possible to avoid secretions and any other patient fluids. Carefusion and Covidien PB go a step further and place a heated filter between the expiratory limb and the flow sensor. The Maquet ultrasonic flow sensor, while not a heated wire system, can have inaccuracies if the piezoelectric emitters become contaminated with water or secretions, so placing the sensors inside the expiratory cassette as far away from the patient interface are employed for the same reason.

Ventilators using a pressure pneumotach (Hamilton, Newport HT70, Drager Oxylog 3000 transport vent) are less impacted by humidity and secretions, so the flow sensor can be closer to the patient interface. Generally, while secretions in the flow sensor on these machines might cause an alarm event, once the secretions are removed the flow sensor continues to function without accuracy impairment. Some companies in their manuals state that a heated expiratory filter is required to protect the flow sensor and exhalation module.[1] Some will even state that the heated expiratory filter is also to protect the caregiver from the patient.[2] This certainly makes sense from the perspective of ventilators that utilize an internal, not easily cleaned exhalation valve. However, not every patient is infectious, and advocacy of filtering every patient by the company might set up a false sense of security and foster a potential relaxing of safety standards among caregivers. Sometimes information can be misleading.

"Truth in advertising"

In two separate discussions in which I was part of, one with a Respiratory Therapists using a ventilator from a company that advocated using a heated expiratory filter, and another discussion with a sales representative from the same company, the following statement was made; "in a 2003 outbreak of SARS in Toronto, Ontario, Canada, a hospital using ventilators without expiratory filters had 396 people contract SARS. During the same year there was another SARS outbreak in a hospital in Vancouver, British Columbia, Canada. The ventilators at that facility had expiratory filters in place and only one person contracted SARS. As a result, the Canadian government mandates that all ventilators used in Canada must incorporate an expiratory filter." Research into the official summary report published by the Public Health Agency of Canada (publichealth.gc.ca) shows that this was not the case. The report cites the lack

of staff to properly and consistently use an N-95 face mask. Only 19 of the 396 patients who contracted SARS required intubation. The report does not mention the use of or the failure to use filters on the expiratory outlet of the ventilator.[3]

Droplet Disease Transmission vs. Airborne Disease transmission

Mosby's Medical Dictionary (Mosby's Medical Dictionary, 8th edition. ©2009, Elsevier) defines droplet transmission and airborne transmission as the following:

> "Droplet transmission involves contact of the conjunctivae or the mucous membranes of the nose or mouth of a susceptible person with large-particle droplets (larger than 5 µm in size) containing microorganisms generated from a person who has a clinical disease or is a carrier of the disease. Droplets are generated from the source person primarily during coughing, sneezing, talking, and performance of certain procedures such as suctioning and bronchoscopy. Transmission of large-particle droplets requires close contact between source and recipient persons because droplets do not remain suspended in the air and generally travel only short distances (usually 3 feet or less). Special air handling and ventilation are not required to prevent droplet transmission because droplets do not remain suspended in the air. Droplet Precautions apply to any patient known or suspected to be infected with epidemiologically important pathogens that can be transmitted by infectious droplets."

> "Airborne droplet nuclei consist of small-particle residue (5 µm or smaller in size) of evaporated droplets that may remain suspended in the air for a long time. Airborne transmission occurs by dissemination of either airborne droplet nuclei or dust particles containing the infectious agent. Microorganisms carried in this manner can be widely dispersed by air currents and may be inhaled or deposited on a susceptible host from the source patient. Special air handling and ventilation are required to prevent airborne transmission. Airborne precautions apply to patients known or suspected to be infected with epidemiologically important pathogens that can be transmitted by the airborne route. Examples include measles (rubeola), varicella zoster virus infections, Legionella infection, disseminated zoster, and tuberculosis."

CDC Recommendations

The Center for Disease Control lists Ebola as a droplet disease.[4] In light of the recent outbreaks, the CDC in review of its isolation guidelines for both droplet diseases and airborne diseases, made one change. It recommended that any device that generated an aerosol have an exhalation filter in place.[4] The leading heated humidified ventilator circuits used in the US utilize a pass over system to humidify the gas in the form of molecular humidity. This does not create any aerosol particles. But nebulization of a medicine does create aerosol. This suggests that if an intubated patient on a ventilator is not receiving an aerosolized medicine there is no need to use an expiratory filter and it would not be outside of CDC guidelines. The CDC guidelines state; "although there are limited data available to definitely define a list of AGP's, procedures that are usually included are Bilevel Positive Airway Pressure (BiPAP), bronchoscopy, sputum induction, intubation and extubations and open suction of airways." This statement allows for futher inclusion and one could infer that the non-ventilated patients receiving aerosolized medicines use a system that incorporates an exhalation filter if the patient is in droplet isolation.[4] When it comes to airborne diseases, the most common one that Respiratory Therapists encounter is tuberculosis. In addition to placing a patient in a negative pressure room, it might be considered prudent to filter the ventilator expiratory flow. However, that is not part of the CDC guidelines, and failure to filter expiratory flow would not be out of the scope of the CDC guidelines.CDC airborne precautions require personnel to wear N95 filtration masks, so expiratory filtration would be redundant. If expiratory filtration is utilized, it requires monitoring of expiratory resistance and potential development of expiratory occlusion and autopeep.

Are all filters created equal?

Not necessarily says James Maguire, PHD, RCP, FCCP, Senior Scientist/Lecture for PALL Life Sciences.[5] When choosing to filter expiratory flow on a mechanical ventilator it is important to use a filter that is hydrophobic. Hydrophobic means that the filter repels water. If using a non-hydrophobic filter on the exhalation side of a ventilator, once humidity condenses onto the filter, it may lose its bacteriostatic properties. This is why ventilators that incorporate a heated exhalation filter on the ventilator must remain dry if they are not hydrophobic to retain bacteriostatic efficiency. When using a ventilator with a heated expiratory filter it is important to not get the filter material wet if a caregiver is draining the expiratory limb into the water trap. If the filter medium gets wet and it is not hydrophobic it may lose its bacteriostatic properties until the heat dries the filter medium. There are two types of hydrophobic filters available for ventilators that do not incorporate a heated exhalation filter, mechanical filters and electrostatic filters. According to Dr Maguire, mechanical filters incorporate multiple layers of filter medium precisely manufactured to eliminate the most common bacterial and viral agents. These types of filters can be distinguished by the many pleats seen inside the filter. Electrostatic filters have an electrical charge applied to the filter medium at the factory. This electrical charge attracts bacteria and viruses much the same way as when two magnets are attracted to each other, thus preventing bacteria from passing through the filter medium. But, Dr Maguire points out if an electrostatic charged filter gets wet and there are pressures as low as 10 cm H2O applied to the filter material, the electrostatic filter loses its bacteriostatic properties and allows infectious agents to pass right through the material. Mechanical ventilators routinely utilize pressures greater than 10 cm H2O.

Dr Maguire also pointed out that until very recently there were no ISO testing standards for bacteria/viral filter efficiency or how that efficiency was measured. Currently, there are several ways to test bacterial filter efficiency. Early ISO standards stated that a filter needed to pass a BFE-VFE (bacterial filtration efficiency-Viral filtration efficiency) rating of 99.99999% (There is disagreement as to if this accuracy rating can actually be achieved) or a NaCL test rating of 99.97%. What ISO did not state in detail though was how the testing should be performed. What does this mean to the caregiver? "In the typical testing for filter efficiency done by independent labs, which are commonly used by most filter manufactures, a polydispersed aerosol challenge is used. This means a carrier gas contains a range of aerosol sizes when used to challenge the filter. Usually, this aerosol challenge is made more meaningful by giving the Mass Median Aerodynamic Diameter (MMAD) of the aerosols used in the challenge. These polydispursed types of tests use aerosols that have a wide size range, meaning that the larger aerosols can carry quite a few of the test organisms. In these independent lab

tests, they often cite the size of the organism being tested, and it's usually 0.3 micron, or, for viral testing, it's 0.02 micron, but they fail to list the size of the actual aerosol that the filter is being tested against, and the MMAD, in both the test for bacteria, and the test for virus is around 3 micron, meaning that the test aerosol is at least a magnitude larger than the test organism. A monodispursed test requires that the filter be tested against an aerosol of a known size, and each aerosol is the stated size. The new ISO standard is a monodispursed test using a salt challenge of .3 micron. In our lab, we initially produce a polydispursed aerosol, then dry the aerosol by adding a sterile dry gas, which evaporates the liquid around the test organism, so that we test the filters against the organism itself, demonstrating the efficiency of the filters against a specific size organism, rather than testing against organisms contained in a rather large aerosol. Many HMEFs and filters also perform quite differently in a wet or humid environment, with electrostatic media potentially degraded in efficiency by these wet environments."

A Heat Moisture Exchange (HME) unit is also a bacterial filter, right?

Not necessarily. Unless a HME is specifically labeled as a bacterial filter/HME, it has no bacteriostatic properties. There are various named bacterial filter HME's on the market, DAR Mechanical filter HME, DAR Electrostatic HME (Covidien-Mansfield, MA), Ultipore 25, Ultipore 100 (PALL Corp.-Medical, Port Washington, NY), Humid-Vent (Teleflex, Research Triangle Park, NC) to name a few. It's also important to note that there are mechanical and electrostatic HME's and the filtering properties are the same as the non-HME filters. If you are uncertain if the HME you are using is also bacteriostatic, look for the filtering efficiency rating on the package insert or on the product website. If there is no rating, then most likely the HME is not bacteriostatic.

Protecting the ventilator vs. protecting the caregiver It is true that cities and countries are seeing more pandemic outbreaks and the medical community needs to be at the forefront of protecting not only it's workers but the public too. However, it is important to do the proper research and not rely on assumptions. Adding a high quality bacteriostatic filter to the expiratory limb of a mechanical ventilator nmay enhance caregiver protection with aerosol generating procedures but should never replace the CDC guidelines for airborne diseases. As of the publishing date of this article, neither the CDC nor the Canadian government has mandated the use of expiratory filters except in the case of aerosol generating procedures (AGP).[4] During the SARS crisis, the Ontario Ministry of health recommended the use of a pleated hydrophobic filter as a precaution, but the summary conclusion was that the outbreak was the result of failure to use N-95 or higher respirators. How many facilities have a policy of using a filtered handheld nebulizer when giving treatments to a non-vented isolation patient?

Every Respiratory Care department should have in place a policy stating how their particular brand of ventilator should be terminally cleaned after use on a patient with an infectious organism. With ventilators that have no direct communication internally on the expiratory side of the ventilator or have exhalation valve components that are easily removed, (Hamilton Medical, Drager, GE Carestation, Maquet Servo I) this should be a rather uncomplicated procedure. With ventilators utilizing an internal exhalation valve, (Covidien PB 7200, 840, 980, Carefusion Avea) this procedure might be more detailed and difficult, hence the use of a heated expiratory filter. Consult your hospital Infection Control department to see if having an expiratory filter alone is enough to qualify for "terminal cleaning" of the expiratory valve. Also remember when placing an expiratory filter in-line to be vigilant in assessing for increased expiratory resistance and the generation of autoPEEP.

Author's note – Attempts were made to contact a representative from Teleflex and Covidien for their input on this article but phone calls and emails were not returned. *Any opinions stated in this article are those of the author and do not necessarily reflect the opinion or policy of Hamilton Medical, Inc.

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   1) Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, Ontario
   2) Toronto Public Health, Toronto, Ontario
   3) Mount Sinai Hospital, Toronto, Ontario
   4) Centers for Disease Control and Prevention, Atlanta, Georgia
   5) North York General Hospital, Toronto, Ontario

4 www. cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html, Infection Prevention and Control Recommendations for Hospitalized Patients with Known or Suspected Ebola Virus Disease in US Hospitals.

5 James M. Maguire, Ph.D., RCP, FCCP, Senior Scientist/Lecturer, Pall Life SciencesSenior Consultant, VA Regional Medical Center, Dartmouth Alliance, President, New England Chapters, American College of Chest Physicians. Office: 802 649-2629.

Medical Devices and EMR Connectivity

Tim France, BS, RRT, Clinical Account Manager, Hamilton Medical, Inc.

In 2009, the United States government enacted the Health Information Technology for Economic and Clinical Health (HITECH) Act. This Act required the use of electronic medical records (EMR) in exchange for increased government healthcare payments.[1] It is mandatory by 2015 that all hospitals use electronic medical records as a way to chart and maintain patient information. Hospitals that do not use an EMR will be fined, and have government reimbursements reduced. Implementing an EMR, if done correctly, is a very costly and time-consuming process.[2] Health systems invest millions into the implementation of an EMR in the form of technology and human

labor, while still maintaining an out of date charting system at the same time.

Employing an EMR has many benefits. Clinical staff are able to document much more efficiently, physicians can order from anywhere, all patient information is accessible from one place and electronic devices can be connected and monitored via the hospital computer network. This article will focus on EMR and medical device connectivity.

Any medical device that either has an RS232 port or wireless capability can be connected to a hospital network. For the purposes of this article we will focus on mechanical ventilators. Ventilators, be it anesthesia machines or ICU ventilators are usually one of the first medical devices that are integrated into an EMR. Respiratory therapists and anesthesiologists monitor many data points and document these data points many times a day. Anesthesiologists sometimes may document every minute. The typical process is to download the data to the EMR, then review for accuracy at the bedside before accepting the data for permanent storage in the patients chart.

What crosses over to the chart can vary depending on the ventilator and the connectivity solution being used. The connectivity solution is what is placed between the device and the hospital network. This is often referred to as middleware. It allows the two to talk to each other. There are several connectivity solution vendors on the market. Some use hardware and software components, while others use software only to gain connectivity.[3] Choosing the right connectivity solution is key. It could mean the difference between downloading a few parameters, to downloading all the data points that are available from the device.

I have worked with the EPIC system for seven years and have witnessed many benefits. Documentation time has gone from minutes to seconds, and information is readily available at the bedside, which means decisions can be made and procedures performed more promptly. Alarms can also be integrated, so a patient can easily be monitored remotely. Also, data can be mined later for retrospective review and analysis.[4]

As with any change in work flow, the early stages can be painful. Clinicians transition from paper charting where everything is written down, to electronic charting. This can be a huge culture shock for many clinicians. Additionally, not all connectivity solutions work the same, or as well as others do, so choosing the right connectivity solution is key. Being able to only download some of the necessary parameters can be frustrating and diminish the potential gains in productivity and patient safety that comes with transitioning to an EMR. Also, making sure your medical device, ie ventilator, can actually transmit the data is most important. Not all ventilators can communicate with every connectivity solution. Ask the vendor for documentation on the capability of their ventilator to download data.

As mentioned earlier, I have worked with the EPIC (Verona, Wisconsin) system since 2008 with device integration starting in 2009. The connectivity solution we utilized was Capsule Technologie (Paris, France) utilizing the DataCaptor software. Our ventilators were HAMILTON-G5 and GALILEO (Bonaduz, Switzerland). All monitored and set parameters were able to download to the EMR seamlessly. I was able to view patient data from any web enabled computer after signing into my hospital account. This was particularly helpful when discussing complex patients remotely with bedside staff.

Utilizing an EMR has been mandated by the government. Hospitals that have transitioned to EMRs are realizing increases in staff productivity and improvements in patient care. Connecting medical devices offers improvements in patient safety. When deciding what connectivity solution to use, be sure to validate that your connectivity solution will work with the medical device, and that all necessary monitored data can be downloaded to the EMR.

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Using a Mathematical Model of Ventilation to Improve Outcomes for Patients with Traumatic Brain Injuries

Chris Campbell

For certain types of medical conditions, proper medical care can't always been planned out in advance. Case in point — a sudden accident that causes a traumatic brain injury (TBI). First responders such as paramedics or air medical personnel arrive on scene with little time to react to such a severe injury. Using ventilation to resuscitate someone who has suffered a TBI is being increasingly seen in the medical community as a vital part of the first-response process. The issue is how to provide first responders with the right training to ensure rescuers don't inadvertently hyperventilate during critical resuscitation — an action that can result in adverse outcomes. Math just might be the answer. New research has been released by D.P. Davis et al through the University of California at San Diego (Mathematical Model of Ventilation in TBI), which aims to improve the education and clinical practice of first responders, referred to as "prehospital providers."

D.P. Davis et al derived a mathematical model they wanted to apply to data collected in regards to ventilation used by paramedics and air medical personnel on TBI patients. The researchers described the problems faced by the TBI population: "the impact of hypocapnia on cerebral perfusion is well documented, and inadvertent hyperventilation as reflected by low end-tidal carbon dioxide (PetCO2) or arrival pCO2 values is associated with increased mortality.[2-4] The hemodynamic effects of PPV in the perfusing patient remain incompletely understood. Furthermore, the impact of excessively fast ventilation rates, independent of the effect on CO2 levels, is not well studied." The team's mathematical model is designed to "predict mean intrathoracic pressure (MITP) with various ventilation strategies during normo- and hypoperfusion states.[5] Here we apply physiological data collected during two prior investigations to this mathematical model to explore the possible hemodynamic impact of ventilation performed by paramedics and air medical personnel in TBI patients. We hypothesized that predicted MITP values would be excessive, driven largely by ventilation rates that are too high, particularly in providers less experienced with use of capnometry to guide ventilation."

Study Methods

The study worked as a retrospective observational analysis using data from two prior studies involving patients in California.[6,7]

As for data analysis, the researchers described the MITP formula as:

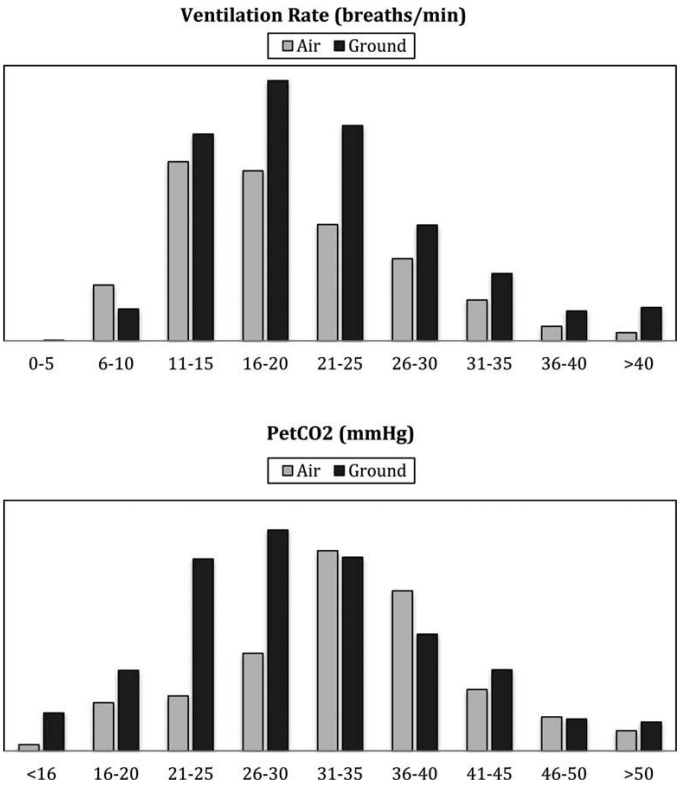

Figure 1. Distribution of ventilation rates (VR) and end tidal carbon dioxide (PetCO2) values in air medical and ground transport patients. Mean VR values were lower in air medical patients ($p < 0.01$), and mean PetCO2 values were higher in air medical patients ($p < 0.01$).

$$MITP = (VR \cdot (PPlat - PEEP) \cdot (2i + e)/120) + PEEP$$

As for the process, the study describes it as: "Plateau pressure (PPlat) was calculated as a function of volume from PEEP added to the tidal volume (VT). Various intrinsic lung characteristics can also be manipulated to simulate particular disease states. However, standard parameters were utilized for this analysis. As stated, the predictive intrathoracic pressure formula requires input of VR and VT, which was calculated using the following formula previously described by Davis and Davis in greater detail:[5]

$$VT = V/VR$$

where V is minute ventilation. The value for V was estimated from the following formula:

$$V = 6,000 \times 40/PaCO2$$

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where PaCO2 is the arterial carbon dioxide value, 40 mmHg represents a normal arterial CO2 (PaCO2) value, and 6,000 mL represents normal minute ventilation.

The value for PaCO2 was calculated from the formula:

$$PaCO2 = PetCO2 + D$$

where D represents the arterial-to-end-tidal CO2 gradient.

The value for D was estimated using two strategies. The first assumed a constant value of 4 mmHg based on established norms. The second strategy assumed an increasing value with higher VR values using the following equation:

$$D = 40 - 40^{*} (VT - 150)/VT$$

where VT represents tidal volume for various VR values, assuming a V = 6,000 mL. This equation accounts for the increasing proportion of dead space ventilation with faster ventilation rates. These two strategies are displayed in Figure 2. Reasoning behind the use of two equations is based on the desire to compare established normal gradients against values affected by changes in ventilation rate, which have been previously well described to affect outcome.[1] Ultimately, this allowed a VT value to be estimated for every data point using VR and PetCO2.

Polynomial regression was then used to generate a best-fit equation describing the relationship between VR and VT with "typical" ventilation for both air medical personnel and ground paramedics during their respective study periods. These equations were used to generate "typical" VT values through a range of values for VR. These VT values were then input into the previously described mathematical model to generate predicted mean intrathoracic pressure values at various VR values for both air medical and ground personnel. The distributions of VR, PetCO2, estimated VT, and MITP were presented graphically for both air medical and ground paramedic patients. In addition, air medical and ground paramedic patients were compared with regard to recorded PetCO2 and VR values as well as estimated values for VT and MITP using Student's t-test. StatsDirect (StatsDirect Software, Ashwell, UK) was used for all statistical calculations. Significance was assumed for a p-value less than 0.05."

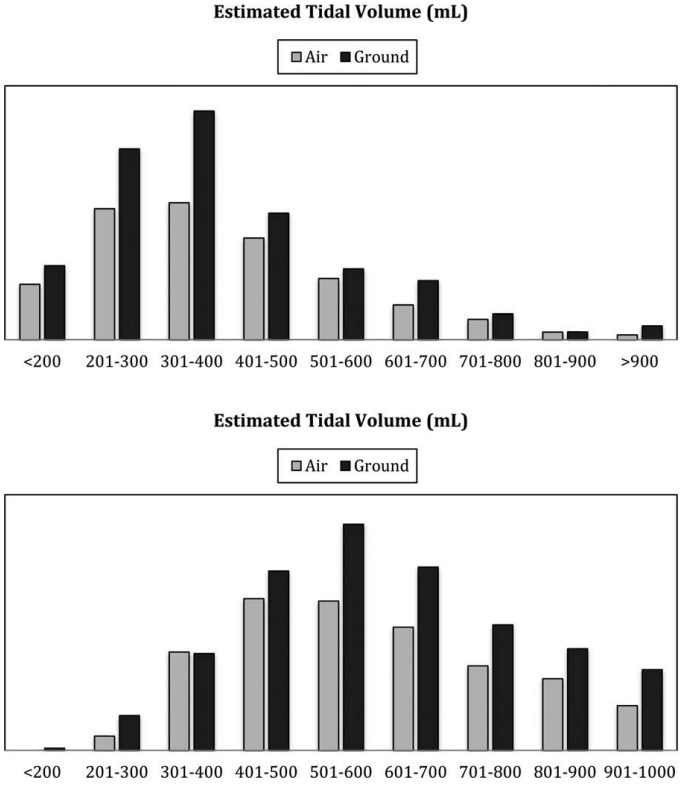

Figure 2. Estimated values for tidal volume (VT) assuming both fixed and variable arterial carbon dioxide- end tidal carbon dioxide (PaCO2 – PetCO2) differences. Estimated VT values assuming a fixed difference were not different between groups (p = 0.072). Estimated VT values assuming variable differences were lower for air medical patient (p < 0.01).

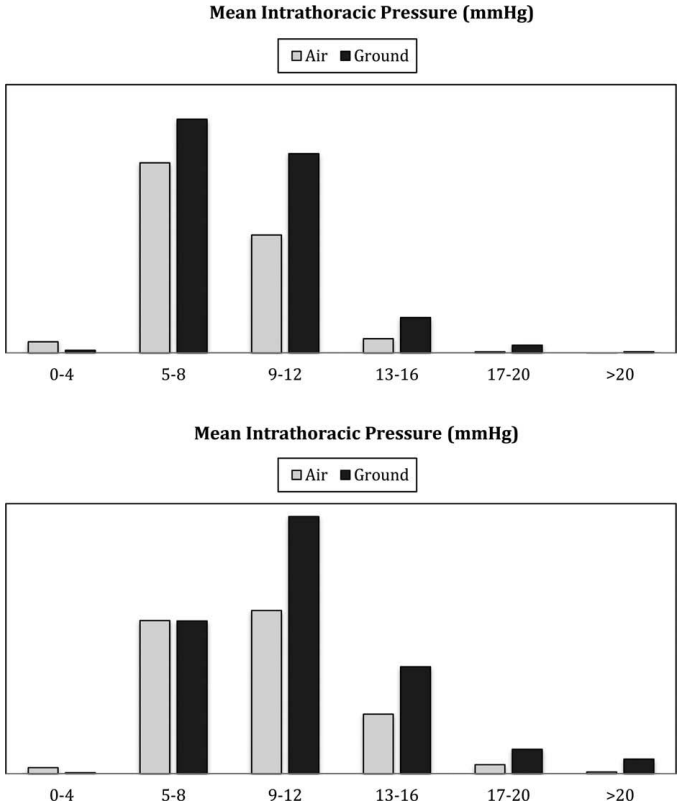

Figure 3. Predicted mean intrathoracic pressure (MITP) values for air medical and ground paramedic patients. Predicted MITP values were lower for air medical patients assuming either fixed (8.1 vs. 9.0 mmHg, p < 0.01) or variable (9.7 vs. 10.9 mmHg, p < 0.01) PaCO2 – PetCO2 differences.

Results

"Physiological data from 76 patients transported by ground paramedics with a total of 6,284 data points and 32 patients transported by air medical crews with 4,363 data points were included in this analysis. This represented a mean monitoring duration of 11 minutes for ground paramedic patients and 18 minutes for air medical patients.

The distribution of VR and PetCO2 values are displayed in Figure 1. Mean VR values were lower in air medical patients (19.7 vs. 21.6 breaths/min, p < 0.01), and mean PetCO2 values were higher in air medical patients (33.8 vs. 30.6 mmHg, p < 0.01). Estimated values for VT assuming both fixed and variable PaCO2–PetCO2 differences for air medical and ground paramedic patients are displayed in Figure 2. Mean estimated VT values assuming a fixed PaCO2–PetCO2 difference were not different between air

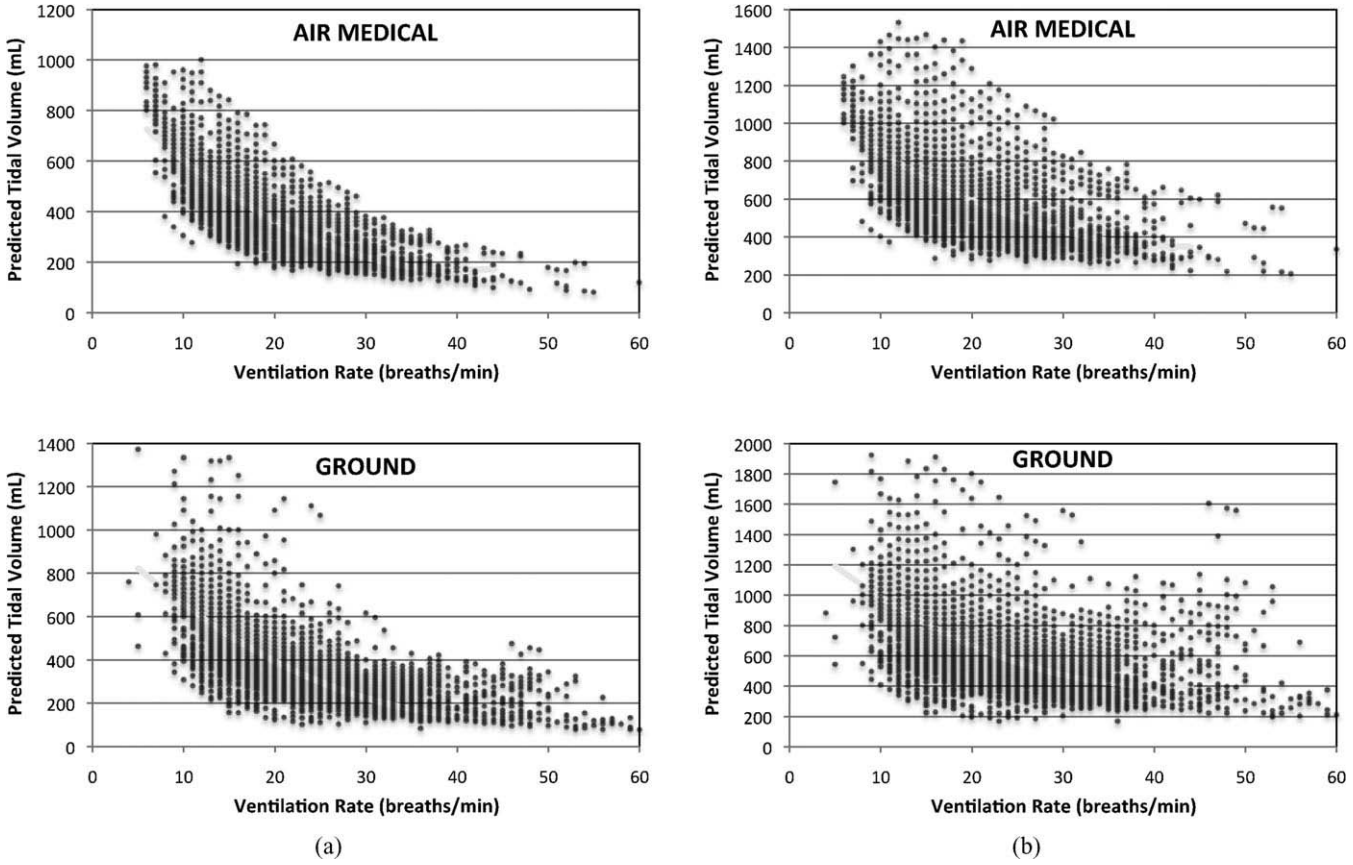

Figure 4. (a) Polynomial regression curve modeling ventilation rates (VR) against estimated tidal volume (VT) for ground paramedic and air medical patients assuming a fixed arterial carbon dioxide- end tidal carbon dioxide (PaCO2 – PetCO2) differences. (b) Polynomial regression curve modeling ventilation rate (VR) against estimated tidal volume (VT) for ground paramedic and air medical patients assuming variable arterial carbon dioxide- end tidal carbon dioxide (PaCO2 – PetCO2) differences.

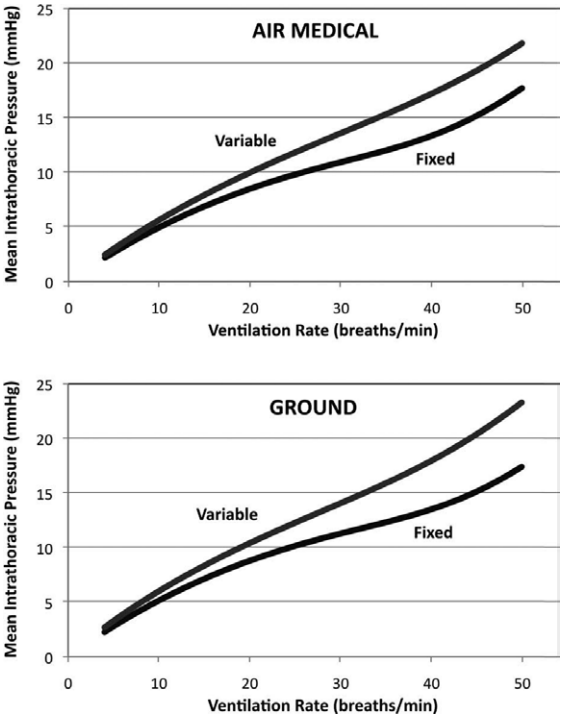

Figure 5. Polynomial regression curves modeling ventilation rate (VR) against predicted mean intrathoracic pressure (MITP) values for ground paramedic and air medical patients assuming both fixed and variable arterial carbon dioxide- end tidal carbon dioxide (PaCO2 – PetCO2) gradients.

medical and ground paramedic patients (392 vs. 399 mL, p = 0.072). Mean estimated VT values assuming a variable PaCO2–PetCO2 difference were lower for air medical versus ground paramedic patients (636 vs. 688 mL, p < 0.01). Predicted MITP values for air medical and ground paramedic patients are displayed in Figure 3.

Predicted MITP values were lower for air medical versus ground patients assuming either fixed (8.1 vs. 9.0 mmHg, p < 0.01) or variable (9.7 vs. 10.9 mmHg, p < 0.01) PaCO2–PetCO2 differences.

Polynomial regression curves modeling VR against estimated VT for ground paramedic and air medical patients are displayed in Figure 4. Polynomial regression curves modeling VR against predicted MITP values for ground paramedic and air medical patients are displayed in Figure 5."

Conclusions

Ultimately, D.P. Davis et al saw enough progress to warrant further study. "Our preliminary report on retrospective data using a novel mathematical model demonstrated that the use of PPV with high respiration rates without the proper adjustments to tidal volume was associated with elevated MITP in two separate EMS systems. Further study should be done to externally validate this model in a larger multicenter prospective analysis. This model has potential implications for the education and clinical practice of prehospital providers."

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Spotlight On Oximetry…continued from page 19

oximetry, established by the United States Department of Health and Human Services: Screening should be performed with pulse oximeters that are motion tolerant, report functional oxygen saturation, have been validated in low perfusion conditions, have been cleared by the FDA for use in newborns and have an accuracy of ±2 digits.[1]

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What type of training and user support programs do you offer?

Through the Professional Affairs and Clinical Education (PACE) Online Platform, (www.covidien.com/PACE), Covidien offers a variety of free, clinical and non-clinical education modules online, including courses intended to develop clinician understanding of pulse oximetry technology, CCHD screening, and initiatives in patient care. Covidien is committed to promoting CCHD awareness activities to ensure clinicians understand how to use pulse oximeters to generate reliable readings. In fact, Covidien offers specific education about recommendations for early screening and monitoring for congenital heart disease in infants. Additionally, Covidien offers complimentary in-servicing and on-site clinical support for customers.

Discuss the cost of your oximetry products.

Pricing is generally structured with multiple pricing tiers based on a customer's commitment/compliance levels within their Group Purchasing Organization or Integrated Delivery Network contract arrangements. Other good information: Monitoring a wide range of critical respiratory parameters, the Sensing Systems of Covidien help caregivers provide faster, more informed interventions for their patients.

The above information provided by Nicole Malcolmson, Senior Product Manager, Covidien.

High-Flow Nasal Cannula Oxygen Versus Non-Invasive Ventilation in Patients with Acute Hypoxaemic Respiratory Failure Undergoing Flexible Bronchoscopy – A Prospective Randomised Trial

Marcel Simon, Stephan Braune, Daniel Frings, Ann-Kathrin Wiontzek, Hans Klose, Stefan Kluge

Abstract

Introduction: Critically ill patients with respiratory failure undergoing bronchoscopy have an increased risk of hypoxaemia-related complications. Previous studies have shown that in awake, hypoxaemic patients non-invasive ventilation (NIV) is helpful in preventing gas exchange deterioration during bronchoscopy. An alternative and increasingly used means of oxygen delivery is its application via high flow nasal cannula (HFNC). This study was conducted to compare HFNC with NIV in patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy.

Methods: Prospective randomised trial randomising 40 critically ill patients with hypoxaemic respiratory failure to receive either NIV or HFNC during bronchoscopy in the intensive care unit.

Results: After the initiation of NIV and HFNC, oxygen levels were significantly higher in the NIV group compared to the HFNC group. Two patients were unable to proceed to bronchoscopy after the institution of HFNC due to progressive hypoxaemia. During bronchoscopy, one patient on HFNC deteriorated due to intravenous sedation requiring non-invasive ventilatory support. Bronchoscopy was well tolerated in all other patients. There were no significant differences between the two groups regarding heart rate, mean arterial pressure and respiratory rate. 3 patients in the NIV group and 1 patient in the HFNC group were intubated within 24 hours after the end of bronchoscopy ($p = 0.29$).

Conclusions: The application of NIV was superior to HFNC with regard to oxygenation before, during and after bronchoscopy in patients with moderate to severe hypoxaemia. In patients with stable oxygenation under HFNC, subsequent bronchoscopy was well tolerated.

Introduction

Flexible bronchoscopy (FB) is a frequently performed procedure for the assessment, diagnosis, and treatment of patients with respiratory disease in the intensive care unit (ICU). The procedure and applications of FB have progressively evolved and expanded since it was first introduced in 1968 and it is now well established as an integral diagnostic and therapeutic tool in respiratory and critical care medicine [1,2].

While bronchoscopy is generally considered a safe procedure [3], it is well known that critically ill patients undergoing bronchoscopy are at an increased risk for complications, most of all the deterioration of pre-existing hypoxaemia [4].

Few randomised controlled studies and case series have shown that the use of continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) is superior to conventional means of oxygen delivery in patients with hypoxaemia in terms of preventing deterioration of gas exchange during bronchoscopy [5-12].

High flow nasal cannula (HFNC) oxygen utilizes higher gas flow rates than conventional low flow oxygen systems. Oxygenation via HFNC is increasingly applied in adult ICU patients with acute hypoxaemic respiratory failure as an alternative to NIV [13]. The devices used deliver heated and humidified oxygen at a flow of up to 60 liters per minute via nasal

cannulas. This results in effective and sustained improvement in respiratory parameters in patients with acute hypoxaemic respiratory failure by several mechanisms [14].

In a pilot study, Lucangelo et al. found that HFNC improves oxygenation in patients undergoing bronchoscopy [15]. However, the patients investigated were not hypoxaemic and there was no comparison with NIV. Therefore, we conducted this prospective randomised trial comparing HFNC with NIV in patients with acute hypoxaemic respiratory failure undergoing FB to assess the ability to maintain oxygen saturation during bronchoscopy as well as changes in blood gases and outcome following bronchoscopy.

Methods

Study design

The study was conducted as a prospective randomised trial. All patients admitted to the Department of Intensive Care Medicine at the University Medical Centre Hamburg- Eppendorf were eligible for study inclusion. Prior to enrolment, all participants or their legal representatives gave written informed consent. The study was approved by the ethics committee of the chamber of

The authors are with The Department of Intensive Care Medicine, University Medical Centre Hamburg- Eppendorf, Martinistr. Department of Respiratory Medicine, University Medical Centre Hamburg.

physicians in Hamburg, Germany, and the trial was registered at ClinicalTrials.gov (registration number NCT01870765, registration date 30 May 2013).

Study population

Medical and surgical patients treated in one of the 10 departmental ICUs were enrolled. Inclusion criteria were 1) respiratory failure with hypoxaemia defined as PaO2/FiO2 below 300 mm Hg, 2) indication for diagnostic and/or therapeutic FB, 3) age 18 years or above and 4) informed consent. Exclusion criteria were 1) contraindications for NIV or HFNC, 2) nasopharyngeal obstruction or blockage, 3) indication for intubation and 4) pre-existing invasive ventilation.

Simplified acute physiology scores II (SAPS II) were calculated according to standard criteria [16]. Immunosuppression was defined as a neutrophil count of less than 1000/mL, immunosuppressive medication, chemotherapy within the last 60 days or acquired immunodeficiency syndrome.

Study protocol

After enrolment, patients were randomised to receive either NIV or HFNC. Randomisation was accomplished by computer-generated random number sequence and the allocation sequence was concealed from the study team enrolling and assessing participants by using numbered, opaque and sealed envelopes.

Arterial blood gases were drawn from a catheter in the radial or femoral artery at baseline, 15 minutes after the institution of NIV or HFNC, after 5 minutes on FiO2 1.0 just before the start of bronchoscopy, at the end of bronchoscopy as well as 10, 20, 30, 40 and 50 minutes after the completion of bronchoscopy. Blood pressure, heart rate, respiratory rate and oxygen saturation recorded by pulse oximetry (SpO2) were monitored constantly throughout this period. For details on study workflow see the flow diagram in Figure 1.

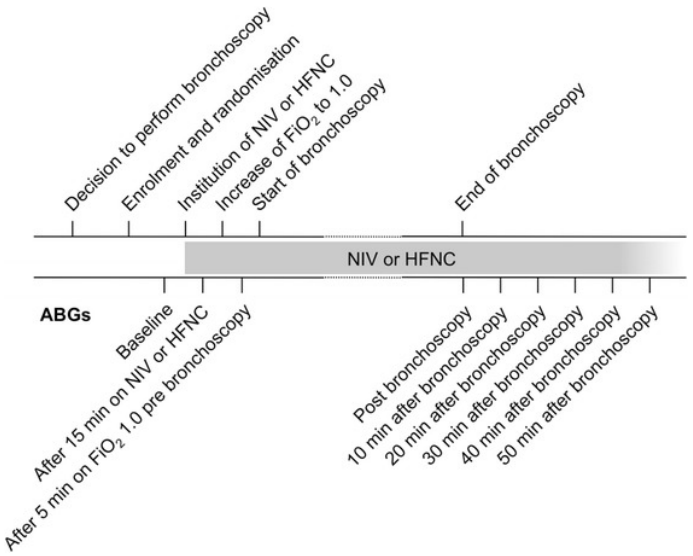

Figure 1. Study workflow. Abbreviations: ABG, arterial blood gas analysis; FiO2, fraction of inspired oxygen; HFNC, high flow nasal cannula; NIV, non-invasive ventilation.

Non-invasive ventilation (NIV)

NIV was administered using ICU ventilators in NIV mode (CarinaTM or Evita Infinity V500TM, Dräger, Germany). A full face mask (Medisize, Neunkirchen-Seelscheid, Germany) secured with elastic banding was used as interface. A swivel connector was inserted between mask and ventilator tubing to allow for the insertion of the bronchoscope. The ventilator mode was set to pressure support mode or pressure controlled mode. Positive end-expiratory pressure (PEEP) was set between 3 and 10 cm H2O and inspiratory pressures between 15 and 20 cm H2O to achieve adequate oxygenation and ventilation. The adjustment of ventilator settings was left to the discretion of the treating intensivist.

High flow nasal cannula (HFNC) oxygen

To deliver high flow oxygen, an OptiflowTM system with a medium size adult nasal cannula as patient interface (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) was used in all cases. The oxygen flow was set to 50 liters per minute.

Flexible bronchoscopy (FB)

All bronchoscopies were performed by experienced pulmonologists. The decision to perform bronchoscopy was not part of the study and was left to the discretion of the treating intensivist. The FiO2 was increased to 1.0 prior to the start of bronchoscopy and adjusted to maintain an arterial oxygen saturation of more than 90% after the completion of bronchoscopy. A flexible bronchoscope (BF-P60TM, Olympus, Japan) passed through the mouth was used for all procedures. The setup using NIV or HFNC is illustrated in Figure 2. Intravenous sedation was achieved in a standardised manner using repetitive bolus applications of 10 to 20 mg of propofol every two to three minutes. Topical anaesthesia was applied to the nasal and pharyngeal mucosa using lidocain gel and spray and to the tracheobronchial mucosa using 5 mL of lidocain 0.8% applied through the working channel of the bronchoscope in aliquots of 1 mL. After inspection of the tracheobronchial tree, the bronchoscope was wedged in the appropriate subsegmental bronchus. Broncho-alveolar lavage (BAL) was performed using normal saline being instilled in aliquots of 20 mL and then aspirated. The number and type of diagnostic tests ordered determined the amount of fluid required. Depending on the underlying condition, BAL fluid was sent for cytological or microbiological analyses. The duration of bronchoscopy was defined as the time between insertion and removal of the bronchoscope from the tracheobronchial tree.

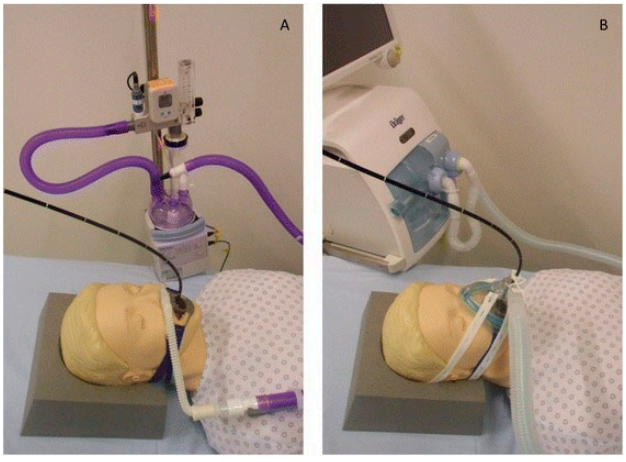

Figure 2. Illustration of bronchoscopy using HFNC (A) or NIV (B). Abbreviations: HFNC, high flow nasal cannula; NIV, non-invasive ventilation.

Outcome parameters

Primary outcome parameter was the lowest oxygen saturation recorded by pulse oximetry during FB. Secondary outcome

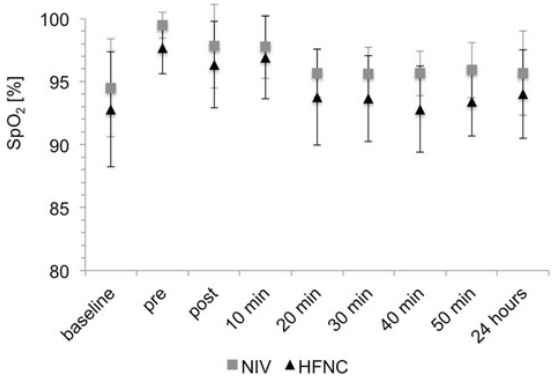

Figure 3. SpO2 at baseline, pre and post bronchoscopy. Changes in SpO2. Values are given as mean and standard deviation. Abbreviations: HFNC, high flow nasal cannula; NIV, non-invasive ventilation; SpO2, oxygen saturation recorded by pulse oximetry.

parameters were 1) changes in blood gases for up to 50 minutes after the procedure and 2) the requirement for intubation within 8 hours of completion of FB and at any other point during ICU stay. Intubation was considered a complication possibly related to bronchoscopy, if it occurred within 8 hours of the procedure. This time frame was adopted from previous studies [7,17,18]. The decision to intubate was left to the discretion of the treating intensivist in accordance with published guidelines [19]. Sample size was calculated to allow the detection of a 3% difference in minimal oxygen saturation during FB assuming an alpha risk of 0.05 and a power of 0.8.

Statistical analysis

Results are presented as absolute numbers and percentages, as mean and standard deviation for continuous data if normally distributed and as median and range if not normally distributed. Comparison between the two groups was performed using the t test or the Mann- Whitney U test for metric data and the chi-square test for categorical data. A two-sided p value of less than 0.05 was considered to be significant. The software used for descriptive analyses was SPSS (version 20.0, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Between July 2013 and December 2013, 44 patients met inclusion criteria and were found eligible to participate in the study. Of these, two patients declined informed consent. Two patients who were randomised to receive HFNC were unable to proceed to bronchoscopy after the institution of HFNC due to progressive hypoxaemia requiring the initiation of NIV: one patient who had previously been breathing spontaneously on HFNC deteriorated due to the retention of secretions, the other patient who had been on NIV deteriorated when transferred to HFNC. Eventually, 40 patients were enrolled in the study and were randomised to undergo FB while on HFNC or on NIV.

Mean PaO2/FiO2 at baseline was 138 ± 69 mm Hg in the HFNC group and 163 ± 64 mm Hg in the NIV group (p = 0.25). Mean PaCO2 levels at baseline were significantly higher in the NIV group (43 ± 13 mm Hg) than in the HFNC group (34 ± 6 mm Hg) (p = 0.01). Table 1 provides further details on patient characteristics.

Tolerance of the procedure

The lowest SpO2 during bronchoscopy was 95 ± 5 % in the NIV group and 92 ± 7 % in the HFNC group (p = 0.07). At the pre-defined time points during the 50 minutes of follow-up as well as at 24 hours after the completion of bronchoscopy, no SpO2 of less than 85% was registered in any of the two groups. SpO2 values before and after bronchoscopy are shown in Figure 3.

A significant increase in PaO2/FiO2 after 15 minutes on NIV compared to baseline (p = 0.04) was observed in the NIV group, while there was no significant change in PaO2/FiO2 in the HFNC group (p = 0.96). Comparing the two groups after 15 minutes on NIV or HFNC, PaO2/FiO2 was significantly better in the NIV group (p = 0.002). This difference in oxygenation was preserved throughout bronchoscopy and during the 50 minutes of follow-up. There were no significant differences between the two groups concerning respiratory rates and the course of PaCO2 values. At 24 hours after the completion of bronchoscopy, there was no significant difference between the two groups concerning PaO2/FiO2 (p = 0.29) or any of the other recorded parameters. Figure 4 shows PaO2/FiO2 and PaCO2 before and after bronchoscopy.

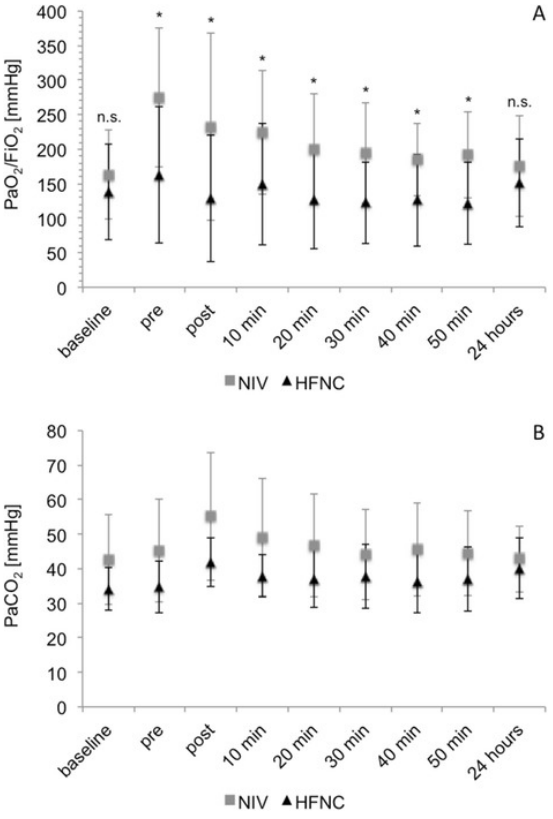

Figure 4. PaO2/FiO2 and PaCO2 at baseline, pre and post bronchoscopy. Changes in PaO2/FiO2 (A) and PaCO2 (B). Values are given as mean and standard deviation. * p < 0.05; n.s. not significant. Abbreviations: FiO2, fraction of inspired oxygen; HFNC, high flow nasal cannula; NIV, non-invasive ventilation; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood.

One patient in the HFNC group deteriorated after the application of intravenous sedation resulting in apnea while on HFNC requiring transitioning to NIV. Subsequent bronchoscopy was completed without further incident. Bronchoscopy was well tolerated by all other patients. The average duration of bronchoscopy was 5.0 ± 2.7 minutes in the HFNC group and 5.5 ± 1.9 minutes in the NIV group (p = 0.56). Concerning the total amount of propofol used for sedation, there was no significant difference between the NIV group (74 ± 36 mg) and the HFNC

Table 1 Patient characteristics

	NIV	HFNC	*P* value
Total number of patients	20	20	
Gender			
Male	13 (65%)	11 (55%)	0.52
Female	7 (35%)	9 (45%)	
Age (years)	68 ± 11	64 ± 12	0.28
SAPS II score	46 ± 10	43 ± 13	0.39
Thrombocytopenia (<50 Mrd/L)	3 (15%)	5 (25%)	0.43
Immunosuppression	8 (40%)	5 (25%)	0.31
Use of vasopressors	10 (50%)	10 (50%)	1.00
Antibiotic therapy	17 (85%)	19 (95%)	0.29
Antimycotic therapy	5 (25%)	6 (30%)	0.72
Antiviral therapy	3 (15%)	7 (35%)	0.14
Main diagnosis			
Haematological disorder	4 (20%)	7 (35%)	0.29
Sepsis	4 (20%)	3 (15%)	0.68
Lung cancer	2 (10%)	3 (15%)	0.63
Extrapulmonary solid cancer	2 (10%)	3 (15%)	0.63
Liver cirrhosis	1 (5%)	1 (5%)	1.00
Trauma	1 (5%)	1 (5%)	1.00
Interstitial lung disease	1 (5%)	1 (5%)	1.00
Alveolar haemorrhage	1 (5%)	0	0.31
Community-acquired pneumonia	1 (5%)	0	0.31
Chronic obstructive pulmonary disease	1 (5%)	0	0.31
Pulmonary arterial hypertension	1 (5%)	0	0.31
Acquired immunodeficiency syndrome	0	1 (5%)	0.31
Ileum perforation	1 (5%)	0	0.31
Indication for bronchoscopy			
Hospital-acquired pneumonia	10 (50%)	14 (70%)	0.50
Community-acquired pneumonia	5 (25%)	3 (15%)	
Suspected retention of secretions	3 (15%)	2 (10%)	
Suspected interstitial lung disease	1 (5%)	0	
Suspected alveolar haemorrhage	1 (5%)	0	
Suspected malignancy	0	1 (5%)	
Therapy at baseline			
Low-flow oxygen via nasal cannula	5 (25%)	2 (10%)	0.23
Low-flow oxygen via face mask	1 (5%)	3 (15%)	
HFNC	9 (45%)	13 (65%)	
NIV	5 (25%)	2 (10%)	
Physiological parameters at baseline			
Heart rate (beats/min)	95 ± 14	101 ± 15	0.27
Mean arterial pressure (mm Hg)	85 ± 11	82 ± 14	0.56
Respiratory rate (breaths/min)	30 ± 8	30 ± 9	0.86
PaO_2/FiO_2 (mm Hg)	163 ± 64	138 ± 69	0.25
$PaCO_2$ (mm Hg)	43 ± 13	34 ± 6	0.01
pH	7.43 ± 0.11	7.46 ± 0.07	0.21

Values are given as mean and standard deviation or as numbers and percentages. FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; SAPS II, simplified acute physiology score II.

group (96 ± 59 mg) (p = 0.24). A BAL was performed in all cases. The amount of BAL fluid instilled was not significantly different between the two groups (p = 0.92).

There were no significant differences between the two groups at any of the pre-specified time points with regard to heart rate and mean arterial pressure.

Patients who were on low flow oxygen therapy at baseline and were randomised to undergo bronchoscopy under NIV, stayed on NIV for a median duration of 20 minutes (range 0 to 9 hours) after the end of bronchoscopy, while patients who were randomised to undergo bronchoscopy under HFNC, stayed on HFNC for a median duration of 7.8 hours (range 1.5 to 103 hours) after the end of bronchoscopy (p = 0.04).

Outcome

One patient in the HFNC group required intubation immediately after the completion of bronchoscopy. He had exhibited the lowest PaO2/FiO2 value (64 mm Hg) of all patients at baseline. None of the other patients in the two groups required intubation within the pre- defined period of 8 hours after the end of bronchoscopy (p = 0.31). During the following course of their ICU stay, 13 patients (65%) in the NIV group and 9 patients (45%) in the HFNC group required intubation (p = 0.20). Overall, 3 patients in the NIV group and 1 patient in the HFNC group were intubated within 24 hours after the end of bronchoscopy (p = 0.29). On average, intubation was performed 59 hours (range 9 to 391 hours) after the completion of bronchoscopy in the NIV group and 75 hours (range 0 to 338 hours) in the HFNC group (p = 0.54). In all these cases intubation was due to progression of the underlying disease and not a consequence of the bronchoscopic procedure. 28-day mortality was 40% in the NIV group and 65% in the HFNC group (p = 0.11).

Discussion

In this randomised study, NIV was superior to HFNC with regard to maintaining adequate oxygenation before, during and after bronchoscopy in patients with acute hypoxaemic respiratory failure. In two patients transition to HFNC was impossible due to progressive hypoxaemia. FB was well tolerated and was not associated with complications.

To our knowledge, this is the first study comparing HFNC with NIV in hypoxaemic patients undergoing FB. Only two previous reports have assessed the use of HFNC for bronchoscopy. Lucangelo et al. compared three groups of patients with mild hypoxaemia undergoing bronchoscopy while being on different types of oxygen supplementation [15]. At the end of bronchoscopy, oxygenation was significantly better in patients receiving HFNC with a high flow rate of 60 liters per minute compared with HFNC with a lower flow rate of 40 liters per minute or oxygen administration through a Venturi mask. Lomas et al. reported the case of a patient with myasthenia gravis and severe acute respiratory failure due to bilateral atelectasis who underwent successful bronchoscopy using HFNC [20].

The concept of high flow oxygen originates from the treatment of premature infants as an alternative to nasal CPAP [21,22]. Due to the ease of application, simplicity and good patient tolerance, HFNC is increasingly used in adult patients with acute hypoxaemic respiratory failure as an alternative to NIV [13]. It has also been shown, that HFNC is better tolerated and more comfortable than oxygen applied via face mask [23]. In addition, the use of this technique has been described as means for pre-oxygenation before intubation [24], in the post-extubation period [25], in patients with do-not-intubate order [26], in the palliative care setting [27], in the emergency department [28] and

in patients with heart failure [29]. Most of these observational studies showed beneficial effects of HFNC compared with conventional oxygen therapy in terms of improved symptoms (dyspnea score), respiratory rate and oxygenation. In one of the few randomised studies, the authors compared HFNC with standard low flow oxygen therapy in patients with mild to moderate hypoxaemic respiratory failure. Significantly more HFNC patients succeeded with their allocated therapy and also had significantly fewer desaturations [30]. However, in relation to its widespread use, there is still little evidence concerning the risks and benefits of this new technology. Moreover, most studies are lacking clinical outcome data and assessment of long-term effects [31].

A number of physiological effects of HFNC have been described. These include the washout of pharyngeal dead space, reduction of airway resistance, increase in end-expiratory lung volume and generation of positive airway pressure [13,14,31]. In our study, after the initiation of NIV or HFNC, oxygenation was significantly better in the NIV group than in the HFNC group ($p = 0.002$). This can at least in part be explained by higher positive airway pressures generated by NIV [32]. Positive airway pressures with HFNC have been documented. In line with other researchers, Parke et al. found a positive linear relationship between oxygen flow and airway pressure. In the study on ICU patients, a significant difference in the degree of positive airway pressure was seen dependent on whether the person's mouth was open or closed: a mean positive airway pressure of 2.7 cm H2O was reported with the mouth closed, while it was only 1.2 cm H2O with the mouth open [33]. Accordingly, in a study on healthy volunteers, a median positive airway pressure of 7.4 cm H2O was observed with the mouth closed, while it was 2.7 cm H2O with the mouth open [34]. Patients with more severe acute respiratory distress may have more inconsistent airway pressures due to their breathing through an open mouth. A fundamental difference between HFNC and NIV is the fact, that HFNC systems maintain a fixed flow and generate variable pressures, whereas many NIV systems generate a fixed pressure by utilizing variable flow [13]. In contrast to the NIV group, where the average PEEP was 5.4 cm H2O, it can be assumed that no relevant PEEP levels were achieved in the HFNC group due to the procedure-related open mouth. This is most likely the main reason for the differences observed in oxygenation between the two groups.

In addition to hypoxaemia, bronchoscopy can be associated with hypercapnia and side effects of sedation. This happened in one case in our study where the need for NIV was due to intravenous sedation. A recent multi-centre study investigating 169 bronchoscopies in spontaneously breathing hypoxaemic patients showed that one third of cases were complicated by an increased need for ventilatory support [12]. Thus, in patients with ventilatory failure (primary ventilatory pump failure or secondary due to sedation) support or maintenance of ventilation by NIV seems advantageous in comparison to HFNC.

The following methodological limitations need to be considered: First, despite randomisation baseline PaCO2 levels were higher in the NIV group. However, subsequent changes in PaCO2 over time were similar in both groups. Second, our results are only applicable to populations with similar characteristics. It is therefore important to note that most critically ill patients in this study had moderate to severe hypoxaemic respiratory failure, high SAPS II values and vasopressor support.

Although oxygenation levels were lower in the HFNC group, all patients who were stable on HFNC for 15 minutes, tolerated subsequent bronchoscopy well. A significant difference concerning the need for intubation between the two groups could not be detected. However, this study was not powered to answer this question and further studies including more patients are needed to assess this topic. Thus, patients stable on HFNC may undergo bronchoscopy without the need for transitioning to NIV. This may facilitate the procedure for ICU staff and provide improved patient comfort due to the avoidance of the potentially unpleasant experience of NIV. The fact that patients on low flow oxygen therapy at baseline remained on HFNC significantly longer than on NIV after the end of bronchoscopy, may be due to improved patient comfort under HFNC. However, this study was not designed to assess this question. Since no benefits for HFNC over NIV for bronchoscopy in hypoxaemic patients have been shown so far and HFNC therapy is at least in our setting associated with higher costs for disposables compared with NIV, assessment of patient comfort should also be a key element in further studies. Considering the improved oxygenation capacity of NIV in comparison with HFNC, we believe that patients with severe hypoxaemia should preferably undergo bronchoscopy using NIV. Intubation prior to bronchoscopy should be considered in patients with most severe hypoxaemia.

Conclusions

In conclusion, the results of this study suggest, that in awake, critically ill patients with moderate to severe hypoxaemia undergoing bronchoscopy, the application of NIV was superior to HFNC regarding oxygenation before, during and after the procedure. However, in patients who were stable on HFNC, bronchoscopy was well tolerated using HFNC.

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Ventilatory Function and Cardiovascular Disease Risk Factors: A Cross-Sectional Study in Young Adults

Vanessa Garcia-Larsen, Patricia Bustos, Hugo Amigo, James Potts and Roberto J Rona

Abstract

Background: The association between impaired lung function and cardiovascular disease (CVD) risk factors has been shown in adults. However, there is little evidence of such an association in young adults, particularly from South America, where the burden of CVD and chronic obstructive pulmonary disease (COPD) is as high as that observed in more developed countries. We therefore investigated the relation between CVD risk factors including metabolic syndrome (MS), and lung function status in young adults from Chile.

Methods: 970 subjects from a sample of 998 adults born between 1974 and 1978 in Limache, Chile, were studied. A Spanish translation of the European Community Respiratory Health Survey (ECRHS) questionnaire was used.

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured. Weight, height, waist circumference (WC), blood pressure, Homeostatic model assessment (HOMA-IR), triglycerides, high density lipoprotein (HDL), glycaemia, and metabolic syndrome (MS) were also assessed.

Results: The prevalence of MS was 11.8%. A lower FEV_1 and lower FVC were associated with having MS (β-coefficient -0.13; 95% Confidence Interval [CI] -0.21 to -0.05, and β-coefficient -0.18; 95% CI -0.27 to -0.09, respectively). Both spirometric measures were also negatively associated with having an elevated HOMA-IR (β-coefficient for FEV_1 -0.08; 95% CI -0.13 to -0.03, and β-coefficient for FVC -0.11; 95% CI -0.17 to -0.05). In males only, a lower FEV_1 and FVC were associated with having elevated triglycerides (β-coefficient highest vs. lowest tertile -0.13, 95% CI -0.24 to -0.03, and β-coefficient -0.13, 95% CI -0.25 to -0.01, respectively). In women, a higher FEV_1 and FVC were statistically significantly related to having higher levels of HDL. Ventilatory function was unrelated to hypertension or WC in this population.

Conclusion: In this population-based study of young adults, a poorer ventilatory function was associated with many CVD risk factors. Endeavours to understand better causality issues of such associations are warranted.

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Background

Poor lung function, usually defined as low forced expiratory volume in one second (FEV_1) is a known risk factor for all-cause mortalities including respiratory and cardio-vascular mortality [1].

Abdominal adiposity, insulin resistance, impaired glucose metabolism, hypertension and dyslipidaemia are known early markers of cardiovascular diseases (CVD) [2,3]. Having three or more of these risk factors leads to metabolic syndrome (MS), a marker of systemic inflammation and a strong risk factor of CVD [3]. MS is a comorbidity factor in as many as 50% of patients with COPD [4]. It has been proposed that Type 2 Diabetes Mellitus (T2DM) may act as an independent factor, negatively affecting pulmonary structure and function, increasing risk of pulmonary infections, disease exacerbations and worsened COPD outcomes [5]. Risk factors of CVD are frequently altered in childhood and adolescence [2]. However, the effect that this pattern might have in triggering the decline in ventilatory function has not yet been investigated in young individuals.

T2DM, MS and hypertension are usually silent and under-diagnosed conditions, especially in their early stages. Most of the evidence on the association between ventilatory function and risk factors of CVD comes from middle age and older adults, where there is increasing evidence of the detrimental effect that higher body fat and lower muscle mass have on the rate of lung function decline [6]. The aim of our study was to investigate the association between ventilatory function in young adults and risk factors of CVD, including MS.

Methods

Setting and sample

The study took place in Limache and Olmue, situated in the Central valley of Chile, 141 km from, Santiago, with a population of 50,000 inhabitants. Agriculture, and more recently 'agro-tourism' are the main economic activities in the area. This study is part of a non-concurrent longitudinal study aimed to assess risk factors in early childhood and in young adults for asthma and poor lung function [7]. A simple random sample of 1,232 subjects was obtained for our initial respiratory disease study based on statistical power estimates

using the effects of birth weight differences on lung function as outcome for the respiratory study. For the cardiovascular study, a sample of 998 out of the 1,232 participants were studied based also on statistical power estimates and the resource implications of tracing the subjects already studied in the respiratory study which started a year earlier. Those who could not be included in the study because of death (3.2%, mostly related to maternal and infancy deaths in the early 70s), emigration (11.3%), serving a custodial sentence, disability or lactation (3.3%) and unwillingness to participate (7%) were randomly replaced using the same sampling frame [7].

Lung function measurement

An adapted and translated version of the European Community Respiratory Health Survey (ECRHS) questionnaire was used to ascertain information on exposure to risk factors related to poor lung function [8]. FEV_1 and forced vital capacity (FVC) were measured by trained nurses, using a Vitalograph device model 2120 Spirotrac IV. The nurses were unaware of the hypothesis being tested to minimise the risk of bias. These measurements were performed according to the recommendations from the American Thoracic Society (1987) because in Chile reference values have been published using these recommendations [9]. Any participant who was unable to produce two technically satisfactory manoeuvres after eight attempts was excluded from the study. Consequently, nine participants were removed from the study. The highest value for FEV_1 and FVC produced in up to five satisfactory measures was used in the analyses. The FEV_1/FVC ratio was also calculated. We used the National Health and Nutrition Examination Survey (NHANES) III prediction equations for white populations to estimate the lower limit of normal (LLN) of each spirometric measurement, which are calculated according to each individual's age and sex [10]. We calculated the prevalence of airway obstruction in this population, estimating the proportion of individuals with a FEV_1/FVC ratio below the LLN (bLLN) and the proportion of individuals with spirometric values bLLN for FEV_1 and FVC too.

Exposures

Lipids and HOMA-IR

Details of methods to calculate lipids and insulin resistance in this study population have been reported elsewhere [7]. Briefly, a 12-hour fasting blood sample was collected and serum was obtained for the measurement of insulin, and lipids. Insulin resistance status was estimated using the Homeostatic Model Assessment (HOMA-IR) method, which is calculated using concentrations of fasting glucose and insulin [11]. We used the cut-off value of 2.53, which has been defined for Chilean adults to indicate abnormal levels of insulin to maintain metabolic homeostasis [12]. For the measurement of glucose levels, a plasma sample with sodium fluoride was used. Insulin was determined by radioimmunoassay (Insulin kit, DPC, Los Angeles, USA) with a coefficient of variation of 7.9%. High density lipoprotein cholesterol (HDL) was determined by the Seigler & Wu method, with a variation coefficient of 4.6% [13]. Triglycerides were determined by an enzymatic method with clarifying factor (Human Diagnostic, Germany), with a coefficient of variation of 4.2%. All measurements were done by trained professionals within the same laboratory following the standards of the International Quality Control Programme of Bio-Rad Laboratories, Inc Hercules, CA. Lipid evaluation methods were carried out in line with the National Reference System for Cholesterol established by the Center for Disease Control and Prevention (CDC).

Table 1 Anthropometry, metabolic measurements and respiratory characteristics of participants

Characteristics studied	Males (n = 429)	Females (n = 541)
Age and Anthropometric measurements		
Age (yr) Mean (SD)	25 (1.56)	24.7 (1.6)
Adult weight (kg) Median (IQR)	70.1 (63.1, 78.5)	62 (55, 70.6)
Adult height (cm) Mean (SD)	168 (6.1)	156.5 (5.7)
BMI (kg/m^2) Median (IQR)	25 (11.7, 27.3)	25.1 (22.6, 28.8)
Weight at birth (g) Mean (SD)	3,201 (482.3)	3,178 (491.6)
Measurements of lung function and lung obstruction		
FEV_1 (L)* Median (IQR)	4.1 (3.8-4.5)	3.1 (2.8-3.4)
FVC (L)* Median (IQR)	4.7 (4.3- 5.2)	3.5 (3.2-3.8)
FEV_1 below LLN (n (%))	18 (4.2)	11 (2.0)
FVC below LLN (n (%))	32 (7.5)	14 (2.6)
Potential confounders (n (%) unless indicated otherwise		
Current smoker	283 (66.0)	266 (49.2)
Ex-smokers	37 (8.6)	70 (12.8)
12 years of full time education	330 (76.9)	394 (72.3)
Number of people with at least 4 of 6 household belongings (SES)	102 (23.8)	104 (18.9)
Components of metabolic syndrome (n (%) unless indicated otherwise)		
Metabolic syndrome (MS)§	53 (12.4)	61 (11.1)
HOMA-IR#	153 (35.8)	182 (33.2)
Abdominal obesity&	18 (4.2)	163 (29.7)
Fasting insulin (μU/mL) Mean (SD)	11.6 (5.8)	11.7 (5.8)
Hypertension†	41 (9.6)	13 (2.4)
High glycaemia†	6 (1.4)	2 (0.4)
High triglycerides†	96 (22.5)	75 (13.7)
Low HDL†	235 (54.9)	419 (76.3)

SD standard deviation.
SES Socio-Economic Status (No of household items used as an estimate of SES in the study population, namely having a washing machine, microwave, gas-fuelled water-heating device, refrigerator or a computer at home).
*Highest of five measurements.
§Metabolic syndrome (MS) – an individual was considered to have MS if three or more of the following components were present: 1) abdominal obesity (waist circumference > 102 cm in men and >88 cm in women); 2) elevated blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg); 3) elevated triglycerides (≥ 150 mg/dL); 4) decreased high density lipoprotein cholesterol (HDL-C; < 40 mg/dL in men and < 50 mg/dL) and 5) elevated fasting glucose (≥ 110 mg/dL).
#HOMA-IR cut off point 2.53 or above considered high for Chilean adults; below 2.53 considered normal (reference value).
&Abdominal obesity defined as indicated in MS.
†Hypertension defined as indicated in MS (normal blood pressure as reference); high glycaemia, high triglycerides, and low HDL defined as indicated in MS.

Metabolic syndrome (MS)

MS was diagnosed following the Adult Treatment Panel (ATP) III guidelines, according to which three or more of the following components must be present: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), elevated blood pressure level (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg), elevated triglycerides (≥150 mg/dL), decreased HDL (<40 mg/dL in men and < 50 mg/dL in women), and elevated fasting glucose (≥ 110 mg/dL) [14].

Anthropometric measures

Waist circumference (WC), body weight, and height were

Table 2 Association between markers of lipid metabolism and ventilatory function*†

Markers of lipid metabolism	Tertile	FEV_1 (L) β-coefficient (95% CI)	FVC (L) β-coefficient (95% CI)
Whole sample (n = 970)			
Triglycerides	1	0	0
	2	0.03 (-0.03 to 0.09)	0.04 (-0.03 to 0.11)
	3	-0.03 (-0.09 to 0.04)	-0.03 (-0.10 to 0.05)
	P value	0.42	0.47
LDL	1	0	0
	2	0.03 (-0.08 to 0.04)	-0.01 (-0.09 to 0.06)
	3	-0.02 (-0.08 0.04)	-0.08 (-0.15 to -0.01)
	P value	0.56	**0.03**
HDL	1	0	0
	2	-0.04 (-0.01 to 0.12)	-0.03 (-0.11 to 0.04)
	3	0.10 (-0.01 to 0.12)	0.04 (-0.04 to 0.11)
	P value	0.10	0.34
Men (n = 429)			
Triglycerides	1	0	0
	2	-0.02 (-0.12 to 0.09)	-0.02 (-0.14 to 0.10
	3	-0.13 (-0.24 to -0.03)	-0.13 (-0.25 to -0.01)
	P value	**0.007**	**0.02**
LDL	1	0	0
	2	0.01 (-0.09 to 0.10)	-0.08 (-0.19 to 0.03)
	3	-0.05 (-0.15 to 0.05)	-0.16 (-0.27 to -0.04)
	P value	0.37	**0.006**
HDL	1	0	0
	2	-0.07 (-0.16 to 0.03)	-0.06 (-0.17 to 0.05)
	3	0.07 (-0.03 to 0.18)	0.03 (-0.10 to 0.14)
	P value	0.25	0.86
Women (n = 541)			
Triglycerides	1	0	0
	2	-0.02 (-0.08 to 0.04)	-0.02 (-0.09 to 0.05)
	3	-0.05 (-0.12 to 0.02)	-0.08 (-0.16 to -0.002)
	P value	0.16	0.05
LDL	1	0	0
	2	0.04 (-0.03 to 0.11)	0.04 (-0.03 to 0.12)
	3	0.01 (-0.05 to 0.08)	-0.01 (-0.08 to 0.07)
	P value	0.72	0.82
HDL	1	0	0
	2	0.02 (-0.04 to 0.09)	0.03 (-0.04 to 0.11)
	3	0.09 (0.02 to 0.15)	0.10 (0.03 to 0.17)
	P value	**0.01**	**0.007**

(*) Multiple linear regressions adjusted for age, gender, height, weight at birth, educational level, smoking, SES, and BMI; CI Confidence Interval.
†p-values in bold letters indicate statistical significance.

measured by trained nurses. Body weight was recorded using a standard beam balance scale, with subjects barefoot and wearing light clothing [15]. Blood pressure was taken with a digital automatic sphygmomanometer, Omron 740, with a self-inflating cuff. The mean of the last two of three blood pressure measurements was used for this analysis. Waist circumference was measured on bare skin, midway between the lowest rib and the iliac crest, during midrespiration on standing subjects. Anthropometric and blood pressure data were collected in local hospitals and health centres, using calibrated equipment and standardised methodology. Body mass index (BMI) was estimated as the ratio of weight to height squared (kg/m2).

Statistical analyses

We investigated the effect of risk factors of CVD on FEV_1 and FVC as continuous outcomes of ventilatory function. The independent variables diastolic and systolic blood pressure, waist circumference, fasting glycaemia, triglycerides, and HDL were individually analysed in relation to each lung function outcome in the regression model. Exposure levels were analysed as tertiles with the exception of HOMA-IR and MS. These exposures are defined according to internationally agreed guidelines and were therefore analysed as binary variables normal/high, and absent/present, for HOMA-IR and MS, respectively. Given the high gender-related disparity in the proportion of individuals with prevalence of markers of CVD risk factors, the analyses are presented for the whole sample as well as by sex. Associations were considered of statistical significance if there was a p-value <0.05. As a measure to correct for possible multiple testing we considered statistically significant those associations with a p-value ≤ 0.01.

The following variables were included as potential confounders in the analyses of ventilatory function and risk factors of CVD: height, sex, age, smoking status, educational level, socio-economic status (SES), weight at birth, and BMI. Number of household belongings was water heater device, personal computer, fridge, washing machine, and microwave oven), which was appropriate to the reality of a semi-rural community in Chile [16].

We also carried out separate multi-variate analyses without BMI and smoking to explore whether there was an effect of these factors in the adjusted models. We observed that the associations were less strong after adjusting for BMI and smoking but remained statistically significant. Although BMI may be part of the chain of events which may explain the associations between CVD risk factors and ventilatory function, the rationale to adjust for BMI was to exclude this variable as a possible explanation for the associations in the analyses carried out. The results are presented including these confounders in the models. Analyses were carried out using STATA v12.0. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Chile and from the St Thomas's Hospital Ethics Committee in London.

Results

The study sample comprised 970 young adults (mean age 25 years old) with complete lung function data and information on relevant exposures. Half of them were at least overweight, and almost two thirds (66.0%) of males and 49.2% of women reported being current smokers (Table 1).

As expected, men had higher lung volumes than women. 7.5% of men and 2.6% of women had an FVC bLLN. 29.7% of females and 4.2% of men had a waist circumference above recommendations for healthy status. Conversely, hypertension was more prevalent in men than in women (9.6% vs. 2.4%). Over a third of the population had elevated HOMA-IR (34.5%) and 11.8% had MS (Table 1).

Table 3 Association between glycaemia, HOMA-IR, metabolic syndrome (MS) and ventilatory function *

Metabolic outcomes	Level compared	FEV_1 (L) β-coefficient (95% CI)	FVC (L) β-coefficient (95% CI)
		Whole sample (n = 970)	
Fasting glycaemia (tertile)	1	0	0
	2	0.01 (-0.06 to 0.07)	0.01 (-0.06 to 0.08)
	3	0.04 (-0.02 to 0.11)	0.03 (-0.04 to 0.10)
	P value	0.19	0.43
HOMA-IR	Normal	0	0
	High	-0.08 (-0.13 to -0.03)	-0.11 (-0.17 to -0.05)
	P value	**0.004**	**<0.0001**
Metabolic syndrome	Not present	0	0
	Present	-0.13 (-0.21 to -0.05)	-0.18 (-0.27 to -0.09)
	P value	**0.001**	**<0.001**
		Men (n = 429)	
Fasting glycaemia (tertile)	1	0	0
	2	-0.01 (-0.12 to 0.09)	-0.001 (-0.13 to 0.12)
	3	-0.06 (-0.16 to 0.04)	-0.06 (-0.18 to 0.05)
	P value	0.24	0.25
HOMA-IR	Normal	0	0
	High	-0.12 (-0.21 to -0.03)	-0.13 (-0.23 to -0.03)
	P value	**0.007**	**0.01**
Metabolic syndrome	Not present	0	0
	Present	-0.18 (-0.32 to -0.05)	-0.20 (-0.35 to -0.04)
	P value	**0.009**	**0.01**
		Women (n = 521)	
Fasting glycaemia (tertile)	1	0	0
	2	-0.002 (-0.06 to 0.06)	-0.03 (-0.07 to 0.06)
	3	0.01 (-0.06 to 0.08)	-0.03 (-0.11 to 0.04)
	P value	0.80	0.41
HOMA-IR	Normal	0	0
	High	-0.03 (-0.09 to 0.04)	-0.07 (-0.14 to -0.004)
	P value	0.43	**0.04**
Metabolic syndrome	Not present	0	0
	Present	-0.09 (-0.18 to 0.01)	-0.16 (-0.26 to -0.05)
	P value	0.08	**0.003**

(*) Multiple linear regressions adjusted for age, gender (where appropriate), height, weight at birth, educational level, smoking, SES, and BMI; Confidence Interval.
†p-values in bold letters indicate statistical significance.

Men had a statistically significantly lower FVC with increasing levels of triglycerides. Such an association was also observed in women but it was attenuated (p = 0.05). Similarly, men had a lower FVC with increasing tertiles of LDL levels, but this was not evident in women, who in turn, had a statistically significantly higher FEV_1 and FVC with increasing levels of HDL (Table 2).

In the whole sample, a reduced FVC (110 ml) was associated with having an increased HOMA-IR. Stratified analyses by gender also showed evidence of a reduced FVC with an increased HOMA-IR in men and women (FVC reduced by 130 ml and 70 ml, respectively). Both FEV_1 and FVC were negatively related to having MS in the whole sample, and in men. The association in women was only statistically significant between FVC and MS (Table 3). Subgroup analyses in never smokers showed no association between any of the exposures studied here and measures of lung function (data not shown).

We found no association between FEV_1 or FVC and high blood pressure or increasing waist circumference. FEV_1/FVC was not related to any of the exposures studied (data not shown).

Discussion

We found a high prevalence of risk factors for MS and for cardio-vascular diseases (CVD) in this population of young adults. Having a lower lung function was associated with having HOMA-IR, dyslipidaemias and MS, but not with high blood pressure or waist circumference. Our study shows that the associations between abnormal lipid and insulin levels with lung function appear already in young adults, and that insulin resistance is present in individuals without declared T2DM.

An advantage of this study is the age group included, which allowed an evaluation of the association of early risk factors for CVD and ventilatory function. The assessment

of respiratory outcomes in our study followed a rigorous international standardised protocol and quality control [8], which provided five high quality measurements of FEV_1 and FVC. In addition, the response rate was high and participants were representative of the area where the research took place. To date, the epidemiological evidence available on the predisposing CVD risk factors on lower lung function in adults comes mostly from adults aged 40 or more [17-19].

Although the mortality for CVD has decreased in recent years in Latin America, it still remains in the first place of causes of death in this region of the world [20]. In spite of being the most important cause of the death, there is still limited knowledge on the distribution and prevalence of risk factors and CVD in Latin American countries. A recent study showed that the adult prevalence of hypertension is over 50% in this region, with Chile showing some of the highest prevalence rates for most CVD risk factors [21]. The epidemiological profile of general and specific mortality for COPD in South America is not very different to that of emerging middle income countries in other continents. It is known that lung function is a predictor of general mortality whilst COPD is currently the third cause of death worldwide [22]. However, the knowledge on lung function decline over time and its related risk factor in adults from developing countries, such as those of Latin America, is very limited.

In line with the high profile that CVD have in South America, we observed a high prevalence of risk factors for CVD, with nearly a third of the studied population having HOMA-IR, and a prevalence of MS of 11.8%. The current overall prevalence observed for these risk factors in Chile at country-level are the highest reported to date in South America [23].

There is epidemiological evidence showing an association between T2DM and MS with lower lung function in adults [24,25]. Exposure to air pollutants, a known risk factor for COPD and reduced lung function, is unlikely to have affected the results of our study because levels of air pollution in Limache and Olmue are very low. Smoking is common in Chile and also in our study area. We have previously demonstrated that smoking in this sample only has a mild association with the FEV_1/FVC ratio, but not with FVC1 and FVC [26]. Our results would indicate that in young adults, factors other than smoking, could explain a lower level of lung function. It is also possible that events occurring during foetal life [27], which have been proposed to affect the attainment of adult lung function, may explain these results.

In our study, women showed a statistically strong positive association between lung function and higher levels of HDL. Higher levels of HDL are known to contribute to the prevention of development of atherosclerosis. The benefits of higher concentrations of HDL expand to other metabolic-related functions, including preventing vascular inflammation and enhancing insulin sensitivity as well as promoting insulin secretion from the pancreas [28]. It might be possible that HDL could be further contributing to the maintenance of an improved lung function through their beneficial effects on other risk factors of MS.

The temporal relationship between MS or its main components, and lung function decline is difficult to disentangle [29]. MS encompasses several individual risk factors known to be involved in the activation of pro-inflammatory pathways in the lungs (e.g. dyslipidaemias, abdominal obesity), which might explain the negative associations found between MS, dyslipidaemias and outcomes of lung function. Our findings are in line to those reported from large population-based studies in adults from Europe. Leone et al found that all individual factors of MS were related to lung function impairment in adults with a mean age of 45 in France [19]. In a study sample of similar age range than that of the Limache Cohort, Li et al found that 'pre-diabetes' risk factors such as elevated fasting glucose and insulin resistance were associated with lower FVC [30]. Several studies have found a positive association between waist circumference with lung function, and other epidemiological studies have reported no association in relation to lung function or lung function decline in people with mild COPD [31]. Our findings rise the question of whether other lifestyle-related factors might explain the associations found.

Lack of physical activity and a sedentary lifestyle are related to a higher prevalence of dyslipidaemias, insulin resistance and obesity, all of which are known factors to increase the risk of CVD [32]. Given the young age group of this population, it would appear appropriate to propose health promotion strategies targeted to young adults in order to prevent or reduce MS risk factors. This might have an added value by contributing to slow down the decline in lung function. To date, smoking cessation is the only intervention shown to slow the decline of lung function. Our study provides evidence to justify the implementation of prospective studies to examine the possible impact of impaired markers of cardiovascular disease on lung function decline. Our results also justify intervention studies to investigate how modifying lifestyle behaviours that lead to prevent an increased insulin resistance, an unfavourable lipoprotein profile and MS, may reduce the losses of lung function over time.

A limitation of this study is its cross-sectional design, which prevents us from establishing a causal relationship between exposure to CVD risk factors and lung function decline. Full lung growth is usually reached after adolescence but it can continue developing in young adults, usually up to the age of 29 years old, or later if there is a history of pre-pubertal respiratory symptoms [33,34]. The decline in lung function might start in the early 20s. In this study we are uncertain whether our results are due to CVD factors which reduce lung growth or induce an early loss of lung function. Longitudinal studies would allow us to examine how this relationship changes later in life and how poor lung function and MS interact and relate to CVD.

Efforts to understand the aetiological risk factors for CVD and COPD in Latin America have started in the last decade. The Limache Cohort study is one of the few cohorts to rigorously investigate early life risk factors for non-communicable diseases in adulthood. New large longitudinal studies are being set up in South America (including Chile) to investigate risk factors for CVD and poor lung function [35,36].

Nutritional risk factors in the first year were unrelated to lung function in our studied population [37], and with the exception of an association with levels of lipoproteins measured in adulthood, nutritional status in the first year of life did not appear to be related to other CVD risk factors [38], These findings lend further support to the notion that exposure to environmental factors from childhood and adolescence might influence the trajectory of lung function.

Conclusion

We found that poorer ventilatory function in young adults was associated with several markers of MS and with CVD risk factors. These findings provide a starting point to investigate mechanisms that could shed light to explain the association between lung function and CVD risk factors.

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Delay of Airway Epithelial Wound Repair in COPD is Associated with Airflow Obstruction Severity

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Abstract

Background: Airway epithelium integrity is essential to maintain its role of mechanical and functional barrier. Recurrent epithelial injuries require a complex mechanism of repair to restore its integrity. In chronic obstructive pulmonary disease (COPD), an abnormal airway epithelial repair may participate in airway remodeling. The objective was to determine if airway epithelial wound repair of airway epithelium is abnormal in COPD.

Methods: Patients scheduled for lung resection were prospectively recruited. Demographic, clinical data and pulmonary function tests results were recorded. Emphysema was visually scored and histological remodeling features were noted. Primary bronchial epithelial cells (BEC) were extracted and cultured for wound closure assay. We determined the mean speed of wound closure (MSWC) and cell proliferation index, matrix metalloprotease (MMP)-2, MMP-9 and cytokines levels in supernatants of BEC 18 hours after cell wounding. In a subset of patients, bronchiolar epithelial cells were also cultured for wound closure assay for MSWC analyze.

Results: 13 COPD and 7 non COPD patients were included. The severity of airflow obstruction and the severity of emphysema were associated with a lower MSWC in BEC ($p = 0.01$, 95% CI [0.15-0.80]; $p = 0.04$, 95% CI [–0.77;-0.03] respectively). Cell proliferation index was decreased in COPD patients ($19 \pm 6\%$ in COPD vs $27 \pm 3\%$ in non COPD, $p = 0.04$). The severity of COPD was associated with a lower level of MMP-2 ($7.8 \pm 2\ 10^5$ AU in COPD GOLD D vs $12.8 \pm 0.13\ 10^5$ AU in COPD GOLD A, $p = 0.04$) and a lower level of IL-4 ($p = 0.03$, 95% CI [0.09;0.87]). Moreover, higher levels of IL-4 and IL-2 were associated with a higher MSWC ($p = 0.01$, 95% CI [0.17;0.89] and $p = 0.02$, 95% CI [0.09;0.87] respectively). Clinical characteristics and smoking history were not associated with MSWC, cell proliferation index or MMP and cytokines levels. Finally, we showed an association of the MSWC of bronchial and corresponding bronchiolar epithelial cells obtained from the same patients ($p = 0.02$, 95% CI [0.12;0.89]).

Conclusion: Our results showed an abnormal bronchial epithelial wound closure process in severe COPD. Further studies are needed to elucidate the contribution and the regulation of this mechanism in the complex pathophysiology of COPD.

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by progressive airflow limitation, variously associating airway inflammation and remodeling, lung parenchymal destruction, systemic inflammation and comorbidities as cardiovascular disease and metabolic syndrome [1,2]. COPD represents a major worldwide health topic in its morbidity, mortality and its large consumption of health care resources, with a limited effect of current treatments [3]. The development of new therapeutic strategies requires a better understanding of the mechanisms underlying the setting and/or progression of COPD.

Airway epithelium plays a major role of structural and functional barrier, preventing inhaled substances from entering the airway tissue, and coordinating the activities of cells of the innate and adaptive immune system. Exposure to tobacco smoke, allergens, airborne particulates, infectious agents and noxious gases can induce injuries of airway epithelium, requiring a regulated repair mechanism to restore its functionality [4].

After injury, epithelial cells initiate several repair process, including spreading and migration of cells neighboring the wound, proliferation, and progressive re-differentiation until a complete regeneration of a pseudostratified mucociliary epithelium [4]. Remodeling of large and small airways have been shown in COPD, including squamous metaplasia, airway wall fibrosis, goblet cell hyperplasia, submucosal gland hypertrophy, increase in bronchial smooth muscle [5]. Chronic and acute injuries by tobacco smoke, environmental irritants, microorganisms are thought to participate to epithelial remodeling [6]. However, whether there is an abnormal wound repair process in COPD airways resulting in altered structure and function of airway epithelium is not established.

To test the hypothesis that wound repair of airway epithelium is abnormal in COPD, we studied primary bronchial and

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bronchiolar epithelial cells from non COPD and COPD patients in a model of wound closure. The relationships between airway epithelium wound closure parameters and clinical, functional and morphological characteristics of patients were studied.

Methods

Patients

Patients scheduled for lung resection for cancer (University Hospital of Reims, France) or transplantation (University Hospital of Grenoble, France) were prospectively recruited for the study following standards established and approved by the institutional review board of the university hospital of Reims, France. Informed consent was obtained from all the patients. Patients with asthma, cystic fibrosis, bronchiectasis or pulmonary fibrosis were excluded. At inclusion, the following characteristics were recorded: age, sex, body mass index (BMI), smoking history, arterial blood gases and pulmonary function tests results. No patient was treated by N-acetyl cysteine. COPD was defined by postbronchodilator FEV_1/FVC < 70% [2]. The severity of COPD was determined by spirometric classification (GOLD 1: $FEV_1 \geq 80\%$ predicted, GOLD 2: $50\% \leq FEV_1 < 80\%$ predicted, GOLD 3: $30\% \leq FEV_1 < 50\%$ predicted, GOLD 4: $FEV_1 < 30\%$ predicted) and by the GOLD combined score (A, B, C, D) (GOLD 2014).

CT-scan were analyzed by two independent investigators (JMP, GD) using a visual emphysema quantification on resected lung from 0 to 4 as previously described [7].

Cell culture and wound closure assay

Primary bronchial epithelial cells were extracted from resected lungs distant to the tumor as previously described [8]. Briefly, bronchi were visually identified and mechanically dissected. Dissected bronchi were transferred in RPMI medium supplemented with 20 mM HEPES (Gibco, Paisley, UK) and antibiotics (200 UI/ml penicillin, 200 Ag/ml streptomycin; Gibco) and then dissociated by 0.05% type XIV collagenase (Pronase E, Sigma Aldrich, St Louis, MO) and incubated in RPMI-HEPES overnight at 4°C. Cells were counted and seeded into flasks coated with type IV collagen (Sigma, Aldrich) with the CnT-17 proliferating medium (CELLnTEc, Bern, Switzerland). Cells were then passed into a 12-well plate coated with type IV collagen and cultured in bronchial epithelial cell growth medium (BEGM) (Lonza, Walkersville, MD).

When confluent and with a similar density, cells were used for wound closure assay by a mechanical injury using a P10 pipette tip as previously described [8]. Cells were washed with PBS and culture media was added. As feasibility experiments had shown that most of wounded areas of non-COPD patients were closed 18 hours after wounding, the closure of wound area was monitored for 18 hours using a digital camera and Axiovision software (Carl Zeiss Vision GmbH, Munchen-Hallbermoos, Germany) at the start of the experiment and each 10 minutes. The wound closure assays were performed in triplicate in separate wells. Images were used to determine wound repair, calculated as percent wound area compared with the initial wound area. We determined the mean speed of wound closure using Image J software (National Institutes of Health, Bethesda, MD, USA).

Seven samples (2 non COPD patients, 2 COPD GOLD II, 3 COPD GOLD IV) have been excluded because of cell culture failure: absence of initial cell proliferation (n = 5), cell death after injury (n = 1), fungal contamination (n = 1). We analysed cell growth in the initial culture depending on COPD status and severity. The time to confluence was: 7.28 ± 1.97 days in non COPD group, 7.73 ± 3.13 days in COPD group, 6 ± 2.82 days in COPD GOLD I, 7.5 ± 3.11 days in COPD GOLD II, 10.33 ± 2.52 days in COPD GOLD III-IV. However, this difference did not reach a significant level.

In a subset of patients, bronchiolar epithelial cells were also extracted from resected lungs. Briefly, bronchioles were identified on the basis of absence of wall cartilage and an outer diameter ≤1 mm [9], and then mechanically dissected. Bronchiolar epithelial cells were obtained from bronchioles following the same process as bronchi then cultured and used for wound closure assay as described above.

Immunofluorescence

Bronchial and bronchiolar epithelial cells were cultured on glass coverslips coated with Purecol bovine collagen solution (3 mg/ml) diluted 1:75 in sterile water. When confluent, mechanical injury was performed on cell monolayer as described above. Cells were then fixed with methanol immediately after (T0) and 18 hours (T18) after the mechanical injury. In order to analyze the dynamics of wound closure parameters, we analysed 2 other time points at 6 (T6) and 12 hours (T12) after wounding. Fixed cells were blocked with 3% bovine serum albumin for 60 min. The coverslips were incubated with a mouse monoclonal antibody against Ki-67 (1:100) (Dako, Denmark), then with Alexa Fluor 488 coupled mouse anti-IgG (1:200) (Molecular Probes, Eugene, OR, USA). Nuclei were stained with 4′,6-diamidino-6-phenylindole (DAPI, Molecular Probes, Eugene, OR, USA). The results are presented as a percentage of Ki-67 positive proliferating cells compared with total cells.

Gelatin zymography analysis

Supernatants of bronchial epithelial cell cultures at T6, T12 and T18 were collected, centrifugated and separated on 10% polyacrylamide SDS gel containing 0.1% gelatin. The gel was washed for 1 h at room temperature in a 2% Triton X-100 solution, transferred to a 50 mm Tris– HCl/10 mm CaCl2 (pH 7.6) buffer and incubated overnight at 37°C. The gel was stained in a 0.1% Coomassie Blue (G250)/45% methanol/10% acetic acid solution and de-stained in a 10% acetic acid/20% methanol solution. The gel was then analyzed by densitometry performed using Multigauge V2.02 (Fuji film, Stamford, CT, USA).

Cytokine analysis

Supernatants of bronchial epithelial cell cultures at T18 were tested for cytokine detection (Interleukin (IL)-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-1β, IFN-γ, GM-CSF, TNF-α) using Human Cytokine Ten-Plex kit (Invitrogen, Carlsbad, CA) following manufacturer's recommendations.

Histological analysis

Part of resected lungs were fixed in formalin and embedded in paraffin before cutting into serial 5 µm section and staining with hematoxylin and eosin, then observed on microscope (x100). Bronchial epithelium was analyzed in 10 different areas in 4 to 7 bronchi per patient. The following major remodeling features were quantified: denuded basement membrane, goblet cell hyperplasia, basal cell hyperplasia and squamous metaplasia. Squamous cell metaplasia was defined as a pseudostratified multilayered epithelium consisting of polygonal cells covered by flattened layer of squamous cells and absence of ciliated cell [10]. The predominant remodeling feature was attributed to

each observed area. Results were expressed as the percentage of remodeling feature per all observed areas per lung.

Statistical analysis

The data are expressed as mean values ± standard deviation or percentages. We compared wound closure parameters (mean speed of wound closure, cell proliferation index, MMPs and cytokines levels) between groups (COPD status, chronic bronchitis) using the Student t test or Fisher exact test. We studied correlations between wound closure parameters and clinical and functional data (FEV_1, FEV_1/FVC, emphysema score, age, BMI, smoking history, dyspnea score, number of exacerbations) using the Pearson correlation test. A p-value < 0.05 was considered significant.

Results

Patients' characteristics

Twenty patients were included, 13 COPD patients and 7 non COPD patients. Eighteen patients underwent lung resection for lung cancer (n = 17) or kidney cancer metastasis (n = 1). Two patients had lung transplantation for emphysema. Characteristics of patients are detailed in Table 1. Pre-operative arterial blood gases were available for 11 patients. COPD patients had a lower PaO2 level compared to non COPD patients (74 ± 11 vs 90 ± 9 mmHg respectively, p = 0.02).

A visual quantification of remodelling features was performed in 17 lungs. We found the main remodelling feature was goblet cell hyperplasia (51.7 ± 23.4 and 48.6 ± 24.4% of epithelium surface in non COPD and COPD groups respectively). Basal cell hyperplasia was found in ± 22.2% of epithelium surface in COPD group. However, the percentage of epithelium surface with remodelling features was not statistically different between COPD and non-COPD groups in our series.

Bronchial wound closure and associations with clinical, functional and histological characteristics

To determine if bronchial wound closure is delayed in COPD, we analysed the speed of wound closure in primary bronchial epithelial cells using a wound closure assay (Figure 1A). Overall, the MSWC of COPD and non COPD patients did not significantly differ (9997 ± 7239 µm²/h vs 11338 ± 3552 µm²/h, p = 0.53). However, as shown in Figure 1B, we found that the mean speed of wound closure (MSWC) was dramatically decreased in spirometric COPD GOLD 3–4 compared to non COPD patients (4165 ± 743 µm²/h vs 11338 ± 3552 µm²/h, p = 0.006). Interestingly, the severity of airflow obstruction (FEV_1 and FEV_1/FVC) was associated with a lower MSWC (Table 2, Figure 2). Analysis of the subgroup of COPD patients confirmed the association between FEV_1 and MSWC ($p < 0.05$). FEV_1 was also associated with the percentage of wound area at T18 (p = 0.02, 95% CI [0.06; 0.77]). The severity of emphysema assessed by a visual score was associated with a lower MSWC (Table 2). Of notes, the MSWC was not associated with age, BMI, smoking history, dyspnea, chronic bronchitis or the number of exacerbations in the past year. Analysis of remodelling features showed that the MSWC was not associated with the percentage of denuded basement membrane (p = 0.22), goblet cell hyperplasia (p = 0.71), basal cell hyperplasia (p = 0.07), squamous metaplasia (p = 0.50) and normal epithelium (p = 0.61).

Cell proliferation during bronchial epithelial cells wound closure assay

We next analysed cell proliferation during bronchial wound closure (n = 11). We performed Ki-67 and DAPI staining at T0, T6, T12 and T18 and determined the percentage of Ki-67 positive proliferating cells compared with total cells (cell proliferation index; Figure 3A). Interestingly, cell proliferation at T18 was significantly lower in COPD patients compared to non COPD patients (19 ± 6% vs 27 ± 3% respectively, p = 0.04; Figure 3B). Analysis of subgroup of COPD patients showed that cell proliferation index in COPD GOLD 3-4 patients was significantly lower compared to non COPD patients (19% ± 0.6% vs 27% ± 3% respectively, p = 0.02). Cell proliferation index in COPD GOLD 1 and COPD GOLD 2 patients did not significantly differ from non COPD patients (18% ± 10% and 22% ± 6% vs 27% ± 3% respectively, ns).

We next studied associations between cell proliferation and clinical characteristics of patients. Cell proliferation index at T18 was not associated with age, BMI, smoking history, dyspnea, chronic bronchitis or the number of exacerbations in the past year (Additional file 1: Table S1). Analysis of remodelling features showed that cell proliferation index was associated with the percentage of goblet cell hyperplasia (p = 0.03, 95% CI [0.06;0.93]) but not with denuded basement membrane, basal cell hyperplasia, squamous metaplasia or normal epithelium.

Table 1 Characteristics of patients

	Non COPD	COPD	p
n	7	13	
Male gender	71%	85%	ns
Age, years	69 ± 10 [58–87]	66 ± 10 [52–84]	ns
BMI, kg/m²	33 ± 9 [26–43]	25 ± 4 [19–35]	0.04
Smoking history			
Never smokers	29%	0%	ns
Ex smokers	43%	54%	ns
Pack-years	29 ± 25 [0–60]	54 ± 22 [25–100]	ns
Symptoms			
Dyspnea ≥2 mMRC	0%	31%	ns
Chronic bronchitis	14%	31%	ns
At least one exacerbation in the last year	na	31%	
Spirometry			
FEV_1,% of predicted value	94 ± 15 [72–113]	68 ± 29 [17–109]	0.04
FVC,% of predicted value	90 ± 13 [77–114]	89 ± 23 [54–117]	ns
FEV_1/FVC,%	77 ± 5 [73–87]	59 ± 17 [27–69]	0.01
Spirometric GOLD 1/2/3-4	na	5/5/3	
GOLD A/B/C/D	na	5/5/0/3	
CT emphysema score for the resected lobe	0.4 + 0.8 [0–2]	1.3 + 1.7 [0–4]	ns
Histological analyses,% of epithelial surface, n = 17			
Denuded basement membrane	3.8 ± 5.0 [0–13]	5.4 ± 4.0 [0–14]	ns
Goblet cell hyperplasia	51.7 ± 23.4 [7–80]	48.6 ± 24.4 [16–82]	ns
Basal cell hyperplasia	4.2 ± 4.6 [0–14]	12.6 ± 22.2 [0–70]	ns
Squamous metaplasia	2.2 ± 1.8 [0–5]	2.1 ± 3.2 [0–9]	ns
Normal	38.0 ± 22.2 [10–87]	32.7 ± 23.0 [3–66]	ns

Data are expressed as mean ± SD or number (%).
FEV_1: Forced Expiratory Volume in one second. FVC: Forced Vital Capacity.

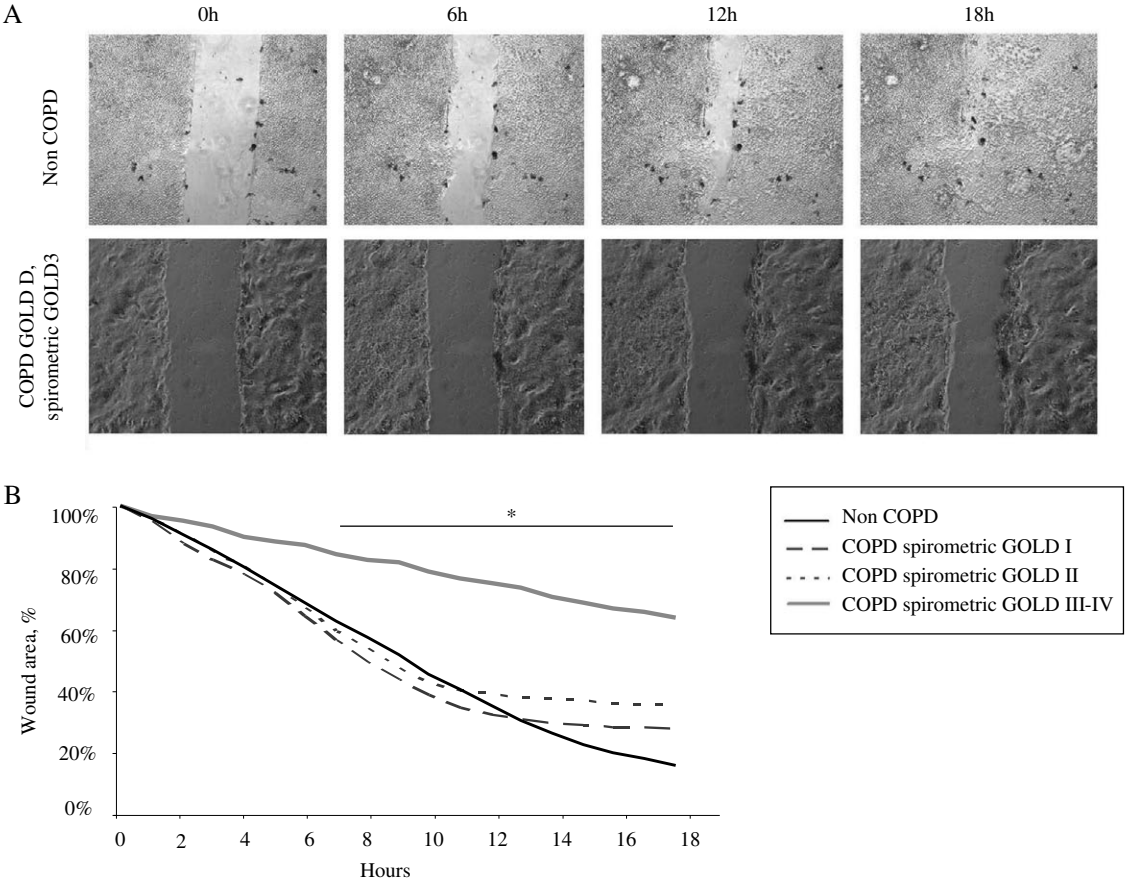

Figure 1 Wound closure assay in bronchial epithelial cells from COPD and non COPD patients. A mechanical injury was performed on confluent bronchial epithelial cell monolayer. Representative photographs at 0, 6, 12 and 18 h in a non COPD and a COPD GOLD D spirometric GOLD 3 patient **(A)**. The mean percentage of remaining wound area in non COPD patients (n = 7), spirometric COPD GOLD 1 (n = 5), GOLD 2 (n = 5) and GOLD 3–4 patients (n = 3) are presented **(B)**. *p < 0.05 vs non COPD.

Finally, we studied association between cell proliferation index and the speed of wound closure. We found that cell proliferation at T18 was not associated with the MSWC (p = 0.76). We further analysed cell proliferation at T0, T6 and T12 and did not find any association between cell proliferation index at T0, T6 and T12 and the percentage of wound closure at T6, T12 and T18 respectively.

MMP-9 and MMP-2 levels during bronchial epithelial cells wound closure assay

We next analysed MMP-9 and MMP-2 levels in supernatants of bronchial epithelial cell cultures by gelatine zymography at T6, T12 and T18. Analysis of clinical characteristics of patients showed that MMP-9 level at T18 was negatively associated with the number of exacerbation in the past year (p = 0.04, 95% CI [−0.87;0.04]) and positively associated with age (p = 0.02, 95% CI [0.11;0.85] but not with BMI, smoking history, dyspnea and chronic bronchitis (Additional file 2: Table S2). MMP-2 level at T18 was associated with body mass index (p < 0.01, 95% CI [0.25;0.93]) but not with age, smoking history, dyspnea, chronic bronchitis and the number of exacerbation in the past year (Additional file 2: Table S2). Interestingly, we found that MMP-2 level at T18 was significantly associated with the severity of airway obstruction (FEV_1/FVC, p = 0.02, 95% CI [0.11;0.86] and was lower in GOLD D patients compared to GOLD A patients ($7.8 \pm 2\ 10^5$ AU vs $12.8 \pm 0.13\ 10^5$ AU, p = 0.04). We did not find any association between MMP-9 levels at T18 and COPD status, COPD severity or emphysema (Additional file 2: Table S2). Analysis of remodelling features showed that MMP-9 and MMP2 levels at T18 were not associated with the percentage of denuded basement membrane, goblet cell hyperplasia, basal cell hyperplasia, squamous metaplasia or normal epithelium. Levels of MMP-9 and MMP-2 in cells supernatants at T6 and T12 were not associated with clinical, functional, morphological and histological characteristics of patients (not shown).

Finally, we studied the associations between MMP-9 and MMP-2 levels and the speed of wound closure. We found that MMP-9 and MMP-2 levels at T6, T12 and T18 were not associated with the MSWC and the percentage of wound closure at T6, T12 and T18 respectively (not shown).

Cytokine secretions during bronchial epithelial cells wound closure assay

We next analyzed pro-inflammatory cytokines levels in bronchial epithelial cell supernatants at T18. We found that the severity of airflow limitation (FEV_1) was associated with a lower level of IL-4 (p = 0.03, 95% CI [0.09;0.87]; Additional file 3: Table S3). The levels of IL2, IL-4, IL-10 and GM-CSF were associated with an older age of patients (p < 0.05 for all). Cytokine levels in bronchial cell supernatants at T18 were not associated with smoking history or respiratory symptoms. Analysis of remodelling features showed that IL-8 level was associated with squamous metaplasia (p = 0.01, 95% CI [0.24;0.92]). IL-2 level was associated with goblet cell hyperplasia (p = 0.03, 95% CI [0.06;0.90]).

Table 2 Associations between the mean speed of wound closure of bronchial epithelial cells and clinical, functional and morphological characteristics of patients

	P	95% CI
FEV1, % of predicted value	0.01	0.15;0.80
FEV1/FVC, %	0.04	0.03;0.76
CT emphysema score for the resected lobe	0.04	-0.77;-0.03
Age, years	0.21	-0.17;0.64
BMI, kg/m^2	0.76	-0.59;0.46
Smoking history, pack-years	0.16	-0.14;0.70
Dyspnea, mMRC	0.75	-0.59;0.46
Chronic bronchitis	0.60	
Exacerbation in the past year, n	0.31	-0.67;0.26

FEV1: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity. Pearson or Student tests were performed.

We further studied the associations between cytokines levels and the speed of wound closure. Interestingly, higher levels of IL-4, IL-2 and GM-CSF were associated with a higher MSWC (p = 0.01, 95% CI [0.17;0.89]; p = 0.02, 95% CI [0.09;0.87]; p = 0.03, 95% CI [0.07;0.86] respectively).

Bronchiolar epithelial cells wound closure assay

In order to determine if bronchiolar epithelial cells wound closure is similar to bronchial epithelial cells wound closure, we next analysed wound closure parameters of primary bronchiolar epithelial cells obtained from 6 non COPD patients and 6 COPD patients (4 COPD GOLD 1, 1 COPD GOLD 2, 1 COPD GOLD 3; Additional file 4: Table S4). Overall, the MSWC of bronchiolar epithelial cells was significantly lower compared to bronchial epithelial cells (9658 ± 3306 vs 13783 ± 5603 µm^2/h respectively, p = 0.048). Analysis of paired bronchial and bronchiolar cells obtained from corresponding patient (n = 12) showed that the MSWC of bronchial and

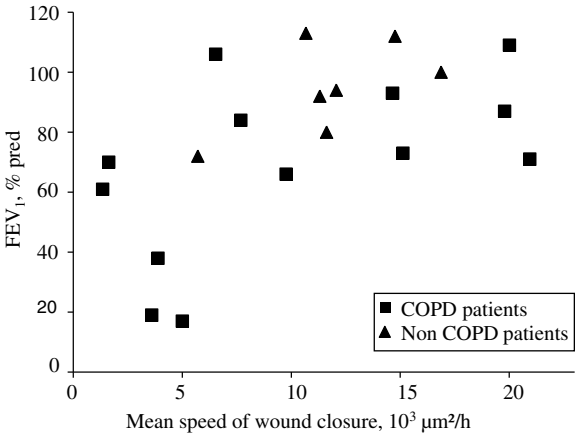

Figure 2 Relationships between mean speed of bronchial epithelial wound closure and FEV_1. Bronchial epithelial wound closure in non COPD (triangle, n = 7) and COPD patients (square, n = 13) was monitored for 18 h, and the mean speed of wound closure (MSWC) was calculated. p = 0.01.

bronchiolar epithelial cells were associated (p = 0.02, 95% CI [0.12;0.89]; Figure 4). The MSWC of bronchiolar epithelial cells was not associated with COPD status or severity.

Discussion

We showed in this study performed in primary bronchial epithelial cells obtained from 20 patients clinically, functionally and histologically characterised that the mean speed of epithelial wound closure decreased with the severity of COPD. We also showed that the speed of wound closure of bronchial and bronchiolar epithelial cells obtained from the same patients were strongly associated.

Repair of airway epithelium after injury is critical for the maintenance of the airway epithelial structure and function. In our study, we analyzed bronchial epithelium repair in

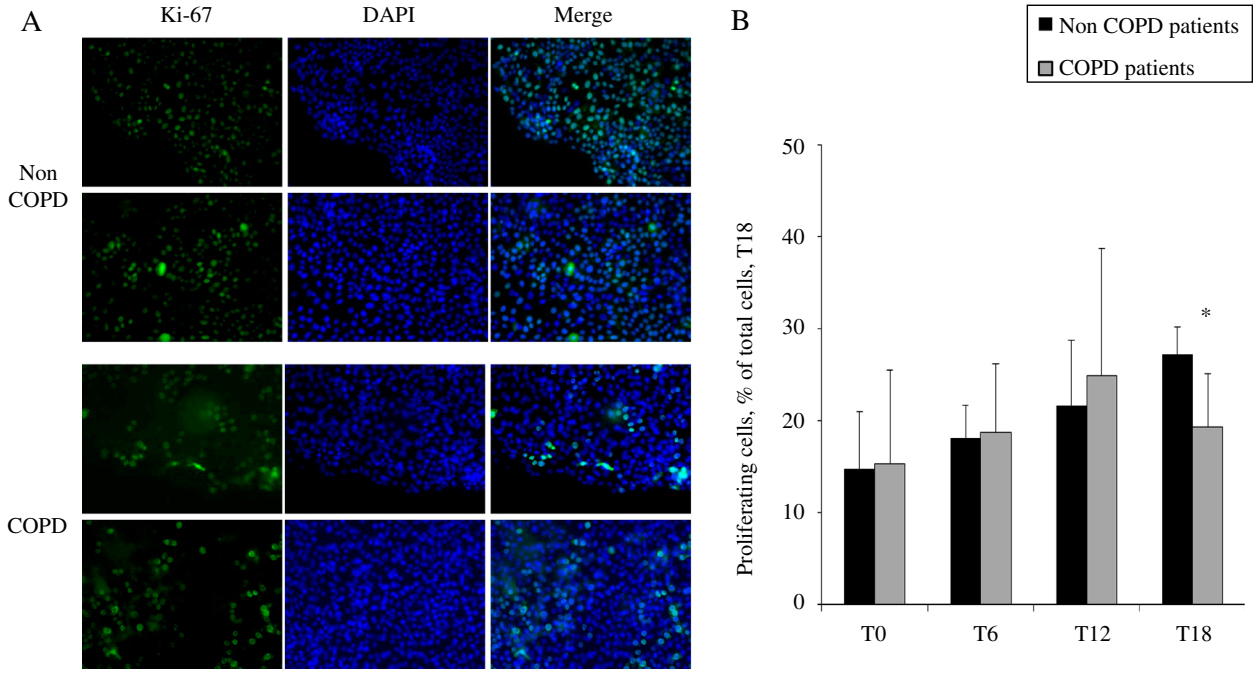

Figure 3 Cell proliferation during epithelial wound closure in non COPD and COPD patients. Representative photographs (x10 enlargement) of Ki-67 and DAPI staining, as well as merge images in non COPD and COPD bronchial epithelial cells after 18 h of repair **(A)**. Quantification of the number of Ki-67 positive cells expressed as a percentage of total cell number at 0 h, 6 h, 12 h and 18 h of repair **(B)**.

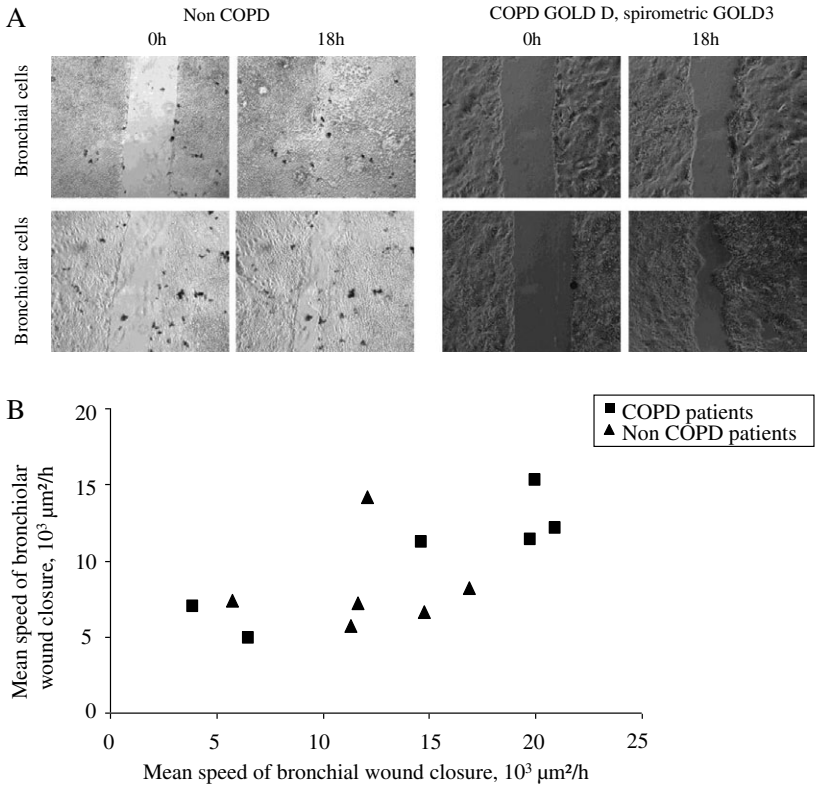

Figure 4 Association between the mean speed of bronchiolar and bronchial epithelial wound closure. Paired bronchial and bronchiolar epithelial cells were obtained in 12 patients and analysed in wound closure assay. Representative photographs at 0 and 18 h in a non COPD and a COPD GOLD D spirometric GOLD 3 patient **(A)** are presented. The association between the mean speed of wound closure of bronchiolar epithelial cells and corresponding bronchial epithelial cells is shown **(B)**. p = 0.02.

the first steps of airway epithelial repair process: migration and proliferation. These processes follow the epithelial to mesenchymal transition, a dedifferentiation of epithelial cells to motile mesenchymal cells playing a key role in degradation and de novo synthesis of extracellular matrix [6]. One of the most striking findings in our study is that the delay of bronchial epithelial wound closure was associated with the severity of airflow obstruction. Moreover, we showed that COPD was associated with a decreased cell proliferation index 18 hours after bronchial epithelial cell wounding, and that cell proliferation index was not associated with the delay of bronchial epithelial cells wound closure. Several important limitations regarding the selection of the patients have to be considered in our study. First, a relatively low number of patients were included. Second, primary bronchial and bronchiolar cells were obtained mainly from lung sections distant from lung cancer. Third, the non-COPD population included ex and current smokers. However, our results strongly suggest that abnormalities in the first steps of airway epithelial repair process may be involved in severe COPD. Additional studies including a higher number of patients and using differentiated airway epithelial cells in the air liquid interface culture model would allow analyzing all different sequential steps of the repair process.

COPD is of high heterogeneity and its evaluation can not be restricted to a threshold of lung function measurement. We further analyzed parameters of clinical phenotypes of COPD patients. Interestingly, previous studies showed that airway epithelial cells repair could be impaired by senescence of airway epithelial cells or cigarette smoke exposure [11,12]. In our study, we did not find any association between MSWC or cell proliferation index and the following clinical characteristics of patients: age, BMI, smoking history, respiratory symptoms and the number of exacerbation in the previous year. Surprisingly, we did not find any statistical difference in airway remodeling features between COPD and non COPD group in our study. This could be explained by the high rate of ex or current smokers in the non COPD group, by the major heterogeneity of airway remodeling features distribution in COPD and by the relatively low number of patients analysed. In our study, goblet cell hyperplasia was associated with a higher cell proliferation index and a higher IL-2 level at T18. Squamous metaplasia was associated with a higher level of IL-8. Previous studies reported the role of cigarette smoke-mediated pro-inflammatory cytokines in the development of bronchial epithelial hyperplasia and squamous metaplasia [13]. Of notes, the MSWC was not associated with bronchial epithelial remodeling features in our study.

We analyzed MMP-2 and MMP-9 levels during wound closure assay. MMP-2 and MMP-9 have been shown to be involved in the pathogenesis of COPD [14,15]. These proteases could play a role in epithelial repair process. During epithelial repair, MMP-9 is secreted by transdifferentiated cells and degrades focal adhesion at the rear of the cell [16]. Moreover, inactivation of MMP-9 has been shown to decrease the migration of bronchial epi-

Numbers of cytokines have been shown to be involved in repair processes in the lung [19]. White and collaborators [20] found that IL-4 stimulated the migration and repair of differentiated primary human bronchial epithelial cells. IL-2 was shown to increase the migration of injured rat alveolar type II cells, and reduce apoptosis of these cells [21]. Interestingly, we found

that higher levels of IL-4, IL-2 and GM-CSF were associated with a higher MSWC. Moreover, we found that IL-4 level in bronchial epithelial cells wound closure assay decreased with the severity of airway obstruction, suggesting that IL-4 could be involved in abnormal bronchial epithelial repair in COPD. Finally, a lower level of IL-4 was associated with a higher frequency of exacerbation. Further studies should explore the potential role of IL-4 as a mechanism underlying delayed repair. As previously described, we found that several cytokines were at a higher levels in older patients [22].

Finally, we analyzed bronchiolar epithelial cells in wound closure assay. Recent studies based on micro-CT imaging and histology showed a decrease in the number and the mean diameter of remodeled bronchioles in COPD [23]. A recent review suggested that bronchiolar remodeling and destruction could be involved in COPD [24]. One of the strength of our study is that we studied paired bronchial and bronchiolar epithelial cells from the same patients in a wound closure assay. We did not find any association between the MSWC of bronchiolar epithelial cells and COPD status or severity, probably because of a low number of patients and the fact that we did not obtain bronchiolar epithelial cells from the most severe patients. However, we showed that the MSWC of bronchiolar epithelial cells was strongly associated with corresponding bronchial epithelial cells.

In conclusion, our results showed that the first steps of bronchial epithelial repair are impaired in severe COPD, possibly involving MMP-2 and IL-4 and IL-10. Our results also suggest that an abnormal bronchiolar epithelium repair could be involved in COPD. Further studies are needed to determine the exact role of bronchial and bronchiolar epithelial repair after repeated injuries in the pathophysiology of COPD.

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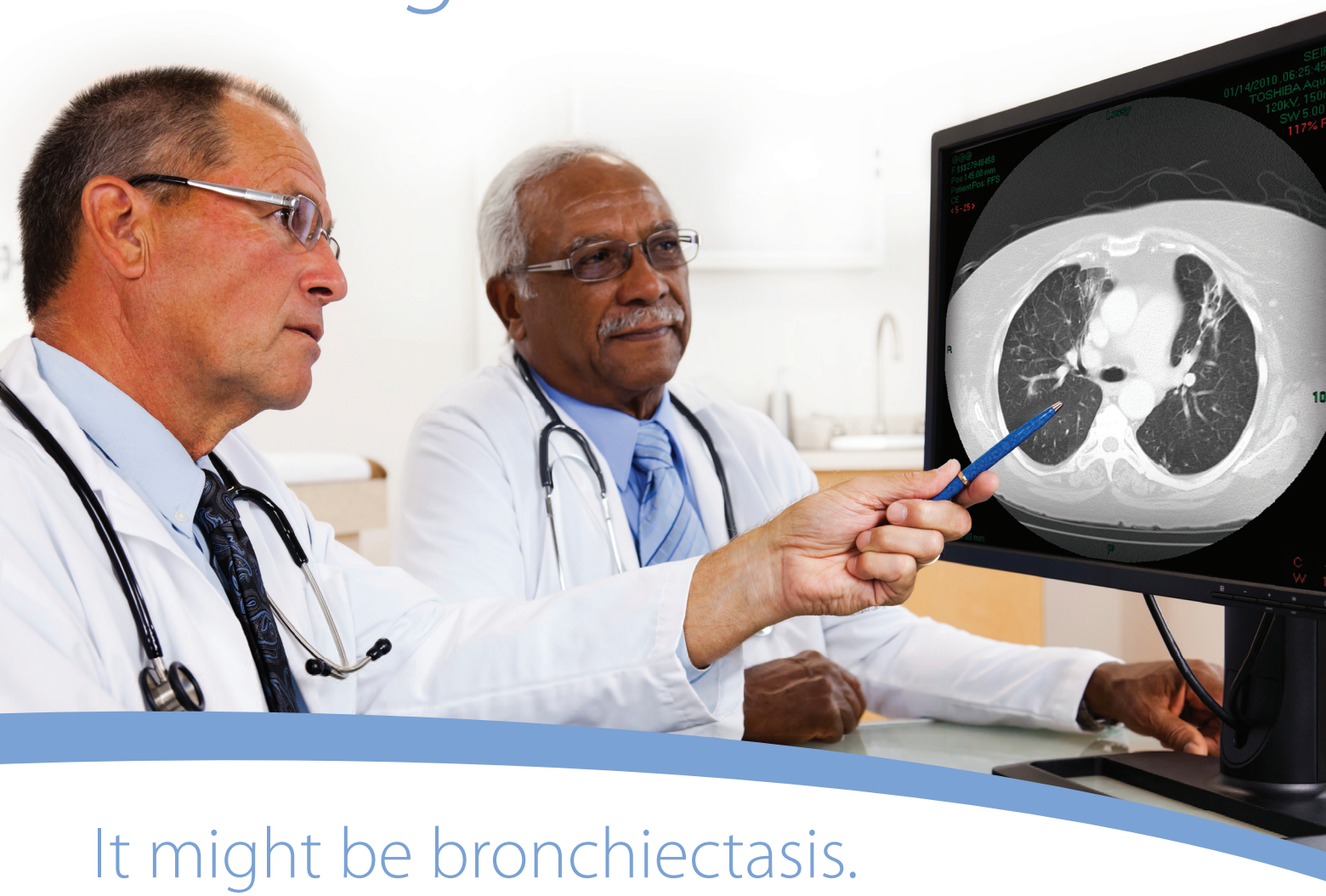

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