Volume 11 Number 2 Spring 2016

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The Journal of Pulmonary Technique

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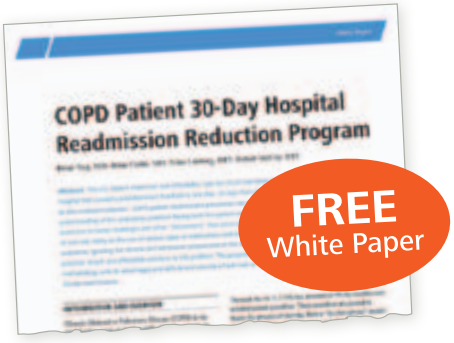

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The Journal of Pulmonary Technique

Vol. 11 No. 2
Spring 2016

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DEPARTMENTS

ARTICLES

A Breath of Fresh Testing Success

Steve Faives

For you boaters out there, we're not talking about Personal Flotation Devices. There's a not-so-new technology in ongoing development designed to identify specific molecules in exhaled alveolar air, leading to early diagnosis of often overlooked diseases. Thus Pulmonary Function Diagnostics.

Of course the idea of medical diagnosis via exhaled odors dates back to the earliest practice of medicine. "Fetor Hepaticus," the fish-like aroma of liver failure. Or the "sour scent" breath of patients with kidney failure. Add the ability of trained dogs to sniff out seizures, stomach, lung, and bowel cancer, and you have the makings for an entirely new diagnostic tool.

Like the early days of PFTs, this experimental technology tends to be large and cumbersome. Our early PFT machines were mammoth contraptions with vertical columns, bellows, and refillable ink styluses. Now we can hold the equivalent machine in one hand. The same can hopefully be said for the future of these breath-reading devices. Yet even despite their size (some as large as a small refrigerator), researchers are already making excellent headway beyond theory. Particularly in the detection of heart failure, TB, lung and upper airway cancers, and liver disease.

With more than 3000 known chemical compounds that can be exhaled, many are only detected in incredibly small amounts. Often in concentrations of parts per billion. The real challenge is finding and identifying the specific compound for an early disease state. One of the best examples are the early markers for heart failure—affecting more than 5 million Americans and one of the most common reasons for hospital admissions in older patients. When the body's tissues are deprived of oxygenated blood from a weakened heart muscle, there is an excess cellular production of pentane and acetone. In preliminary studies, the heart failure breath test has been accurate every time.

Likewise, a breath test for TB has similar encouraging results. Second only to HIV as a cause of death related to infection, an early and fast diagnosis has the potential to decrease mortality and prevent outbreaks. Especially with a less-than-10-minute trace detection result. Also avoiding costly chest X-rays or the lengthy three-day sputum analysis and isolation.

Some of the most exciting research is in early cancer detection, especially lung cancer. Presently, early diagnosis relies on chest X-rays and CT scans. Both costly, and complicated with false alarms. Detecting the compounds found in the lungs of cancer patients could tell the difference between general lung damage from smoking and cancer. Especially since half of all patients with lung cancer are smokers. Recent preliminary studies had an 80 percent accuracy detection rate. Furthermore, researchers have mapped a breath footprint that could single out stomach cancer with near 90 percent accuracy.

In addition to the obvious diagnosis, breath testing can open a door to other types of early detection. The EPA is investigating its potential to screen for environmental pollution effects. As opposed to blood and urine tests, a breath test could produce an

Continued on page 8…

A **NEW** Direction for **Subglottic Secretion** Management

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Jerry Gentile, BSRT, BSHA, MBA, EdD(c), RT, RRT
Partner, Sevara Health, LLC
Director of Respiratory Care Services
Eastchester Rehabilitation & Healthcare Center
Bronx, New York

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Editorial…continued from page 6
instant result by detecting inflammatory reactions in the lungs. The exciting correlation is early detection of lung infections that parallel Cystic Fibrosis. If we can diagnose a related infection before the patient develops actual symptoms, it can be treated early or perhaps prevented. This application for other chronic diseases has far-reaching preventative possibilities.

Even though the potential for breath testing is immense, researchers are aware of the challenges necessary to catalog this library of chemical molecules. It's all made possible by the alveoli catching capillary "waste" molecules during exhalation. There is a mixture of substances from input to blood stream. The natural remnants of metabolism, and the dead space molecules that have been inhaled and rereleased. The trick is correlating the diagnostic indicators from the innocent bystanders.

Approved Tests

Lactose malabsorbtion	Hydrogen molecules	1997
H pylori infection	CO2 molecules	2001
Asthma	Nitric oxide	2003
Heart transplant rejection	Methylated alkanes	2004

When researchers know exactly which molecular footprint needs to be measured relative to early symptoms, there's little doubt that technology will prevail. We already have alcohol detecters that plug into a smart phone. Imagine early disease complications displayed on our ventilator screens. Already there's promising detection for early ARDS.

Respiratory Therapists could play a large role in Pulmonary Diagnostics. Who better to fine tune breath collection from ventilated patients. Especially when dead space/rebreathed air play a significant role. Likewise, as we already know from PFTs, patient effort and technique are paramount for accurate findings. With a head start and baseline of expertise, hopefully RRTs will be the "go to" leaders for Pulmonary Breath Testing.

Steve Faives RRT is a Respiratory Therapist based in Florida.

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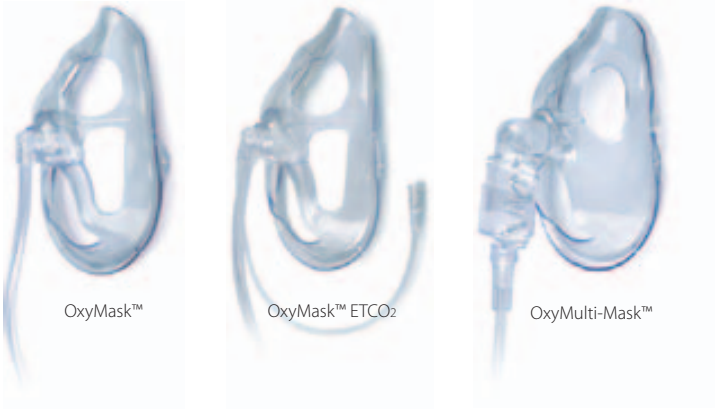

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News

■ Spring 2016

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Adult Autologous Stem Cell Research

3B Medical has made a major commitment to allocate a significant portion of its profits to fund research into proof-of-concept studies in use of adipose derived autologous mesenchymal stem cells. "We spend a lot of resources treating the symptoms of diseases, and not enough trying to target the actual causes. The use of autologous stem cells in regenerative medicine shows considerable promise in changing so many lives. That has always been the core mission of 3B." said Thomas Thayer, Sr., President, "We are going to lead the way by committing a portion of our resources to try and bring some of this technology to market".

Lab Acquired by ResMed

ResMed, the world's leading innovator in sleep-disordered breathing and respiratory care, announced it had finalized its agreement to acquire Inova Labs Inc., a privately-held medical device company specializing in the development and commercialization of innovative oxygen therapy products. Oxygen therapy is the largest non-drug delivery medical device segment for the treatment of COPD. "COPD is the third leading cause of death in the United States and, sadly, the disease is on its way to achieving the same ranking globally," said Mick Farrell, CEO of ResMed. "We are excited to expand our offerings and solutions for the global COPD epidemic and to progress even more swiftly toward our ResMed goal of improving 20 million lives by 2020. With the acquisition of Inova Labs, ResMed is delivering on its commitment to find further ways to improve the quality of life for tens of millions of people as they deal with COPD, this chronic, progressive disease that literally takes patients' breath away when untreated." ResMed's current respiratory care offerings include world-leading patient interface products, the AirCurve 10 series of cloud-connected non-invasive ventilators, the Stellar series of non-invasive ventilators, and the flagship Astral series, ResMed's award-winning lightweight non-invasive life support platform, with internal and external batteries that provide up to 24-hours of freedom for patients. With the acquisition of Austin, Texas-based Inova Labs, ResMed's respiratory care portfolio encompasses both innovative portable oxygen concentrators as well as the necessary stationary options for the home. Key products include: LifeChoice Activox — lightweight, portable oxygen concentrators that lead the industry in offering extended battery life for freedom and mobility; Activox DUO2 — the industry's first fully-integrated stationary and portable oxygen concentrator system. "ResMed is the global leader in connected healthcare solutions for sleep and respiratory conditions," said John Rush, CEO, Inova Labs. "That's a perfect fit with our mission to offer oxygen therapy solutions that empower individuals to stay active and sleep well. We are excited about joining forces with ResMed and benefiting from their global expertise and innovative culture, to improve patient engagement and adherence to treatment, to create business efficiencies for home medical equipment providers, and to help enhance the quality of life for those suffering from COPD and other chronic respiratory conditions." The financial terms of the transaction were not disclosed. This transaction is subject to customary closing conditions, including regulatory approvals.

New Adapter Tracks Airway Pressure

Monaghan Medical Corporation, a leader in the development, manufacture, and marketing of respiratory devices, announced the release of a new Manometer Adapter for its Aerobika Oscillating Positive Expiratory Pressure (OPEP) device — a drug-free, clinically supported device that reduces coughing and breathlessness, increases lung hygiene, and improves gas transfer. The Manometer Adapter serves as a visual compliance tool for the Aerobika OPEP to assist respiratory therapists and patients in assessing respiratory therapy that calls for active exhalation. The MMC Aerobika OPEP device improves respiration by clearing mucus from the lungs through exhalation. OPEP therapy is highly effective in postoperative patients for airway clearance and lung hygiene, and for patients with chronic respiratory conditions such as cystic fibrosis. With the addition of a Manometer Adapter, respiratory therapists, clinicians, and patients can literally see with their own eyes how well the patient is using the device. The Aerobika OPEP device works by using active exhalation: The patient wraps his or her mouth around the OPEP mouthpiece and exhales, while the device uses pulses of air resistance to release mucus trapped in smaller air pathways. The Manometer Adapter allows clinicians to measure the pressure exerted by active exhalation to determine therapeutic effectiveness. It is ideal for clinical training, ensuring that the OPEP device is used properly. The Manometer Adapter — which has an easy-to-read scale that shows green when active exhalation is in the target zone of 5 cm to 20 cm H_2O — provides immediate patient feedback and confirms that the patient is achieving therapeutic pressure every time the OPEP device is used. "Postoperative patients and

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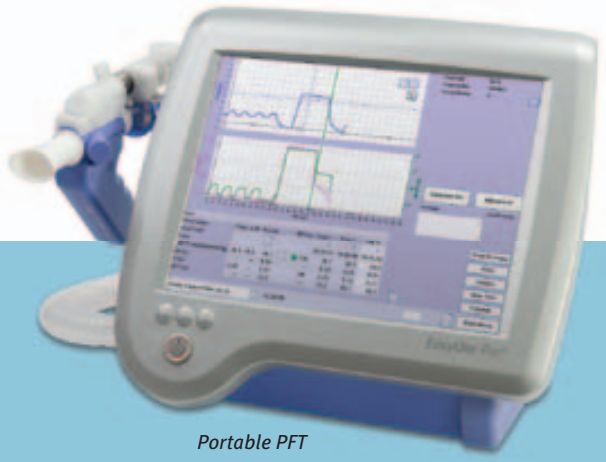

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patients with severe respiratory conditions needed a new kind of respiratory treatment," says Dom Coppolo, Vice President of Clinical Strategy and Development at Monaghan Medical Corporation. "That's why we developed the Aerobika OPEP Therapy System — to help treat ailments with a productive cough seeking a non-therapeutic method of removing mucus from the lungs. With the addition of the Manometer Adapter, we now have an OPEP device that is easy to use and easy to monitor. The Manometer Adapter provides a baseline for active exhalation therapy so practitioners can measure patients' recovery progress. "We are committed to providing products that ensure patients continue treatment and control their symptoms," Coppolo says. "Providing metrics to measure treatment efficacy only speeds recovery." The Aerobika OPEP is suitable for various patient treatments, such as post-operative thoracic recovery, lung volume expansion therapy, and atelectasis treatment, reducing the risk of pulmonary complications. The Aerobika OPEP is easy to use, has no side effects or interactions since it is drug-free, and, with the new Manometer Adapter, makes it easier than ever to monitor therapeutic pressure levels.

Critical Care Hospital Solutions Launched

Maquet Medical Systems USA announced the availability of its two new intensive care ventilators, SERVO-U, and its dedicated neonatal intensive care solution, SERVO-n. The launch of SERVO-U and SERVO-n marks the latest advancement in Maquet's longstanding leadership in mechanical ventilation and innovation with the SERVO brand. SERVO-U and SERVO-n were cleared by the U.S. Food and Drug Administration in December 2015. "SERVO-U and SERVO-n are quintessential Maquet products as each boasts our rich heritage in, and company-wide commitment to innovation in ventilation," said Raoul Quintero, President, Americas, Getinge Group. "Both ventilation platforms will allow us to bring additional, user-friendly support tools to clinicians at a time when care practice optimization is more important than ever. A clinician's ability to tailor ventilation to individual patient needs, through the intuitive user interface and the system's advanced capabilities like NAVA, is essential within the critical care environment. We believe that once our customers have tried SERVO-U and SERVO-n, they will never look at mechanical ventilators in the same way again." SERVO-U represents the next step to making protective ventilation more accessible, understandable and easy to implement, putting solutions at clinicians' fingertips to support the delivery of tailored patient care. At the foundation of SERVO-U is a completely touch-based interface that empowers users to manage ventilation in a highly intuitive and timesaving manner. The platform, which can be used on neonates through adults, supports efficient workflow in the fast-paced intensive care environment through on-screen, context-based guidance and clinical support tools that help facilitate the implementation of the various ventilation protocols. Available on each SERVO-U are innovative technologies such as NAVA (Neurally Adjusted Ventilatory Assist) and Edi monitoring for enhanced patient-ventilator interaction and greater insight into patient respiratory condition. In addition to the solutions that SERVO-U brings to patients and clinicians, the platform is designed to grow with the customer. When patient needs change or new functionalities become available, SERVO-U can be upgraded easily and cost-effectively. The intuitive ventilation platform is the result of a comprehensive development process that involved collaboration with intensive care experts from around the world. The launch of SERVO-U marks the latest offering in Maquet Medical System's SERVO franchise which has been a longstanding leader in the global mechanical ventilation market.

Get Off Their CHEST

The treatment of central sleep apnea in heart failure patients was debated at CHEST 2015, as experts discussed whether or not to reject the use of adaptive servo ventilation in this patient population in light of recent findings from the SERVE-HF trial. In that trial, all-cause mortality was 28% higher in the ventilation group than in the placebo group, and cardiovascular mortality was 34% higher. The current recommendation from the American Academy of Sleep Medicine (AASM) is to "not start anybody on adaptive servo ventilation who would have qualified for this trial."

Antibody Gets Nod From FDA

The monoclonal antibody reslizumab was recommended for approval by the US Food and Drug Administration's (FDA's) Pulmonary and Allergy Drugs Advisory Committee yesterday for use in treating adults aged 18 years and older with moderate to severe asthma. The committee said safety and efficacy data weren't strong enough for it to recommend approval of the drug for children aged 12 to 17 years. As to whether the safety and efficacy data support approval of the monoclonal antibody at a dose of 3 mg/kg by intravenous injection once every 4 weeks, the committee voted 11 to 3 in favor of treating adults and a resounding no (14 to 0) for children. The meeting was called to discuss the biologics license application for reslizumab for injection, submitted by Teva Pharmaceutical Industries Ltd to reduce exacerbations, relieve symptoms, and improve lung function for people 12 years old and older with asthma and elevated blood eosinophils whose condition is inadequately

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controlled with inhaled corticosteroids. Reslizumab is not currently marketed in the United States or any other country. If approved by the FDA, it would be the third monoclonal antibody approved for asthma, after mepolizumab and omalizumab. Reslizumab binds to human interleukin-5 (IL-5). Several cytokines can affect eosinophils, but IL-5 is the main cytokine involved in regulating blood and tissue eosinophils.

Orphan Drug Approved

The US Food and Drug Administration (FDA) has approved the orphan drug selexipag (Uptravi, Actelion) for treatment of adults with pulmonary arterial hypertension (PAH), a chronic and progressive rare lung disease that can lead to premature death or the need for transplantation. Selexipag is an oral IP prostacyclin receptor agonist that relaxes muscles in the walls of blood vessels to dilate blood vessels and decrease the elevated pressure in the vessels supplying blood to the lungs. The safety and efficacy of selexipag were demonstrated in a clinical trial of 1156 adults with PAH who were treated for a median of 1.4 years. The drug proved effective in reducing hospitalization for PAH and the risk for disease progression compared with placebo, the FDA said. The benefit of selexipag was "consistent across pre-specified patient subgroups such as disease etiology, functional class and baseline PAH therapy, including patients already receiving combination therapy with an endothelin receptor antagonist and a PDE-5 inhibitor," the company said in a news release. Common adverse effects seen in the trial included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, and flushing. The company expects selexipag to launch in the United States in early January. Selexipag is currently under review in Europe, Australia, Canada, New Zealand, South Korea, Switzerland, and Taiwan, the company said.

Asthma Rates Studied in US

Rates of asthma prevalence in the United States are leveling off and possibly declining, but not among the poor, according to a study. Overall prevalence of childhood asthma doubled from 1980 (3.6%) to 1995 (7.5%), increased at a slower rate from 2001 (8.7%) to 2009 (9.7%), and dipped in 2010 (9.3%). The 1980s saw no or little disparity in asthma prevalence between black and white children, but asthma prevalence doubled for black children by 2010. Because deeper understanding of the epidemiology of asthma could aid prevention, Lara J. Akinbami, MD, from the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland, and colleagues extended analysis of asthma prevalence from 2001 to 2013. They analyzed subgroup differences in answers to the questions "Has a doctor or other health professional ever told you that your child had asthma?" and "Does your child still have asthma?" from the National Health Interview Survey (NHIS). The results confirm that asthma prevalence among children (aged 0-17 years) increased from 2001 to 2008. After 2008, prevalence plateaued and then declined. In 2012, it was 9.3%; in 2013, 8.3%. After adjustment for factors including gender, age group, poverty status, race/ethnicity, family structure, urbanicity, and geographic region, four characteristics were significant: age group, poverty status (ratio of family income to the federal poverty level: "poor," "near poor," and "nonpoor"), race/ethnicity, and geographic region. Prevalence was similar among 5- to 9-year-olds and 10- to 17-year-olds, but lower among 0- to 4-year-olds. Asthma prevalence increased linearly significantly among poor children, whereas prevalence change was nonlinear for near poor and nonpoor children. There was no significant trend for non-Hispanic white or Puerto Rican children, but a significant nonlinear trend for non-Hispanic black and Mexican-American children.

Wheezing in Babies

Pregnant women cannot dramatically reduce the risk of wheezing in their babies by taking vitamin D supplements, two new studies suggest, but the studies did show enough benefit that researchers remain optimistic. "[A] clinically important protective effect cannot be excluded, and a protective effect is suggested by the observed effect on airway immunology and symptomatic episodes," write Bo L. Chawes, MD, PhD, from the University of Copenhagen, Denmark, and colleagues. Asthma often begins in early childhood and is the most common chronic childhood disorder. The incidence has increased during the last half-century in developed countries. Vitamin D deficiency has also become a common health problem in developed countries, possibly caused by a more sedentary indoor lifestyle, use of sunscreen, and decreased intake of vitamin D-containing foods. Vitamin D possesses a range of immune regulatory properties, and it has been speculated that vitamin D deficiency during pregnancy may affect fetal immune programming and contribute to the development of asthma.

Risks Reduced

For infants with acute bronchiolitis, nebulized hypertonic saline (HS) can reduce the risk for hospitalization in outpatients and reduce the length of hospital stay among inpatients, a new study suggests from Federal University of Rio Grande, Brazil, and colleagues. published the results of their systematic review and meta-analysis online September 28 and in the October issue of Pediatrics. "[T]his new systematic review shows that nebulized HS is associated with a mean reduction of 0.45 days (~11 hours) in [length of stay (LOS)] among infants admitted for acute bronchiolitis and a mean reduction of 20% in the risk of hospitalization among outpatients," the authors write. "This review also suggests that nebulized HS is a safe treatment in infants with bronchiolitis, especially when administered in conjunction with a bronchodilator." Acute bronchiolitis is the most frequent lower respiratory tract infection and the leading cause of hospitalization in children younger than 2 years. It is usually caused by a viral infection, most commonly resulting from respiratory syncytial virus. In the United States, the estimated annual cost of hospitalization for children with acute bronchiolitis is US$500 million. According to the authors, hospital admissions for acute bronchiolitis are also increasing, rising from 21,330 in 2004 and 2005 to 33,472 in 2010 and 2011.

Pressure Controller Launched for Mechanical Ventilators

After successful FDA approval, Hamilton Medical is launching the IntelliCuff pressure controller in the US. Previously available as an option for the ventilator HAMILTON-G5, the innovative IntelliCuff technology has now been given its own housing. The ergonomic, hand held device is now available for use with all mechanical ventilators. The IntelliCuff pressure controller continuously measures and automatically maintains the cuff pressure during mechanical ventilation of adults, pediatrics, and neonates using a cuffed endotracheal tube or tracheostomy. This handy device ensures an optimal cuff pressure, which increases patient safety. It also delivers cost savings and greater efficiency within daily routines in hospitals. It can be used in intensive care units, operating rooms and for inter-hospital transport. The leakage of oral secretions past the endotracheal tube (ETT) is a causative risk factor in the development of ventilator associated

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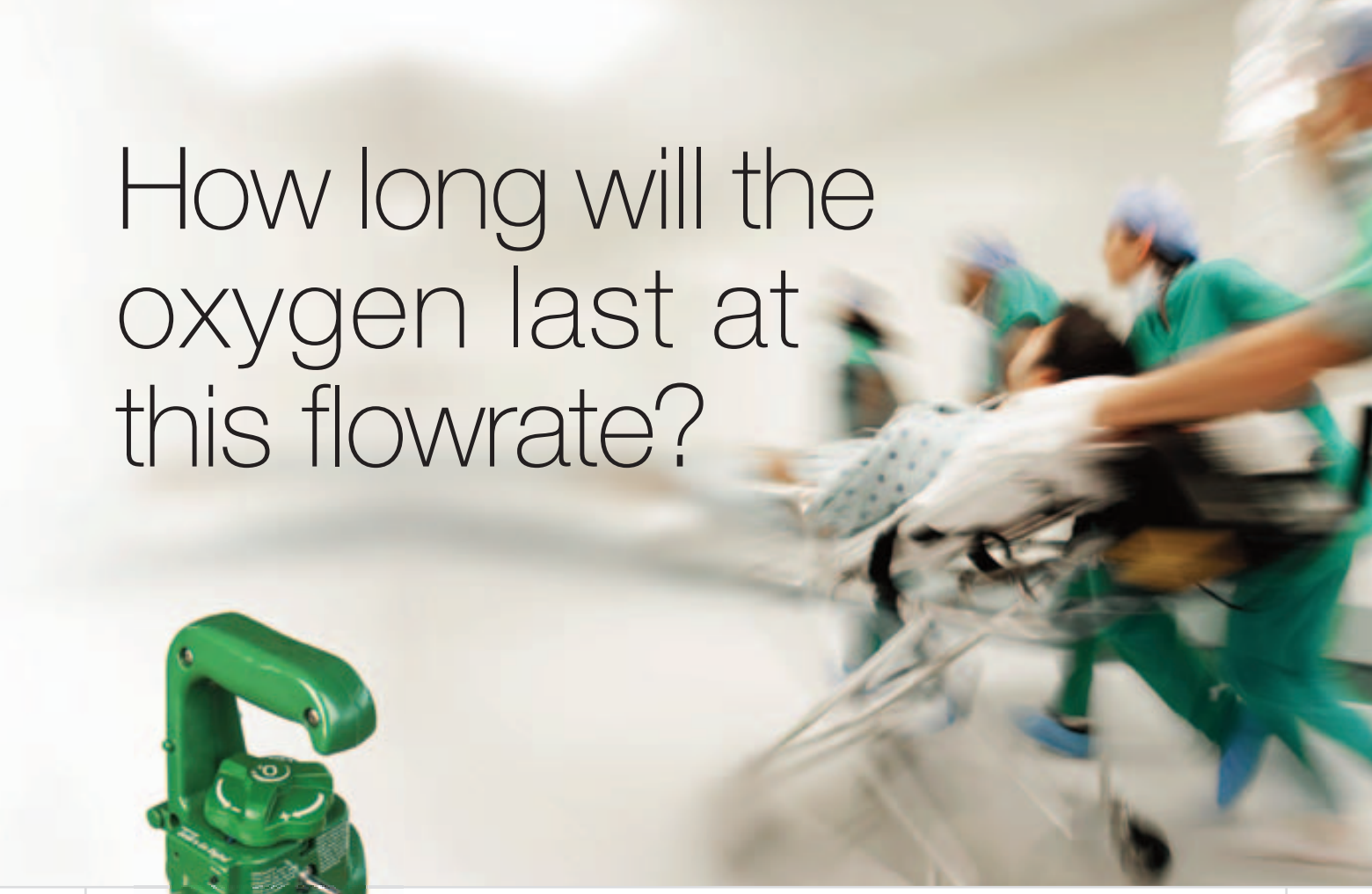

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pneumonia (VAP), and excessive cuff pressure is a risk factor in tracheal injuries. Continuously optimized and controlled cuff pressure supports ventilation therapy and protects patients. Hamilton Medical has developed IntelliCuff to make mechanical ventilation more efficient and, above all, safer. Existing solutions for endotracheal tube cuff pressure management require manual monitoring and adjustment of cuff pressure, which is a critical aspect of the ICU staff workload. It has been shown that up to eight manual adjustments of cuff pressure are required daily to maintain recommended cuff pressure ranges. The cuff pressure controller of Hamilton Medical permanently maintains and measures the set cuff pressure with two sensors working independently. The device is designed for immediate use; no calibration is required. It operates in a wide but still safe range of desired cuff pressures for various cuffed endotracheal tubes to provide suitable solutions for various clinical situations. In critical situations, clinical staff can increase the cuff pressure for a user-defined period of time to secure the airway and avoid aspiration or unintended extubation; for example, in the event of vomiting, repositioning of the tube, or changes in patient positioning. Short-duration pressure increases—typical during coughing or retching—are tolerated by the device to maintain the self-sealing functions of high-volume low-pressure cuffs and to avoid needless alarms. To simplify a safe extubation, the IntelliCuff deflates the cuff on command. A large-scale display and convenient interaction buttons make adjusting and verifying settings easy. At all times, the important data is visible supporting an intuitive operation. IntelliCuff generates an alarm when a leaking cuff or disconnected tubing is detected, as well as in cases of excessive pressure, low battery, or a technical fault. When appropriate, it is also possible to silence some alarms while medical staff remedy the situation. The IntelliCuff disposable tubing is designed to fit the Luer connector on a variety of cuffed tubes. The shut-off valve prevents loss of cuff pressure in case of an accidental disconnection between the device and the tubing.

When Lung Problems Overlap

Asthma and chronic obstructive pulmonary disease (COPD) are both common and well-recognized airway disorders. They have usually been considered discrete entities with treatments that are described by different guidelines, but with considerable overlap. Recently, however, allergists and pulmonologists, believing that the two disease categories overlap, have designated a new category of airways disorder known as asthma-COPD syndrome (ACOS). Postma and Rabe recently published a discussion of ACOS, including its principal features and suggestions for its management. Asthma is an inflammatory disorder that typically develops in childhood and is often accompanied by allergies. Reversible airways obstruction is a typical feature of asthma that is amenable to corticosteroid administration. Inflammation in asthma is characterized by the presence of eosinophils and type 2 helper T lymphocytes. COPD is an inflammatory disorder that typically develops in cigarette smokers in middle age. Airways obstruction is a hallmark of COPD disorder, and the response to corticosteroids is modest or absent. COPD-related inflammation is predominantly the result of neutrophils and involves CD8 lymphocytes. Both asthma and COPD have several phenotypes, which adds to the challenge of precise identification. Reversibility of airways obstruction by bronchodilators has often been taken as a feature of asthma that is not present in COPD, but this has been shown to be incorrect because the two disorders cannot be differentiated by their response to bronchodilators. Postma and Rabe address the issue of whether and when it is appropriate to apply the diagnosis of ACOS to a patient with some features of both airway disorders. They also discuss what treatment should be administered to patients with ACOS. As they state, "the answer to these questions cannot be evidence-based because studies addressing ACOS as a disease entity have yet to be conducted."

TB Outbreak in Alabama

The small rural Alabama town of Marion in Perry County is in the midst of an outbreak of tuberculosis (TB), with two additional cases identified February, according to the Alabama Department of Public Health (ADPH). "This town historically has had no TB," Pam Barrett, director, Division of TB Control, ADPH, noted. "Since early 2014, we've had 29 cases of active TB that are either genotypically or epidemiologically linked to the town of Marion. A lot of those have completed treatment. We only have 11 currently being treated for active TB in Marion," Barrett said. Three adults with TB have died. The latest two cases involve an adult and a child aged less than 15 years. "The child was diagnosed very early through the Health Department's screening program before having symptoms of TB disease. The child had been in very close contact with an adult who had TB disease. Both of the new patients and another adult patient whose TB disease was confirmed earlier are on TB medication and doing well," according to an ADPH press release. As of February 2, 2016, ADPH had screened 2023 patients in Marion, Perry County. A total of 394 children were tested as part of the screening process and seven children were identified as being exposed to the TB bacteria. Altogether, a total of 151 patients have tested positive for TB. Most of these patients have received chest X-rays and have started treatment to prevent them from getting TB disease and spreading it. The TB case rate in Marion (roughly 253 per 100,000) "far exceeds" the TB case rate for the entire state of Alabama, ADPH says, and many developing countries, according to the World Bank.

Benefits of Using Steroids

A National Institutes of Health study has shown that infants born at 34 to 36 weeks of gestation can benefit from antenatal steroids in much the same way that younger preemies do. In a study of 2831 women, the use of antenatal betamethasone reduced the chance of respiratory complications in "late" preterm infants, who constitute about 8% of all deliveries. The study results were presented by Cynthia Gyamfi-Bannerman, MD, from the perinatal clinic at the Columbia University Medical Center in New York City, here at the Society for Maternal-Fetal Medicine 2016 Pregnancy Meeting, and were published online simultaneously in the New England Journal of Medicine. Women who participated in the study were in weeks 34 to 36 of their pregnancies and were at high risk of delivering before 37 weeks. Prenatal steroid therapy for women delivering late preterm infants could greatly reduce the rate of serious respiratory complications. The investigators defined a high probability of delivery as preterm labor with intact membranes and at least 3 cm dilation or 75% effacement of the cervix; spontaneous rupture of the membranes; or expected preterm delivery for any other indication by induction or cesarean 24 hours to 7 days after planned randomization, as determined by the obstetric provider.

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Automated Patient-Ventilator Interaction Analysis During Neurally Adjusted Non-Invasive Ventilation and Pressure Support Ventilation in Chronic Obstructive Pulmonary Disease

Jonne Doorduin[1], Christer A Sinderby,[2,4] Jennifer Beck,[3,4] Johannes G van der Hoeven[1] and Leo MA Heunks[1]

Abstract

Introduction: Delivering synchronous assist during non-invasive ventilation (NIV) is challenging with flow- or pressure-controlled ventilators, especially in patients with chronic obstructive pulmonary disease (COPD). Neurally adjusted ventilatory assist (NAVA) uses diaphragm electrical activity (EAdi) to control the ventilator. We evaluated patient-ventilator interaction in patients with COPD during NIV with pressure support ventilation (PSV) and NAVA using a recently introduced automated analysis.

Methods: Twelve COPD patients underwent three 30-minute trials: 1) PSV with dedicated NIV ventilator (NIV-PSV_{Vision}), 2) PSV with intensive care unit (ICU) ventilator (NIV-$PSV_{Servo-I}$), and 3) with NIV-NAVA. EAdi, flow, and airway pressure were recorded. Patient-ventilator interaction was evaluated by comparing airway pressure and EAdi waveforms with automated computer algorithms. The NeuroSync index was calculated as the percentage of timing errors between airway pressure and EAdi.

Results: The NeuroSync index was higher (larger error) for NIV-PSV_{Vision} (24 (IQR 15 to 30) %) and NIV-$PSV_{Servo-I}$ (21 (IQR 15 to 26) %) compared to NIV-NAVA (5 (IQR 4 to 7) %; $P < 0.001$). Wasted efforts, trigger delays and cycling-off errors were less with NAVA ($P < 0.05$ for all). The NeuroSync index and the number of wasted efforts were strongly correlated ($r^2 = 0.84$), with a drastic increase in wasted efforts after timing errors reach 20%.

Conclusions: In COPD patients, non-invasive NAVA improves patient-ventilator interaction compared to PSV, delivered either by a dedicated or ICU ventilator. The automated analysis of patient-ventilator interaction allowed for an objective detection of patient-ventilator interaction during NIV. In addition, we found that progressive mismatch between neural effort and pneumatic timing is associated with wasted efforts.

Introduction

Non-invasive ventilation (NIV) plays an important role in managing patients with acute respiratory failure, in particular in patients with chronic obstructive pulmonary disease (COPD). In patients with acute hypercapnic exacerbation of COPD, NIV improves outcome.[1-3] Accordingly, NIV utilization has increased over time among patients hospitalized for acute exacerbation of COPD, whereas the need for intubation has declined.[2] Despite these positive reports, some patients treated with NIV fail and require invasive mechanical ventilation.[3,4] Poor patient-ventilator interaction may contribute to NIV failure.[5,6] Delivering synchronous non-invasive assist is challenging with flow- or pressure-controlled systems,[7] especially when using excessively leaky or highly compliant interfaces.[8] Using ventilators not dedicated to NIV, up to 46% of patients exhibit severe asynchrony.[9] The introduction of dedicated NIV ventilators and NIV algorithms in ICU ventilators improved patient-ventilator interaction, yet their performance varies and the inherent limitations of using flow or pressure to control assist remain.[10]

As recommended,[11,12] patient-ventilator interaction can be evaluated by using the diaphragm electrical activity (EAdi).[13] Besides its monitoring capabilities, EAdi is used during neurally adjusted ventilatory assist (NAVA) as a controller signal for ventilatory assist.[14] Recent studies in heterogeneous groups of critically ill patients show that non-invasive NAVA (NIV-NAVA) improves patientventilator interaction relative to non-invasive pressure support ventilation (NIV-PSV).[15-18]

To our knowledge, there are no studies of patientventilator interaction strictly in COPD patients receiving NIV-NAVA, while these patients are more likely to exhibit severe patient ventilator asynchrony.[19] In addition, no study has used the EAdi signal to evaluate patient-ventilator interaction with dedicated NIV ventilators. Moreover, a new automated analysis method has recently been introduced in this journal for quantifying patient-ventilator interaction in a standardized fashion.[20] This automated analysis allows detection of asynchronies, such as wasted efforts, but also makes it easy to detect the more subtle dyssynchronies, such as trigger delays and cycling-off errors. The present study is the first to use this analysis method to quantify patientventilator interaction during non-invasive ventilation.

For the above-stated reasons, the aim of the present study was to evaluate patient-ventilator interaction, using an automated analysis, in COPD patients with NIV-PSV delivered by a dedicated NIV ventilator, and NIV-PSV and NIV-NAVA delivered by an ICU ventilator.

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Materials and methods

Study subjects

Adult patients with acute respiratory failure and a medical history of COPD, admitted to the ICU for non-invasive ventilation were eligible for inclusion in the study. Patients with a known neuromuscular disorder, severe hypoxemic failure (PaO_2/FiO_2 < 100 mmHg), or hemodynamic instability requiring high-dose norepinephrine (>0.5 µg/kg/min) were excluded. The study was approved by the ethics committee of the Radboud University Medical Center (NL33351.091.11) and is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to the study.

Study design

All patients undergoing NIV in our hospital receive a nasogastric tube to allow adequate feeding and prevent gastric hyperinflation. COPD patients undergoing NIV receive a nasogastric tube with a multiple array of electrodes placed at the distal end (NAVA catheter, 12 French; Maquet Critical Care, Solna, Sweden). Correct positioning was established by use of dedicated software. After enrollment and clinical stabilization, each patient received three 30-minute ventilation protocols in the following order:

1. PSV with the BiPAP Vision (Philips Respironics, Best, The Netherlands), a dedicated NIV ventilator, with pressure support and positive-end expiratory pressure (PEEP) levels set by the treating physician ($NIV\text{-}PSV_{Vision}$).
2. PSV with the Servo-I (Maquet Critical Care, Solna, Sweden, NIV software v3.0), an ICU ventilator with NIV algorithm, with similar PEEP and pressure support levels ($NIV\text{-}PSV_{Servo\text{-}I}$).
3. NAVA with the Servo-I (Maquet Critical Care, Solna, Sweden, NIV software v3.0), where NAVA level was adjusted to match peak pressure of NIV-PSV, using manufacturer-supplied software (NIV-NAVA).

BiPAP Vision uses the Auto-Trak Sensitivity algorithm to trigger and cycle off the ventilator and cannot be set individually. With NAVA, the back-up mode for triggering was set at flow triggering. In order to reduce the amount of leakage on ventilator performance, we chose to use a tightly fitted oronasal mask (Respironics PerforMax, Philips, Best, The Netherlands), a frequently used interface.[21] Switching between ventilators required modifications in measurement setup and short disconnection of the patient from the ventilatory circuit. In order to minimize discontinuation of assist, the order of interventions were not randomized.

At the end of each ventilator mode, respiratory discomfort was scored by use of a Visual Analog Scale (from 0 mm (no discomfort) to 100 mm (maximal imaginable discomfort)) and arterial blood gas analysis was performed from an indwelling arterial line.

Data acquisition

Flow, airway pressure (Paw) and EAdi were acquired from the serial port of the Servo-I at a sampling rate of 62.5 Hz and recorded using dedicated acquisition software (Neurovent Research Inc., Toronto, ON, Canada). The BiPAP Vision does not have a data output port. Therefore, flow was acquired by placing a pneumotachograph (Fleisch no. 3, Phipps & Bird, Richmond, VA, USA) between the airflow port of the ventilator and its tubing, and Paw was acquired by placing a connection piece between the end of the tubing (after the leakage port) and the face mask, connected to a pressure transducer (range ±50 kPa, Freescale Semiconductor, Tempe, AZ, USA). Both Paw and flow were recorded at a sampling rate of 62.5 Hz and synchronized with the EAdi using dedicated acquisition software (Neurovent Research Inc., Toronto, ON, Canada).

Data analysis

Study parameters were calculated from a stable 5-minute period at the end of each mode on a breath-by-breath basis using a software routine developed for Matlab (Mathworks, Natick, MA, USA). Measuring tidal volume by expiratory flow integration is not precise in the presence of leaks, therefore, tidal volumes are not presented in the manuscript. Neural respiratory rate was calculated as the number of EAdi peaks/min.

Patient-ventilator interaction was evaluated by comparing Paw and EAdi waveforms with automated computer algorithms.[20] Trigger and cycle-off error (that is dyssynchrony) were calculated as percentages of neural inspiratory and expiratory time periods, respectively. Events where EAdi and Paw were completely dissociated (that is asynchrony), such as wasted efforts, auto-triggering, multiple assist during EAdi peak (double

Table 1 Patient characteristics at study inclusion

Number	Age (y)	BMI (kg/m^2)	FEV1 (% pred.)	FVC (% pred.)	FEV1 /FVC	GOLD class.	PF ratio	Reason for admission	Total NIV duration (days)
1	37	25				I	316	Haemoptysis	5
2	74	23				I	308	Exacerbation COPD	3
3	68	38	45	79	42	III	185	Exacerbation COPD	3
4	67	34	69	98	70	II	176	Pneumonia	4
5	67	27	72	100	53	II	180	Exacerbation COPD	5
6	64	26	31	52	43	III	220	Trauma	3
7	58	26				II	143	Exacerbation COPD	6
8	70	28	67	90	55	II	215	Post-op lobectomy	2
9	78	22	77	88	64	II	110	Exacerbation COPD	3
10	75	17	23	61	28	IV	219	Exacerbation COPD	1
11	76	25	62	101	45	II	246	Exacerbation COPD	5

Recent lung function tests for patient 1, 2 and 7 were unavailable in our hospital, but clinical pictures of these patients were consistent with COPD and patient correspondence stated a history of COPD. BMI: body mass index; FVC: forced vital capacity; FEV1: forced expired volume in 1 second; GOLD class: Global Initiative for Chronic Obstructive Lung Disease classification; PF ratio: PaO_2/FiO_2.

Table 2 Ventilator settings

Patient	PS level (cmH2O)	PS rise time (s)	PS cycle off (% peak flow)	NAVA level (cmH2O/μV)	NAVA trigger (μV)	PEEP (cmH2O)	FiO_2 (%)
1	6	0.20	30	0.1	0.5	6	70
2	10	0.20	50	0.8	0.5	8	50
3	8	0.20	70	0.4	0.5	8	50
4	5	0.20	50	0.1	1.0	7	60
5	6	0.20	50	0.1	0.5	4	40
6	5	0.05	50	5.0	0.5	5	30
7	10	0.00	50	0.2	0.5	6	55
8	6	0.20	50	0.2	0.5	6	45
9	6	0.20	50	0.2	0.5	6	70
10	8	0.00	60	0.1	0.5	5	35
11	6	0.20	50	0.2	0.5	6	40

Pressure support (PS) levels and rise time hold for both ventilators, whereas cycle-off criteria is only set for NIV-$PSV_{Servo-I}$. The BiPAP Vision uses the Auto-Trak Sensitivity algorithm to trigger and cycle off the ventilator and cannot be set individually. PEEP and FiO2 were similar for all three ventilatory modes. FiO_2: inspired oxygen fraction; NAVA: neurally adjusted ventilatory assist; PEEP: positive end-expiratory pressure.

triggering) and multiple EAdi peaks during assist, were assigned 100% error. To estimate the overall extent of asynchrony and dyssynchrony, we calculated the NeuroSync index by averaging the percentage errors for all breaths.

Statistical analysis

The D'Agostino and Pearson test was used to test the normality of distribution. NIV-PSV_{Vision}, NIV-$PSV_{Servo-I}$ and NIV-NAVA were compared using the Friedman test with Dunn's *post hoc* testing. Exponential regression analysis using a least squares fit was performed to test the relationship between the NeuroSync index and wasted efforts. A P value <0.05 was considered significant. Statistical analyses were performed with Graphpad Prism 5 (Graphpad Software, San Diego, CA, USA). Results are reported as median with interquartile ranges.

Results

Twelve patients (one female/eleven male) were enrolled. One patient was excluded from the offline analysis due to an EAdi signal with too low an amplitude for automated patient-ventilator interaction analysis.[20] Patient characteristics and ventilator settings are shown in Tables 1 and 2, respectively. After study completion, NIV failed in two patients and invasive ventilation was required. From these two patients, one deceased.

Breathing pattern and respiratory drive

Results for breathing pattern and respiratory drive are presented in Table 3. EAdi amplitude was higher with NIV-$PSV_{Servo-I}$ compared to NIV-PSV_{Vision} (P <0.05). Peak airway pressure and peak flow were higher with NIV-PSV_{Vision} (P <0.05) compared to NIV-NAVA and NIV-$PSV_{Servo-I}$.

Table 3 Breathing pattern and respiratory drive

	NIV-PSV_{Vision}	NIV-$PSV_{Servo-I}$	NIV-NAVA
Peak EAdi (μV)	25.6 (18.6 - 43.5)*	34.7 (18.8 - 49.0)	23.8 (17.1 - 48.0)
Peak airway pressure (cmH_2O)	15.3 (13.0 - 18.5)*#	12.5 (10.4 - 15.2)	12.9 (11.7 - 16.0)
Inspiratory peak flow (L/min)	92.5 (72.1 - 110.0)*#	54.1 (46.8 - 63.2)	45.6 (38.7 - 61.1)
Neural resp. rate (breaths/min)	22.7 (17.6 - 27.0)	25.2 (18.5 - 28.2)	25.1 (18.3 - 31.7)

*NIV-PSV_{Vision} vs. NIV-$PSV_{Servo-I}$ (P <0.05), #NIV-PSV_{Vision} vs. NIV-NAVA (P <0.05). EAdi, electrical activity of the diaphragm; NAVA: neurally adjusted ventilatory assist; NIV: non-invasive ventilation; PSV: pressure support ventilation.

Patient-ventilator interaction

Figure 1 depicts median values for trigger delays and cycling-off error during each mode for all individual patients. NIV-NAVA showed lowest trigger delay compared to NIV-PSV_{Vision} and NIV-$PSV_{Servo-I}$ (P <0.0001). NIV-PSV_{Vision} and NIV-$PSV_{Servo-I}$ had comparable trigger delays, but NIV-$PSV_{Servo-I}$ showed more early cycling off (P <0.05). In absolute values, NIV-PSV_{Vision} (95 ± 22 ms) and NIV-$PSV_{Servo-I}$ (91 ± 19 ms) showed more cycling-off error compared to NIV-NAVA (12 ± 6 ms); P <0.05.

Patient-ventilator interaction, calculated with the NeuroSync index, was significantly higher (larger error) with NIV-PSV_{Vision} (24 (interquartile range (IQR) 15 to 30) %) and NIV-$PSV_{Servo-I}$ (21 (IQR 15 to 26) %) compared to NIV-NAVA (5 (IQR 4 to 7) %; P <0.001).

Figure 2 depicts the correlation between the number of wasted efforts and the NeuroSync index. The relationship shows as timing errors progressively increased with NIV-$PSV_{Servo-I}$ and NIV-PSV_{Vision} a positive association with the number of wasted efforts, which was certainly more pronounced above 20% error.

For all three modes of NIV studied, Figure 3 shows a plot of the relative timing errors of triggering (Y-axis) versus the relative timing error for cycling off (X-axis), for every breath, in all patients. Based on the data from Figure 2, we have inserted a box suggesting 'acceptable' synchrony to be ≤20% of neural timings, whereas larger errors (>20%) represent dyssynchrony.

In the form of a pie chart, Figure 4 plots the distribution of synchrony (≤20% error, that is inside the box in Figure 3), dyssynchrony (>20% error, that is outside the box in Figure 3), and asynchronies for each mode. Wasted efforts were the most prevalent type of asynchrony and differed between ventilator modes (P <0.001). *Post hoc* analysis indicated significantly more wasted efforts with NIV-PSV_{Vision} compared to NIV-NAVA. Other asynchronies, such as multiple EAdi during assist, double triggering and auto-triggering were uncommon.

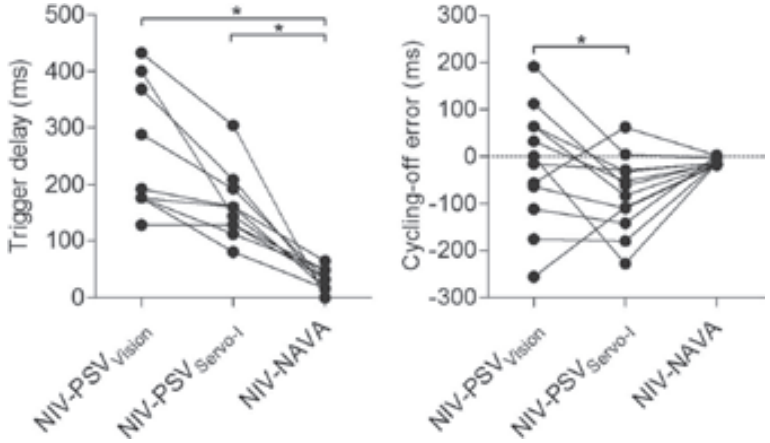

Figure 1 Trigger delay (left) and cycling-off error (right) for the different ventilator modes. Y-axis for cycle-off error: positive values indicate late cycling off, and negative values indicate early cycling off. *P <0.05. NAVA: neurally adjusted ventilatory assist; NIV: non-invasive ventilation; PSV: pressure support ventilation.

Blood gas values and respiratory discomfort

There were no differences in blood gas values (Table 4) and respiratory discomfort with NIV-PSV_{Vision} (45 (IQR 31 to 69) mm), NIV-$PSV_{Servo-I}$ (60 (IQR 41 to 65) mm), and NIV-NAVA (45 (IQR 33 to 75) mm).

Discussion

This study provides insight into the interaction between patient and ventilator during non-invasive ventilation with different types of ventilators and modes in patients with COPD. First, we show that neurally adjusted noninvasive ventilation synchronizes assist to inspiratory effort in patients with COPD, whereas dedicated NIV ventilator or ICU ventilator pressure support modes do not ensure acceptable patient-ventilator interaction in individual patients. Second, wasted efforts increase drastically after timing errors between EAdi and airway pressure reach 20%. Third, automated analysis of patient-ventilator interaction using computer algorithms allows objective detection of patient-ventilator interaction during NIV.

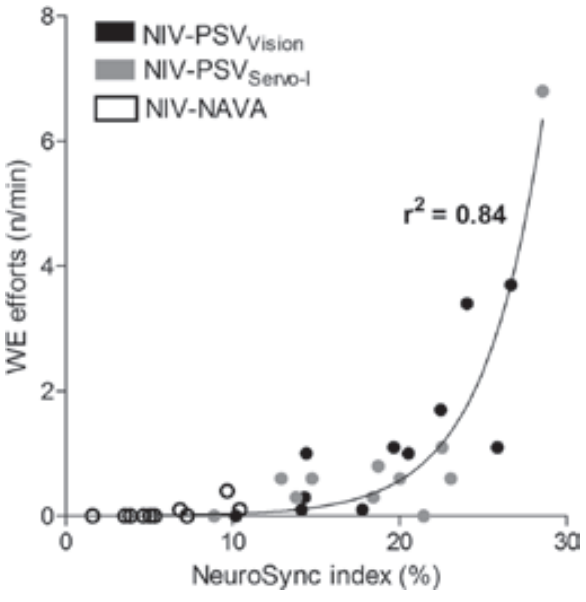

Figure 2 Correlation between the number of wasted efforts and the NeuroSync index. Note that for this regression analysis, the NeuroSync index was recalculated without wasted efforts to avoid mathematically coupled variables, and is thus consequently primarily a measure of dyssynchrony (trigger and cycle-off errors). Accordingly this correlation shows that progressive dyssynchrony, increases the number of wasted efforts. NAVA: neurally adjusted ventilatory assist; NIV: non-invasive ventilation; PSV: pressure support ventilation.

Patient-ventilator interaction

For effective unloading of the respiratory muscles with NIV, the ventilator should cycle in synchrony with the patient's neural respiratory drive.[5] Our results are consistent with previous studies that showed improved patient-ventilator interaction with neurally compared to pneumatically controlled mechanical ventilation,[15-18] however, several differences between these and the current study should be noted. First, we included only patients with COPD, which are more likely to exhibit poor patientventilator interaction.[19] Second, dedicated NIV-NAVA and NIV-PSV software was used instead of software for invasive ventilation in the previous studies.[16,17] This is important as the software for invasive ventilation lacks leakage compensation thereby allowing auto-triggering at high leakage. Indeed, auto-triggering up to 6 breaths/min was found with NIV-NAVA using the invasive software,[16] whereas we found only up to 1 breath/min. Third, a dedicated NIV ventilator was evaluated in the present study. In bench-test comparisons, including the ventilator used in our study, PSV delivered by dedicated NIV ventilators allowed better patient-ventilator interaction than ICU ventilators with NIV algorithms.[10,22] Lastly, an automated analysis method for quantifying patient-ventilator asynchronies and the more subtle dyssynchronies was used,[20] allowing a more objective detection of patient-ventilator interaction.

The present study showed a small trigger delay with NIV-NAVA, which substantially increased with NIV-$PSV_{Servo-I}$ and NIV-PSV_{Vision}. These findings agree with previous work comparing NIV-$PSV_{Servo-I}$ and NIV-NAVA,[15] but oppose a previous bench test showing longer trigger delay for NIV-$PSV_{Servo-I}$ compared to NIV-PSV_{Vision}.[22] NAVA triggers on the increase in EAdi and thus represents the duration to increase EAdi, to process the signal and to open the inspiratory valve. Our average trigger delay of about 50 ms with NIV-NAVA is in the range previously reported for NIV-NAVA.[15,16,18] In contrast, pneumatic triggering is more complex and considerably affected by leakage, which can only be partly compensated for by dedicated NIV algorithms.[7]

Synchronized termination of assist is another key component to maintain good patient-ventilator interaction. As depicted

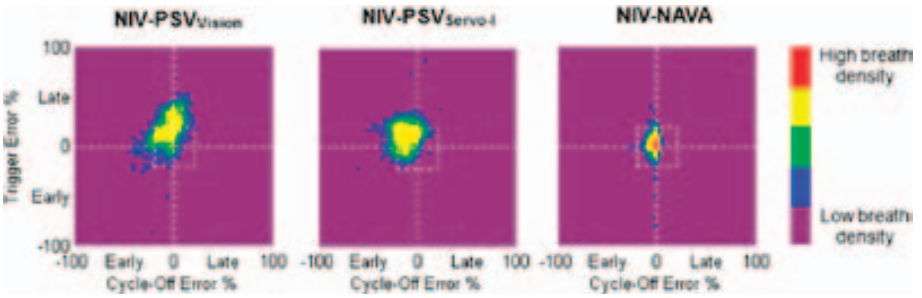

Figure 3 Breath density graph for relative trigger (Y-axis) and cycling-off (X-axis) errors, for all breaths in all patients, during each ventilator mode. The small white 'box' in the center of each graph indicates the limit between synchrony (neural efforts matched to assist delivery with less than 20% error - inside the box) and dyssynchrony (neural efforts poorly related to assist delivery, >20% error - outside the box). These breath-density graphs show for NIV-NAVA a concentrated breath density in the center, which should be anticipated since it is driven by EAdi. With NIV-PSV$_{Vision}$ and NIV-PSV$_{Servo-I}$ breaths are more spread out and have considerable proportions of dyssynchronous breaths compared to NIV-NAVA. NAVA: neurally adjusted ventilatory assist; NIV: non-invasive ventilation; PSV: pressure support ventilation.

in Figure 1, NIV-PSV$_{Vision}$ showed large intersubject variability in early and late cycling off, whereas NIV-PSV$_{Servo-I}$ showed primarily early cycling off. Cycling-off error in NIV-NAVA was negligible, which could be anticipated since its definition for cycling off is similar to the algorithm used to quantify cycling-off error (70% of peak EAdi). These findings agree with previous suggestions that NIV algorithms for ICU ventilators tend to increase the incidence of premature cycling off.[7]

Wasted efforts are inspiratory efforts not rewarded by ventilatory assist, which can increase the work of breathing.[5,6] In the present study, 4.3% and 2.5% of inspiratory efforts were unnoticed by the ventilator for NIV-PSV$_{Vision}$ and NIV-PSV$_{Servo-I}$, respectively. In contrast, NIV-NAVA effectively prevented wasted efforts, confirming previous studies.[15,16,18] Furthermore, as depicted in Figure 2, we found that wasted efforts increase drastically after timing errors reach 20%. This suggests that the limits of the NeuroSync index and the definition of 'acceptable' synchrony should be kept below 20%, as indicated by the centered boxes in Figure 3.

Breathing pattern and respiratory drive

EAdi in the present study was higher with NIV-PSV$_{Servo-I}$ compared to NIV-PSV$_{Vision}$, which is difficult to explain. Lack of difference in blood gases or respiratory rates contradict that increased EAdi with NIV-PSV was ventilation related. Premature cycling off with NIV-PSV$_{Servo-I}$ could be a probable cause for increased EAdi, since this results in unassisted inspiration in the last part of inspiration. It should also be noted that the design of the respiratory circuit and assist delivery of the BiPAP Vision is fundamentally different from the Servo-I. For example, the BiPAP Vision system has a large intentional leakage. Consequently, from Ohm's law it follows that higher flow is required to maintain the preset pressure level (Table 3). Higher flow might have resulted in higher CO_2 clearance in the interface and upper airways and a consequent reduction in dead space leading to reduced respiratory drive.

Clinical implications

Good patient-ventilator interaction is one of the key factors for clinical success of NIV, thus solving poor patient-ventilator interaction in COPD patients is of potential clinical value. In our study, we demonstrate that progressive mismatch between timing of the patient's neural drive and the response of the ventilator is associated with increased number of wasted efforts. It is tempting to speculate that improving synchrony between patient neural effort and ventilator assist improves outcome in COPD patients, but it should be noted that our study is a short-term physiological study performed in a center with extensive experience in NIV, both with PSV and NAVA. In addition, a limitation of the present study is the limited number of patients, which hamper drawing generalized conclusions.

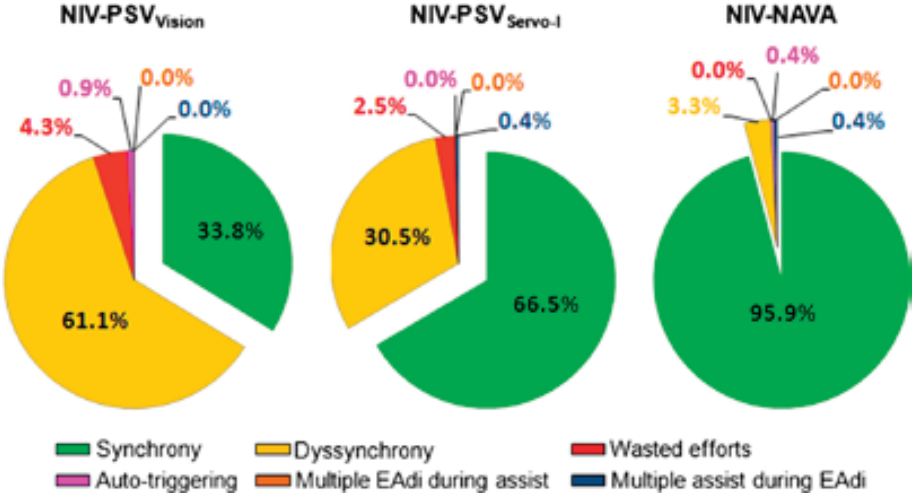

Figure 4 Percentage of synchronous, dyssynchronous and asynchronous (wasted efforts, auto-triggering, multiple EAdi during assist, and multiple assist during EAdi) breaths for the different ventilator modes. NAVA: neurally adjusted ventilatory assist; NIV: non-invasive ventilation; PSV: pressure support ventilation.

Table 4 Blood gas values

	NIV-PSV$_{Vision}$	NIV-PSV$_{Servo-I}$	NIV-NAVA
pH	7.38 (7.36 - 7.46)	7.38 (7.36 - 7.45)	7.38 (7.36 - 7.45)
PaO_2 (mmHg)	92 (77 - 106)	105 (84 - 113)	95 (77 - 98)
$PaCO_2$ (mmHg)	44 (39 - 64)	44 (33 - 59)	41 (32 - 60)
$HCO3^-$ (mmol/L)	27 (23 - 32)	26 (21 - 31)	27 (22 - 30)

NAVA: neurally adjusted ventilatory assist; NIV: non-invasive ventilation; PSV: pressure support ventilation.

Differences in patient-ventilator interaction between ventilator modes did not affect blood gas values, in particular pH, and respiratory discomfort. In part, this results from the timing of study inclusion, after initial stabilization on NIV. At inclusion in the study, blood pH (around 7.38) was already increased, making it more difficult to detect changes in pH and respiratory discomfort caused by different ventilator modes. In this context it should also be mentioned that NIV modes were not performed in a random order. Nevertheless, we performed our measurement after initial stabilization on NIV making it unlikely that the patients' respiratory status was worse at the beginning of the study than at the end. Future studies, which randomize between NAVA and PSV at admission, are necessary to ascertain whether or not improved patient-ventilator interaction in the acute phase of NIV translates to better NIV outcomes.

Conclusions

Automated analysis of patient-ventilator interaction showed that non-invasive NAVA improves patient-ventilator interaction compared to PSV in COPD patients. Moreover, this is not different when PSV is delivered by a dedicated NIV ventilator. In addition, progressive mismatch between neural effort and pneumatic timing is strongly associated with the number of wasted efforts. Whether NAVA is more successful in correcting pH in patients with acute hypercapnic exacerbation of COPD should be addressed in future studies that randomize between NAVA and PSV at admission.

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A Connected Health Model to Optimize Asthma Care

Anna Cushing, Melissa Manice

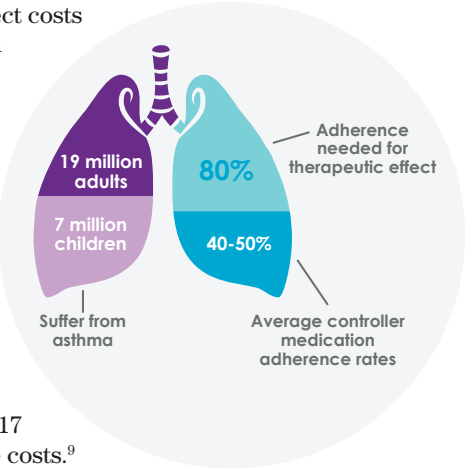
Asthma

Asthma is one of the most common chronic diseases in the US and the single most common chronic illness among children.[1] In the US, approximately 19 million adults and 7 million children suffer from asthma.[2] Currently, the standard of care for patients diagnosed with asthma is to receive a personalized "asthma action plan", a peak flow meter, and prescriptions for quick-relief and long-term controller medications.[3] Controller medication adherence rates are estimated at 40-50% on average, significantly less than the minimum 80% adherence needed for therapeutic effect.[4-6] Thus, a significant population is living with uncontrolled asthma leading to unnecessary patient suffering and costly treatment expenses.

Anna Cushing received her BSE in Biomedical Computation from Stanford University and is currently in her third year of medical school at Icahn School of Medicine at Mount Sinai. At Stanford she received the Stanford Bio-X fellowship and has multiple first author publications for her work at the Stanford Genome Technology Center on a technique for detecting rare mutations from next generation sequencing data. At Mount Sinai she has continued her interest in the use of technology to improve research technique and quality of patient care. She is a member of Mount Sinai's Student High Value Care Committee, dedicated to creating solutions to improve outcomes and decrease costs for inpatients in the hospital. She joined Cohero Health as a research coordinator in 2013 to implement the first feasibility study of a technology-based platform to improve pulmonary patient care. Ms. Cushing later became the Clinical Project Manager, overseeing subsequent clinical trials and partnerships with medical centers such as Connecticut Childrens Hospital and Dartmouth Hitchcock.

Dr. Melissa Manice received her PhD in Clinical and Translational Research from the Icahn School of Medicine at Mount Sinai. She has spent her career as a clinical researcher, specializing in pediatric chronic disease and health informatics. The fully integrated pulmonary solution that she has built with Cohero Health grew out of her career in academic clinical medicine, specifically, in building models for sustained behavior change for patients with chronic illness. She has designed studies and implemented ongoing county-wide programs to enhance patient engagement and shared decision-making, resulting in demonstrated improvements in treatment plan compliance and improved patient outcomes. Dr. Manice received a Masters in Public Health in Community Health Education from Hunter College, and has years of clinical research and managerial experience at health systems including Mount Sinai Hospital. Dr. Manice received a fellowship from the National Cancer institute to study cell regulation and carcinogenesis. She was invited to speak at the National Institutes fo Health and the Keystone Symposium on her work with transforming growth factor beta (TGFβ) and has published her research in peer-reviewed journals such as Molecular Cell.

Annually, asthma direct costs are over $50 billion in the US, accounting for one-quarter of all ER visits and nearly 500,000 hospitalizations.[7,8] It is estimated that improved patient adherence could prevent more than 50% of the 2.1 million yearly ER visits due to asthma and save more than $17 billion in asthma care costs.[9] Equally problematic is the burden that poorly controlled asthma poses to individuals and their families. Asthma is the number one cause of school absenteeism among children each year, accounting for more than 13 million total missed days of school.[10]



Successful treatment of chronic disease necessitates long-term partnerships between patients, providers, and health insurers to guarantee all parties have the most current information needed for personalized treatment.[5] Currently, physicians are unable to obtain real-time data on their patient's medication compliance. Instead, physicians must rely on patient self-report to get an idea of how frequently they take their medication. This lack of objective data makes it difficult for physicians to make personalized clinical decisions that could greatly benefit their patients' respiratory health.

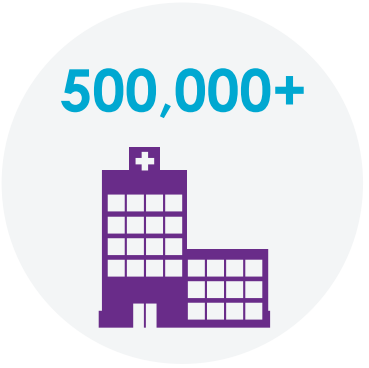
Adherence

Addressing medication adherence is a key priority for improving health outcomes. Non-adherence includes failure to fill prescriptions for inhalers, failure to use daily controller medications, and failure to follow outlined treatment plans. Reasons for non-adherence range from basic forgetfulness to medication access and cost.[5] Improved adherence rates depend on both patient compliance and physician communication and planning.[11] The disparity between current and optimal adherence rates remains

Optimal asthma care

+ Adherence to daily medications must be 80% to avoid acute events
+ Inclusion of a spacer device improves efficacy of drug delivery via inhaler
+ Lung function should be captured at home and understood in real-time

Asthma direct costs



Hospitalizations

could be saved in emergency visits

Spirometry is an objective and reproducible test to assess pulmonary function

+ How can digital tools and state-of-the-art technology be deployed to interface with asthma patients and increase their adherence rates?
+ Reminding and motivating around real-time adherence

a major barrier to effective care that is not sufficiently managed under current treatment guidelines. Past research shows that self-reported medication compliance is inaccurate and patients significantly over-report their medication use.[12] New treatment models show that digital tracking and reminders successfully address the adherence gap, and accurate adherence data yields improved clinical treatment decisions and outcomes.

Spacer

A prescribed treatment is only as effective as a patient's ability to correctly administer it. Asthma patients often struggle with proper use of their daily medication, with less than 10% of patients correctly using their metered-dose inhaler.[13,14] In the modern era of inhaler technique, a valved spacer is commonly used to improve inhaler administration and drug delivery. It works by collecting the dose released by the inhaler in a chamber through which a patient inhales the medication to increase the dose delivered to the lungs by up to 35%.[15] This translates into patients who use spacers having fewer symptoms and missing fewer days of school or work.16 Use of a spacer also prevents oral irritation and yeast infections caused by corticosteroid deposition in the mouth and throat.[17,18] Thus, a spacer device enhances both the ease and efficacy of asthma inhalers while minimizing medication side effects and is now considered standard of care for both pediatric and adult asthma patients.[17]

Lung function at home

Self-monitoring is crucial to the control of asthma at home. Currently, the primary tool is the peak flow meter, a cost-effective device to quickly measure peak expiratory flow at home. Use of a peak flow meter increases patients' understanding of their asthma and improves subsequent adherence to asthma medication.[19] Unfortunately, peak flow meters are limited in the scope of information they provide and produce unreliable measurements. As such, peak flow meters alone are not adequate for routine asthma management.[20]

of patients correctly use their inhaler

Spirometry is a quick, noninvasive, and safe test that goes beyond peak flow and can be used to assess the degree of airway obstruction, severity, and potential reversibility of asthma's pathologic process. While spirometry has traditionally been used to establish a diagnosis, it also holds the power to assess lung health in response to treatment and thus measure the efficacy of medication for a specific patient. To date, spirometry's role in the management of chronic asthma has not been fully elucidated. Spirometers carry a high price tag (>1000 USD) and are often too bulky for at-home use.

Adherence

Electronic reminders such as text messages are effective tools to improve medication adherence. One such text-based reminder system for patients with hypertension has been shown to increase medication usage by 43% (from 50% to 93% adherence).[21]

Electronic reminders

are effective in improving medication adherence

It is not enough to simply remind patients to take their medication. Meaningful long-term behavior change requires that patients feel both motivated and empowered. Successfully implemented health management tools employ behavior models like that of BJ Fogg, who advocates that behavior change requires motivation + ability + trigger.[22-24] Using previously established gaming and engagement frameworks, mobile health interventions have the ability to create and reinforce behavior change via mobile phones and other electronic devices that patients already access on a consistent basis.[25,26]

Well-designed, game-based engagement tools align educational content to individual patients' treatment needs and contribute to each patient's growing ability to prevent asthma attacks and additional adverse events.[27] Diabetes management tools have led the way in technological development with mobile health tools like Bant, using games, incentives and social media interactions to encourage patients to increase frequency of at-home glucose monitoring and medication usage.[28] Despite the development of engaging mobile health tools for diabetes, hypertension, depression, and many other chronic diseases, no such tool currently exists for asthma. There is a clear need for the development of new management tools to build upon these existing frameworks for respiratory diseases.

At CoheroHealth, we advance traditional methods of asthma care by empowering patients to engage in their care through

a proprietary connected health platform, comprising offline sensors, mobile spirometer, gamified mobile application and real-time analytics, revolutionizing the care landscape. Coupling sensors that measure adherence and persistence with innovative methods to motivate patients to better manage their asthma for the long term elevates the framework of current standard of care goals.

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Capnographic Monitoring Can Decrease Respiratory Compromise and Arrest in the Post-Operative Surgical Patient

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Capnographic monitoring of patients at high risk for respiratory compromise substantially reduced "CODE BLUE" events on three post-operative surgical care floors of Providence St. Peter Hospital in Olympia, Washington. These outcomes actually save lives — should capnography become a best practice in this setting?

Health care providers (HCPs), including respiratory therapists and nurses, typically rely on a combination of oxygen saturation, intermittent vital signs, and subjective clinical assessments to evaluate respiratory status on the general care floor[1] and the post-anesthesia care unit.[2] However, these are indirect indicators of ventilatory competence with important limitations.[3] Without a direct, continuous and objective measurement of the adequacy of ventilation, clinical personnel cannot quantify accurately the effects of disordered breathing or drug administration on respiratory status. There is a need for a cost-effective, real-time solution to these challenges. While capnography has long been recognized as the standard of care in the operating room, only recently has the utility of this monitoring modality in the general care floor setting received increased attention. Capnography and the Integrated Pulmonary Index™ (IPI) algorithm[4] (comprising four monitored parameters: end-tidal carbon dioxide [$EtCO_2$], respiratory rate, arterial concentration of oxygen [SpO_2] and pulse rate) are valuable tools for bedside monitoring of patients who may be at increased risk for respiratory compromise, which can cause oxygen and CO_2 abnormalities and their sequelae, including respiratory failure, arrest and even death.

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Such patients include but are not limited to those receiving procedural sedation or opioid analgesia.

In 2011, the Anesthesia Patient Safety Foundation (APSF) concluded that intermittent "spot checks" of oxygenation by pulse oximetry and ventilation by nursing assessment are not adequate for reliably recognizing clinically significant evolving drug-induced respiratory depression in the postoperative period.[5] APSF also concluded that capnography or other monitoring modalities that measure the adequacy of ventilation are indicated when supplemental oxygen is needed to maintain acceptable oxygen saturations. Accordingly, Providence St. Peter Hospital in Olympia, Washington, decided to assess surgical patients preoperatively for risk factors of respiratory compromise, and then selectively utilize capnography ($EtCO_2$ monitoring) to try and reduce the risk of adverse outcomes.

Identifying Patients at Increased Risk for Respiratory Compromise on a Post-Operative Care Units

The STOP-BANG questionnaire is a scoring system that is routinely administered during preoperative assessment to screen for obstructive sleep apnea (OSA).[6] The acronym STOP-BANG stands for **S**noring loudly, **T**iredness in daytime, **O**bserved apnea during sleep, high blood **P**ressure, **B**ody mass index >35 kg/m^2, **A**ge >50 years, **N**eck circumference >40 cm, and **G**ender. STOP-BANG scores range from 0 to 8; a score ≥3 means that the patient is at risk of OSA, while a score ≥5 indicates that the patient is at high risk for OSA. The STOPBANG questionnaire has been shown to have a high sensitivity and a negative predictive value, especially for patients with moderate to severe OSA. STOP-BANG screening has also been used to stratify the risk of respiratory compromise in other clinical settings, and, for example, high scores recently have been shown to be predictive of adverse intra-operative and postoperative respiratory adverse events.[7]

In 2012, Providence St. Peter Hospital started using capnography to monitor patients undergoing moderate sedation and procedural sedation during, for example, gastrointestinal and pulmonary endoscopy for early detection of respiratory compromise in some outlying procedural areas. Then, in August 2013 we began using the STOP-BANG questionnaire to monitor higher risk postoperative populations more selectively. We did this in conjunction with the IPI. The IPI value on the patient monitor indicates the patient ventilatory status, where a score of 10 is normal, indicating optimal pulmonary status, and a score of 1 or 2 requires immediate intervention.

Attachment 1

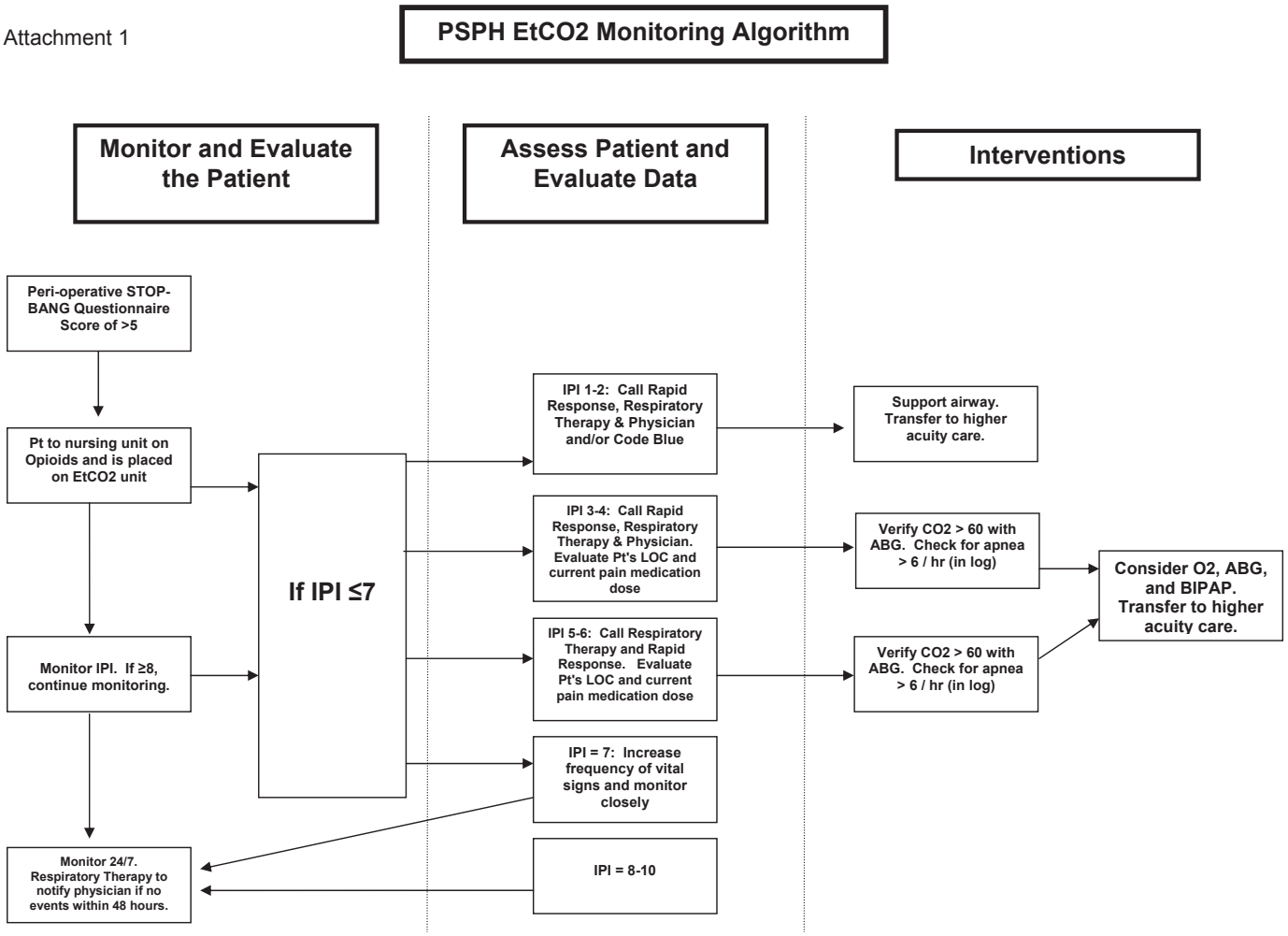

Figure 1. The algorithm above is used as a guide to reduce the rate of adverse events and poor outcomes. The process is described in the Capnography Flow Chart.

Capnography Flow Chart

The procedure is summarized below:

1. A physician's order must be present or obtained and signed on the chart for all patients receiving monitoring.
2. Set-up and assure monitor has stabilized.
    A. Set up oximeter probe
    B. Set up $EtCO_2$ sampling cannula or flow tube
3. Remote patient monitoring at the following target values
    A. SpO_2 greater than 92%
    B. $EtCO_2$ less than 65 mmHg
    C. Respiratory rate greater than 6/min
    D. IPI greater than 7
4. Intervention (call physician and recommend intervention) if target values not maintained
    A. Decrease PCA rate
    B. Increase FiO_2
    C. Initiate CPAP/BiPAP
    D. Call rapid response
5. Documentation including SpO_2, $EtCO_2$, respiratory rate, and IPI in the electronic medical record with each assessment

Implementation Requires Staff Education and Buy-In

Healthcare professional education is critical to reinforce staff awareness of the interference of supplemental oxygen administration on detection of progressive hypoventilation when pulse oximetry is the only continuous electronic monitor.[5] Staff buy-in is just as important, since HCPs not only must complete the STOP-BANG questionnaire but also are responsible for capnography, setting and adjusting alarm sensitivity to minimize "non-actionable alarms," and responding to alerts, often as a multidisciplinary team.[8] Finally, patients (and their relatives) don't understand why they are monitored by capnography on a general care floor, so patient/family education is also necessary.

Outcome: Effect on Code Blue Events

"Code blue" events were compared to the previous 20 months on each patient care unit prior to implementation as the primary outcome measure. Capnographic monitoring of patients at high risk for respiratory compromise on three surgical care floors (Orthopedic, General Surgical and Neurosurgical) together with the IPI algorithm was implemented in September 2013. This resulted in a 65% reduction in code blue events over the following 24 months (September 2013 to Sept 2015). These improved outcomes actually save lives. The OSA screening and monitoring program is a product of data-driven analyses. None of our high-risk patients who were on capnography have experienced a code blue event since starting the program. This has led us to consider expanding capnographic monitoring to other at-risk populations to further reduce or eliminate code blues. The results are summarized in the graph.

Summary and Conclusions

Providence St. Peter Hospital utilized the STOP-BANG

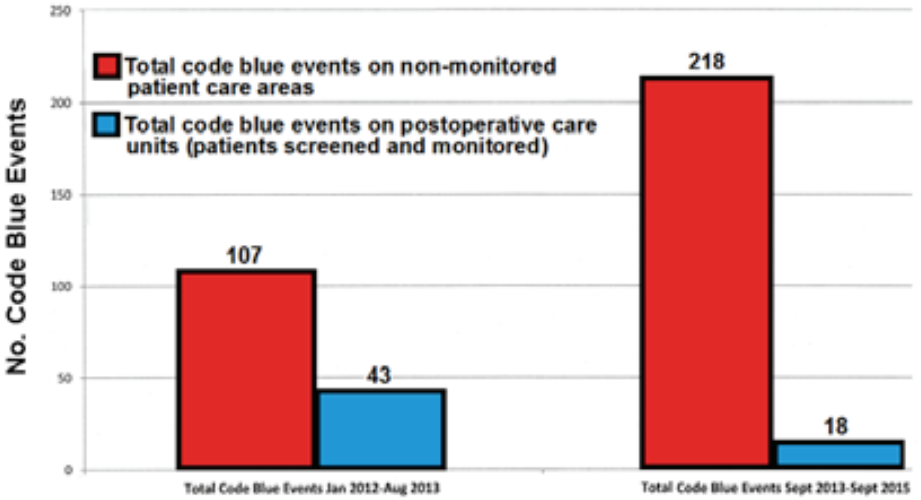

Figure 2. Code Blue Data Post-Implementation of STOP-BANG Screening and Capnographic Monitoring

questionnaire to identify patients at high risk for respiratory compromise on the post-operative care units and monitored those at increased risk with capnography and the IPI algorithm. This resulted in a dramatic decline in code blue events from respiratory depression in screened postoperative patients. Broader application of this protocol may permit HCPs to identify and monitor at-risk patients on the general care floor preventing adverse patient outcomes. By precluding the need for cardiopulmonary resuscitation (CPR), it may also provide hospitals with a substantial cost benefit. The CPR cost-effectiveness ratio including equipment and training, physician and nursing time, and medications plus post-CPR expenses has been estimated to be $50,412 per year of life saved.[9]

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The Optimization of Lung Volume Re-Expansion Therapy for the Post-Operative Open Heart Patient

Michael Richardson AAS,RRT-NPS and Kelly Cresci, MS,RRT-NPS

Abstract

Purpose: To optimize bedside volume re-expansion therapy provided to post-operative open heart patients.

Objective: Upon extubation a respiratory patient driven protocol is initiated within 1-2 hours. Positive airway pressure[2] and vibratory therapies[2] are initiated Q6. The patient is re-evaluated in 48 to 72 hours. Volume re-expansion therapy is performed in synchrony with bedside nursing, the patient's sleep protocol, and in synchrony with the patient's pain therapy. The respiratory therapist utilizes a "rule of three" thinking which incorporates the predicted inspiratory capacity, mobility, and oxygen requirement. A rule of three is used to dictate whether positive airway pressure[2] therapy is discontinued.

Results: In review of 400 CVTS open heart patients we note that if a patient achieves 80% of their predicted inspiratory capacity upon extubation, they have a probability of 66.50% to be off their oxygen in 24-48 hours. Also, if the patient achieves < 80% on their initial inspiratory capacity they have a probability of 28.96% to be off their oxygen in 72 hours. The overall average for oxygen days is 2.37 days, a median of 2.1 days, and a standard deviation of ± of 0.66 days. 40 patients audited for 2014-2015 yield 100 % patient satisfaction in regards to pain control and the times of the volume re-expansion therapy.

Introduction

Prior to the initiation of a volume re-expansion protocol, our cardio-thoracic surgery patients in our facility used oxygen for > 3days. Volume re-expansion therapy was performed > 3 days, or until discharge. The volume re-expansion therapy consisted of IPPB,[2] chest physiotherapy,[2] vibratory PEP therapy,[2] and was performed 4 times a day. The utilization of a respiratory driven protocol has led to the development of an effective protocol geared towards optimization of bedside respiratory therapies. This optimization has resulted in a decrease of oxygen utilization, a decrease in length of post-operative volume expansion therapy, improved workflow, and increased interdisciplinary collaboration at the bedside while improving or maintaining patient satisfaction.

Patients who undergo open heart surgery are at risk for post-operative atelectasis.[1] It is the role of the Respiratory Therapist to provide essential volume re-expansion therapies post-operatively to aid in a decrease in oxygen days, support patient mobility, lung volume re-expansion therapy in synchrony with pain therapy, and to potentially assist with achieving the goal of anticipated day of patient discharge. The skills needed to correctly manage our patients post-operatively can be divided into 3 categories: Patient assessment, synchrony of care, and respiratory driven protocols. Patient assessment includes comprehensive understanding of respiratory physiology and determining the level of volume re-expansion therapy needed. Synchrony of care equates to cluster care between the respiratory therapist and the bedside RN in regards to pain therapy and the patient sleep protocol. The respiratory driven protocol gives the therapist the autonomy to set a treatment plan of action, measurement of progress of the delivered bedside therapies, and setting of goals for the patient based on frequent assessments.

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Methods and Materials

Respiratory Patient Driven Volume Re-expansion Protocol

To assess the efficiency of the therapy the respiratory therapist provides, the following guidelines have been set into practice: The open heart patient is evaluated within 30 minutes post extubation using the patient driven protocol. Respiratory therapy evaluates the patient's medical history, home regimen, physical assessment with vitals, and obtain their inspiratory capacity. The therapist places the patient on a regimen similar to their home regimen of nebulizers and inhalers.

Positive Airway Pressure and Vibratory PEP devices,[2] cluster care and synchrony of care.

Every open heart patient is placed on positive airway pressure[2] and vibratory PEP therapy[2] every 6 hours. The therapist re-evaluates the need for positive airway pressure therapy[2] within 48 hours initially, then every 24-48 hours until discontinued. The goal is to have the patient back to their pre-operative baseline oxygen requirement within 48-72 hours.

Secondly, therapist work flow and patient satisfaction are important components to providing effective care. Volume expansion therapies are set around the clock in synch with the patient's sleep protocol, as well as with pain therapy. The patient sleep protocol is to rest from 2200 to 0400. Therefore, bedside respiratory therapy is performed 1000 1600 2130 0430. The therapist poses the following question to the patient prior to their therapies; "how is your pain?" "Are you able to perform your bedside therapy at this time"? If the patient responds

Discussion

Modified Q6: Improved respiratory workflow. Treatment times promote RRT availability at bedside rounds and interdisciplinary rounds.

Respiratory Therapy & RN Cluster Care: Volume re-expansion therapies performed within 30 minutes post administration of additional pain therapy, and around the patient's sleep protocol.

Rule of Three: To discontinue positive airway pressure therapy. Patient achieves their minimal inspiratory capacity, are mobile, and back to their baseline pre-operative oxygen requirement.

negatively, then communication is made with the bedside RN to deliver additional pain therapy. The therapist checks back in 20-30 minutes to deliver the necessary therapies. After each treatment the respiratory therapists decreases the oxygen liter flow of the patient to maintain a Spo2 > 94%.

The third guideline determines when to stop the volume re-expansion therapies. Once the patient is back to their baseline oxygen demand, mobile, and achieving their minimal inspiratory capacity, the positive airway pressure therapy[2] is discontinued. The patient is maintained on vibratory PEP[2] therapy until discharge. If the patient is placed back onto oxygen, positive airway pressure therapy is re-started, and is re-evaluated every 24 hrs.

Results and Discussion

Volume re-expansion therapy is performed around the clock, in synchrony with the patient's sleep protocol, and pain therapy. Volume re-expansion therapy is continued until the patient is back to their baseline pre-operative oxygen requirement, mobile, and achieving their minimal inspiratory capacity. Respiratory patient driven protocols are performed every 24-72 hours. Oxygen utilization days and volume expansion therapy days have decreased from an average of 3-4 days to an average of 2.37 days. In looking at 400 patients, the savings in patient oxygen consumption dropped from 3-4 days ($574,632 – $766,176) to 2.12 days ($406,073.28), yielding savings of $360,102.72.

Conclusion

The volume re-expansion therapy protocol has decreased oxygen days, promoted cluster care and improved team collaboration. The volume re-expansion therapy performed around the clock and in synchrony with the patients pain therapy has decreased patient oxygen days, and has maintained patient satisfaction. Utilizing the rule of three thinking ensures progressive recovery.

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Analysis of Tidal Volume and Expiratory Pressure during Oscillatory PEP Therapy in Healthy Subjects

Doug Pursley, M.Ed, RRT-ACCS, FAARC

Introduction

Airway clearance techniques have changed dramatically since the author's entry into the field of respiratory care in the early 1970's. Back then "bronchial hygiene therapy" consisted primarily of IPPB with a bronchodilator, ultrasonic nebulization with half-normal saline, and chest physical therapy. The axiom was "open 'em up, wet 'em down, beat it out." These therapies were performed separately or as a triad on COPD patients although any patient with accumulated secretions may have received any or all of these forms of therapy.

Blow bottles were also prescribed for patients recovering from post-operative abdominal and chest surgery. This device consisted of two, approximately one liter plastic containers — one empty and one filled with dye-colored water — connected together with Tygon tubing. The idea was for the patient to take a deep breath and transfer water, as much they could, from one container into the other. The goal was to prevent atelectasis by producing positive pressure on exhalation. The therapy ended up causing the opposite effect and produced more complications than benefits ultimately resulting in its demise — most likely due the effects of excessive transpulmonary pressure. On the positive side, it did provide much entertainment and competition for many respiratory therapists with the goal of seeing who could transfer the most fluid on a single breath!

Today, positive expiratory pressure therapy or PEP therapy can be looked at as a kinder, gentler, and safer version of the positive pressure expiratory techniques of the 1970's. Oscillating PEP or OPEP therapy adds airway vibrations with positive pressure on exhalation. Common instructions for OPEP therapy include: 1) starting at resting expiration (FRC), have the patient take a deeper breath than normal, 2) perform a short breath hold of approximately two seconds, and 3) exhale through the device for approximately four seconds. The process is repeated 10-20 times with huff coughing between sessions over a 15-20 minute treatment time. The oscillations produce wide swings in expiratory air flow and pressure as the patient exhales, which hypothetically assists in mobilizing secretions. Resistance can be adjusted to help patients maintain a four second expiratory time.

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It has been noted in at least one publication that tidal volume during OPEP therapy lands somewhere between 10 ml/kg and forced vital capacity.[1] We agree with this reasoning but wondered objectively, "what exactly constitutes a deeper than normal breath" and how consistent is this volume across a population when corrected for age, height, and gender. We were also curious about the average positive expiratory pressures achieved in this population when using a resistance setting commonly seen in the clinical setting. Therefore the objective of this study is to determine the tidal volume and percentage of predicted inspiratory capacity subjects achieved as they took a "deeper than normal" breath and to measure the pressure midway through a sustained expiratory maneuver.

Method

Forty-two students and faculty without history of lung disease were recruited from the Allied Health Department at Ozarks Technical Community College in Springfield, MO. There were 15 males and 27 females. The range of age was 19-65 (mean 29). After obtaining approval from the college's institutional review board — each subject was educated about the procedure and each signed a consent form agreeing to participate in the study. Information about the subject's age, height, and gender was stored in the database. A predicted inspiratory capacity was also calculated for each subject.[2]

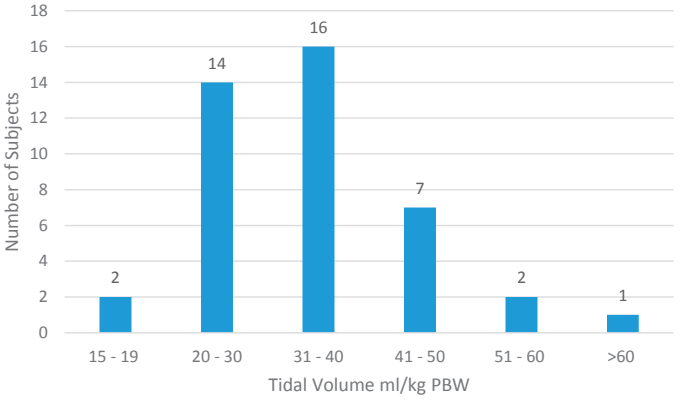
A Fluke VT Plus HF gas flow analyzer with VT for Windows software (Fluke Corporation, Everett, WA) was used in the data acquisition and analysis. A not-previously-used Acapella (green) OPEP device (DHD Healthcare, Wampsville, NY) set at adjustment level 3 (mid-resistance setting) was then connected to the high flow exhaust of the instrument using a 22 mm ID straight rubber adaptor. Each subject had their own bacteria filter which attached to the opposite side on the instrument's high flow inlet. Participants were seated in an upright position and instructed to take a "deeper than normal" breath, hold their breath for two seconds, and exhale through the device for at least four seconds. This procedure was repeated multiple times and the following data was collected: tidal volume (ml/kg PBW), mid-expiratory pressure (cmH2O), and percent of predicted inspiratory capacity each subject achieved as they took a deeper than normal breath. Values are expressed as an average of ten breaths.

Results

The mean exhaled tidal volume in our group of 42 healthy subjects was 33.5 ml/kg PWB. The range of tidal volume was

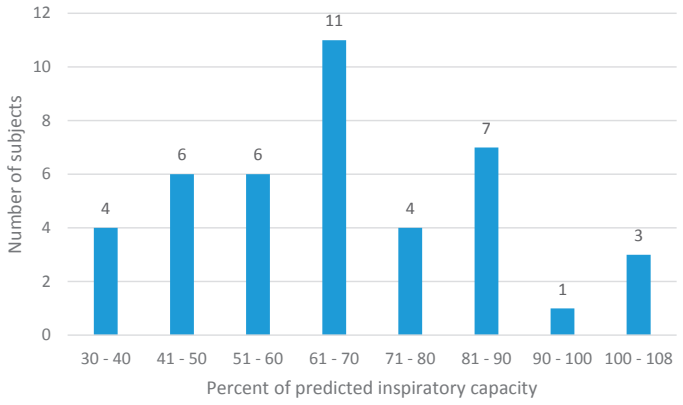
15.4-60.7 ml/kg PWB. SD was 10.6. Chart 1 shows the number of subjects that fell into each incremental range.

Chart 1. Tidal volume distribution (ml/kg PBW)



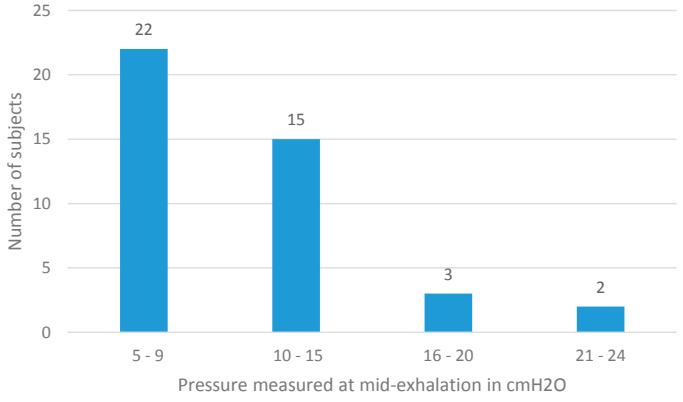
The mean percent of predicted inspiratory capacity achieved during OPEP therapy was 65.4% with a range of 31.4-107.6%. SD = 19.85. Chart 2 shows the number of subjects falling in each incremental range.

Chart 2. Distribution of % predicted inspiratory capacity



The mean pressure midway through a sustained expiration was 10.6 cmH2O with a range of 5.9-24.0 cmH2O. SD was 4.16. Chart 3 shows the number of subjects that fell in each incremental range.

Chart 3. Mid-expiratory pressure distribution (cmH2O)



Discussion

Our study found there was wide variation in the percentage of predicted inspiratory capacity achieved when subjects were asked to take a deeper breath than normal during OPEP therapy. Taking a "deeper than normal" breath did not have the same meaning to all of our subjects. Some achieved only one-third of their predicted inspiratory capacity while a few exceeded it. Most fell between 40-80% of their predicted inspiratory capacity.

In addition, even though 40 of 42 subjects (95%) achieved expiratory pressures in the prescribed range of 5-20 cmH2O for PEP therapy,[3] slightly over one-half (22/42) fell in the lower part of that range. Patients with lung disease and/or airway obstruction may follow this pattern as well. The efficacy of OPEP therapy not only depends on the patient being able to achieve an adequate mean expiratory pressure but it also depends on the device being able to create an oscillatory frequency similar to the frequency of the mucociliary escalator (13 hz).[4] Both of these traits are dependent upon adequate flow through the device.

In this study, we had the advantage of observing graphical analysis of subjects' efforts as they performed OPEP therapy. Figures 1 and 2 show good instructional compliance in a healthy subject that achieved an adequate tidal volume over a four second expiratory time (mid-resistance setting). This in turn produced an adequate expiratory flow, which resulted in a mean expiratory pressure of approximately 12 cmH2O, a mean oscillatory frequency of 15 hertz, and a mean oscillatory amplitude of 6 cmH2O in this subject.

Figure 1. Flow, pressure, and volume scalars of a healthy subject performing OPEP therapy.

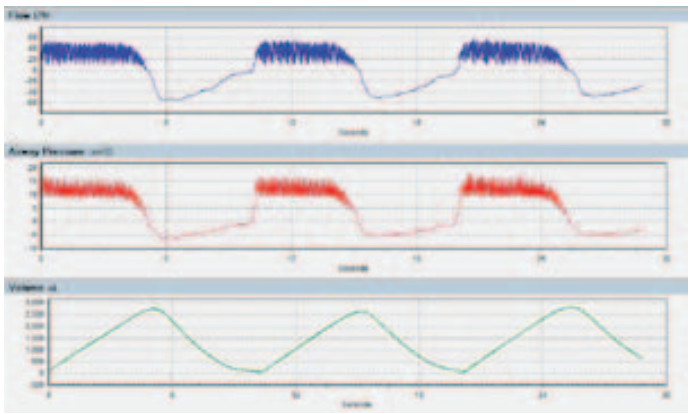
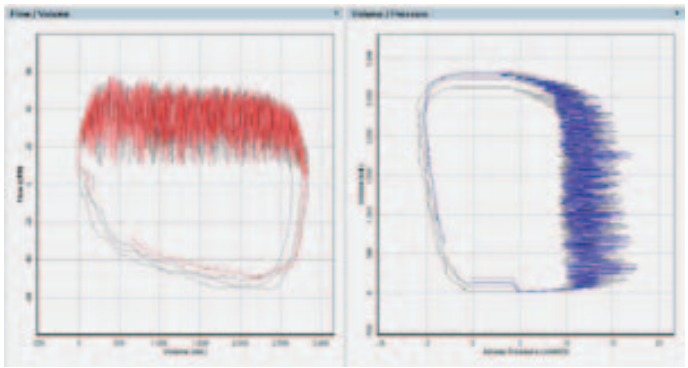


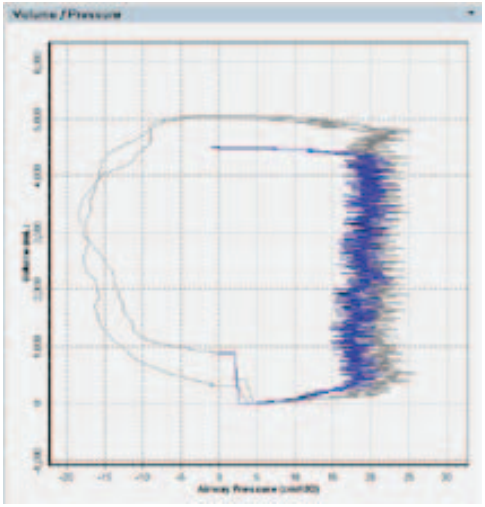
Figure 2. Flow-volume and pressure-volume loops showing a healthy subject performing OPEP therapy.



Eleven subjects in our study had predicted inspiratory capacities of 80% or greater in spite of being told to simply take a deeper breath than normal. Three of those subjects exceeded their

predicted value. Had these subjects been patients and again having the advantage of monitoring volume, we would have instructed them to not take in such a deep breath. Figure 3 shows the volume-pressure loop of one of these patients, a 33 year old male.

Figure 3. Pressure-volume loop showing excessive volume and pressure in a 33 year old male.



Also note in in Figure 3 that as a result of the high volume, the mean airway pressure of our subject is at the upper limit of normal. Had this been a patient, we most likely would have decreased the resistance to bring the pressure down to a more acceptable level.

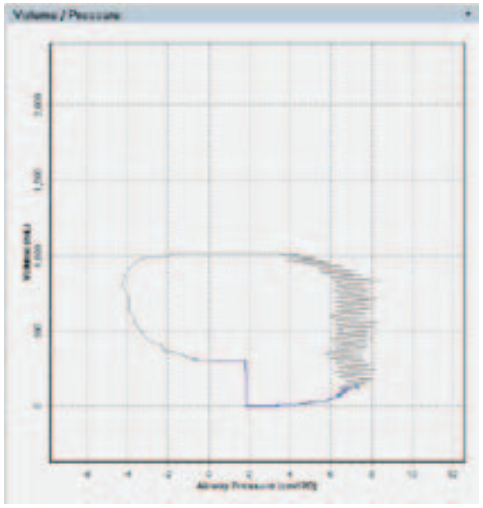
As stated earlier, twenty-two subjects in our study (52%) had mean expiratory airway pressures of between 5-9 cmH2O. This is considered the lower end of the prescribed range. In a clinical setting, assuming we were able to monitor pressures, we probably would have increased resistance to produce a more therapeutic target pressure. If the low pressures were secondary to low tidal volume, we might also have encouraged the patient take a slightly deeper breath in order to produce more expiratory flow. It is interesting to note that nine subjects in our study had what we considered to be less-than-optimal breaths at 45% or less of their predicted inspiratory capacities. These lower volumes were associated with lower expiratory pressures (6.3-8.2 cmH2O) in eight out of nine subjects. Only one subject in the lower volume group had a sustained expiratory pressure greater than 10 cmH2O.

Figure 4 shows the volume-pressure loop of a subject that demonstrated marginal tidal volume and mean expiratory pressure. Notice as a result of the low flowrate through the device, the oscillatory amplitude is only 2 cmH2O. This subject, if a patient, would benefit from an increase in resistance and/or expiratory flowrate.

Conclusions

Since the days of IPPB, ultrasonic nebulizers, and blow bottles, the field of Respiratory Care has evolved into an evidenced-based, efficacy-driven, scientific practice. Most everything we do calls for a way to measure effectiveness—except when it comes to a few procedures like OPEP therapy where for the most part we still use a blind technique in the evaluation process. Therefore, when coaching patients and changing resistance

Figure 4. Pressure-volume loop showing low expiratory pressure and amplitude in a 20 year old female.



settings during OPEP therapy, this study has demonstrated the advantage of using adjunct monitoring devices to assure adequate tidal volume and flow, to make sure patients meet therapeutic pressure thresholds, and to warn of excessive expiratory pressure that may occur if patients perform this therapy incorrectly. More studies are needed to determine if maximizing the quality of OPEP therapy relates to better outcomes.

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Advances in Subglottic Secretion Drainage

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

Abstract
Subglottic secretion drainage (SSD), the aspiration of subglottic secretions above the ballooned cuff of endotracheal (ET) and tracheal tubes (TT) containing an integrated suction lumen, is key to preventing Ventilator-Associated Pneumonia (VAP). Subglottic secretion drainage prevents contaminated secretions consisting of saliva, oropharynx secretions, and gastric reflux aspirate, from leaking around the ballooned cuff into the lower airways, causing VAP and life-threatening, costly complications. Mechanically ventilated patients, and other intubated patients without the ability to swallow are at high risk. Traditional SSD, using manual syringes or wall suction, has been shown in randomized, controlled studies, to be effective in reducing the incidence of VAP, but has been impractical, inconsistent, and improvisational in practice. Suction devices and methodologies have not kept pace with incremental improvements in subglottic ET and TT design. This paper presents a history of SSD spanning 20 years, including trial results showing the benefits and limitations of traditional SSD. A new, FDA-cleared, and SSD-specific system (Simex *cuff* system), offering fully automated intermittent subglottic secretion drainage, is described.

Keywords
Ventilator-Associated Pneumonia (VAP), Subglottic Secretion Drainage (SSD), Mechanical Ventilation, Pneumonia, Respiratory Tract Infections, Automated Intermittent Subglottic Secretion Drainage

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Introduction

Ventilator Associated Pneumonia (VAP) is the second most common nosocomial infection in the United States.[12] It is estimated to occur in 9-25% of all ICU patients alone and is a costly complication of hospitalization that increases length of stay and increases morbidity and mortality.[6,12,19]

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Aspiration of oropharyngeal pathogens, or leakage of secretions containing bacteria around the endotracheal or tracheal tube cuff, have been identified as the primary routes of contamination of the lower respiratory tract.[18]

Over the last 20 years subglottic tracheal and endotracheal tubes have been developed that enable the aspiration of subglottic fluids through a specially designed integrated suction lumen. Randomized Controlled Clinical Studies have demonstrated that it is possible, through proper aspiration of secretions, to control and reduce the incidence of Ventilator-Associated Pneumonia (VAP). While these special subglottic tubes have been a very important development, the development of suction devices specifically designed to work with these tubes have not kept pace. Clinicians have found ways to improvise using currently available suction modalities but until now there has been no device specifically designed to work with these specialty tubes and optimize the results of SSD. Failure of proper suction or poor suction techniques can lead to exogenous contamination of the respiratory tract which in turn can lead to VAP.[3]

The majority of the literature on the subject of subglottic secretion drainage and the prevention of VAP, presents results in terms of reductions in VAP rates. Prior to 2013, surveillance was limited to VAP, and commonly used definitions of VAP were found to be less than ideal, because of the subjectivity of radiographic technique, interpretation, and reporting, and because of reliance on clinical signs and symptoms, which are subjective and may be poorly or inconsistently documented in the medical record.[26]

In 2011, the CDC convened a Working Group to address the limitations of the NHSN (National Healthcare Safety Network) pneumonia definitions, and to propose a new approach to surveillance — Ventilator-associated Events (VAE), implemented in January of 2013. There are three definition tiers within the VAE algorithm: 1) Ventilator-Associated Condition (VAC); 2) Infection-related Ventilator-Associated Complication (IVAC); and 3) Possible VAP (PVAP).[26]

The current VAE surveillance system is now considered to be based on more objective, streamlined, and potentially automatable criteria that identify a broad range of conditions and complications that occur in mechanically-ventilated adult patients. The VAE definition algorithm is for use in surveillance; it is not a clinical definition algorithm and is not intended for use in the clinical management of patients.[26]

In 2010 a first-of-its-kind fully automated subglottic aspiration pump, specifically engineered for the automated intermittent aspiration of subglottic secretions, was introduced in Europe. Four years later, with over 500 patients treated, clinicians are reporting no complications with the use of the SIMEX Automated Intermittent Subglottic Aspiration System, and are achieving up to a 10-fold increase in the amount of secretions collected. It has now been adopted by those facilities as their standard of care.

This device has now been cleared, by the FDA, for use in the US. It is the first and only suction pump cleared by the FDA that is specifically indicated for the intermittent aspiration of subglottic secretions to be used specifically with specialty subglottic endotracheal and tracheal tubes. It provides automated, customizable intermittent aspiration, which can be tailored to each patient's needs. Randomized control studies are now under way in the US to quantify the benefits of this technological breakthrough.

In order to properly evaluate this new modality it is helpful to fully understand the use of SSD in all its forms over time and to understand where over 20 years of research have led us. It is helpful to examine where we are today and how we should assess, choose and evaluate current modalities of treatment. This document will present a brief history of SSD and explore the clinical benefits and limitations of traditional modalities of treatment, currently in wide use. In addition, new modalities now available will be presented.

Purpose of Subglottic Secretion Drainage

The purpose of subglottic secretion drainage (SSD) is simple – to prevent saliva and gastric secretions, which carry bacteria, from leaking down into the lungs of ventilated patients. Most people create at least one liter of saliva daily, which is typically swallowed.[5] When the ventilated patient is unable to swallow, this saliva turns into an infectious fluid that can infiltrate the lungs and cause infection.

- **Aspirating at the source.** SSD is designed to collect and remove secretions at the source (above the ballooned cuff of Tracheal or Endotracheal tubes), where they are highest in the airway and easiest to remove.
- **Preventing infectious material from entering the lungs.** By removing the secretions "above the ballooned cuff," SSD prevents this infectious material from entering the lungs.
- **Endotracheal aspiration is required as a result of the failure of subglottic secretion drainage.** Endotracheal aspiration, where fluid is removed from the lower airways and lungs, is time-consuming, very invasive and painful for patients. It can be prevented by removing more of the secretions above the ballooned cuff, before leakage into the lungs occurs.
- **Preventing ventilator-associated pneumonia.** Subglottic secretions are the primary source of the infectious material that leads to VAP. Collecting them before the bacteria in the saliva can colonize the lungs significantly reduces the incidence of nosocomial infection, reduces length of stay, and saves lives.
- **Lowering antibiotic use.** By preventing the lungs from being exposed to infectious material, SSD can also reduce the use of antibiotics for ventilated patients.
- **Reducing costs.** All of these factors combine to make subglottic secretion drainage highly cost effective. It is faster and easier to remove the liter of saliva near the source (above the ballooned cuff) than trying to remove it after it enters the lungs. Preventing VAP and lowering antibiotic use, while allowing patients to recover faster, reduces major cost burdens on the facility. VAP is associated with more than $40,000 in increased hospital costs per patient.[12]

Traditional Modalities of Treatment

Ventilator-Associated Pneumonia (VAP) is one of the most common and deadly forms of nosocomial infection in healthcare facilities.[12,19] Mechanical ventilation causes oral or gastric secretions to aspirate into the lungs and cause infection. The best way to prevent VAP is to remove these secretions before they reach the lungs.

Subglottic Secretion Drainage (SSD) is the method by which these secretions are removed. Either a wall suction regulator or syringe is attached to the integrated suction lumen of the subglottic tracheal or endotracheal tube and used to pull the oral and gastric secretions from the tube, where they can be disposed of safely.[18]

Endotracheal tube with subglottic port used for SSD

Tracheal tube with subglottic port used for SSD

Figure 1. Examples of subglottic Endotracheal and Tracheal tubes with integrated suction lumen.

Endotracheal (Bronchial) Aspiration

If subglottic secretions are not drained at the source, they leak down into the airways and the lungs. Left alone, they often cause pneumonia. In this situation the only option is to use a catheter inserted into an endotracheal tube to suction the lower airways and lungs to remove these secretions.

Ineffective subglottic secretion drainage that allows these secretions to escape into the airway and lungs leads to more of these procedures, which are highly invasive for the patient, take substantial staff time to perform, and can actually increase secretions due to increased irritation to the airway. Proper subglottic secretion drainage above the ballooned cuff and before it penetrates the lungs and bronchi can greatly reduce the need for endotracheal aspiration procedures as well as incidences of VAP.

Suction Systems in Traditional SSD: Performance and Contamination Considerations

In traditional subglottic secretion drainage, if syringes are not used as the source of manual intermittent suction, other traditional suction systems are used. The traditional suction systems, whether centralized, built-in systems, or other general purpose systems, have component parts in which design and methods of use directly affect the risk of infection and VAP. The components are the pump, piping, suction regulator, suction collection canister, and the patient attachment. The regulator, frequently used in combination with wall suction in acute care

settings, and the protocols for disposal of canister collections, are of particular importance in SSD.

The clinical application of suction depends on appropriate levels of pressure, and on adequate flow, the volume the system is able to withdraw per unit time. The National Fire Protection Agency (NFPA) requires the wall suction outlets to provide a minimum flow of approximately 85 liters per minute. In a study of 5 brands of commonly used continuous regulators, the majority could not deliver adequate flow unless set at potentially unsafe pressure levels.[23]

In traditional intermittent suction, an intentional, and high frequency backflow from the regulator is created (as many as 3600 aspirations daily). The most commonly used traditional protocol pauses suction for intervals of only 16 seconds, a virtually continuous application of suction, which may be damaging to tissue, and because of backflow from the regulator, may create a contributory infection vector to the patient.[25]

In a study of regulators used in hospitals, it was found that 37% (173 of 470), were found to be colonized with pathogens, including well-established nosocomial infections.[11] The same study included a suction circuit model that showed pathogens can disseminate throughout the circuit (retrograde and antegrade). It showed that contaminants can spread from a suction regulator to the wall-side canister within 30 minutes, and can also spread back to a simulated patient stomach within 24 hours. Most suction protocols recommend that collection canisters be changed a minimum of every 24 hours, although in a literature review of published canister change protocols, no evidence was cited in support or to disprove the 24-hour minimum.[25]

Backflushing of regulators using 100cc of a cleaning agent commonly is recommended by regulator manufacturers, but has been shown to be inadequate for cleaning and decontaminating the internal passages of regulators.[24] Not all regulators are alike in performance and in susceptibility to colonization. However, traditionally-used devices still in wide use have been shown to have many drawbacks with regard to preventing the spread of infection.

Two prospective, observational studies, in a 496-bed university-affiliated hospital in San Antonio, Texas, one in 2013 and one in 2014, recorded actual suction pressures applied among intubated medical-surgical ICU patients (38 patients and 18 patients, respectively). In the 2013 study, the mean negative pressure recorded was -335.3 mmHg ±99.8, with the maximum recorded -516 mmHg, far higher than the AARC recommended -150 mmHg. In 2014, the mean negative pressure recorded was -210.5 mmHg ±32.9, a statistically significant improvement, but still out of adherence with the AARC guideline.[9,22]

Continuous Drainage uses wall suction or general suction devices that are not FDA cleared for subglottic secretion drainage. The pump operates continuously at very low pressure. The guideline for continuous pressure is -20 mmHg in order to protect the airways from undue pressure that can be irritating and cause an increase in secretions and to prevent drying of the mucous membrane. The benefit of this method is that minimal staff time is needed. The drawback of this is that pressure levels are often not powerful enough to remove secretions. In some situations, in order to facilitate better drainage, pressure levels are increased beyond the recommended levels. It also yields minimal amounts of secretion — an estimated 10-30 ml per day. Three Randomized Controlled Clinical Trials involving 601 patients, using continuous suction resulted in a combined average of 45.8% reduction in incidence of VAP[17,18,20] (see Fig. 8-9).

Traditional Intermittent Drainage is virtually continuous but at a much higher pressure, with short pauses in aspiration of less than 30 seconds. An example would be a device that aspirates for 8 seconds and then pauses for 16 seconds. Wall suction or general purpose suction are generally used for intermittent subglottic secretion drainage, but are not designed or FDA-cleared for such use. The American Association for Respiratory Care (AARC) guidelines call for pressures not to exceed -150 mmHg. Pressure levels on these devices cannot be completely regulated to ensure compliance with guidelines. Nominal amounts of secretions are collected with this method. Three Randomized Controlled Clinical Trials involving 813 patients, using intermittent suction resulted in a combined average of 49.3% reduction in incidence of VAP[1,3,19] (see Fig. 8-9).

Manual Intermittent Drainage uses a syringe to remove subglottic secretion drainage. Studies show that the pressure exerted by the syringe is between 4 and 5 times higher than the AARC recommended pressure (-150 mmHg).[7] Most protocols recommend hourly secretion drainage, though this can be difficult given limited staff time, and can take a respiratory therapist two hours per bed per day to administer. The procedure yields approximately 30 ml of fluid daily.[2] Three Randomized Controlled Clinical Trials involving 758 patients, using manual intermittent suction resulted in a combined average of 53.2% reduction in incidence of VAP[2,4,16] (see Fig. 8-9).

Fully Automated Intermittent Drainage is the only device cleared by the FDA and indicated for subglottic secretion drainage. The aspiration pressure can be adjusted according to the patient and based on the AARC recommended range of -80 to -150 mmHg, and the aspiration frequency can be adjusted to anywhere from 5-60 seconds of ON time and for 1-60 minutes of OFF/Pause time. It utilizes a specially engineered, virtually silent pump with a self-contained collection canister that prevents cross contamination. The device operates automatically and requires very little staff time. The volume of secretions collected with this method has been shown to be up to 10 times higher than collected with continuous or, wall suction intermittent and manual intermittent aspiration[7] (see Table 1).

The Proven Clinical Benefits of SSD

Summary: In the last 15 years, at least nine randomized, controlled clinical trials have been conducted to observe the benefits of SSD in preventing Ventilator-Associated Pneumonia. These studies with a total of 2,172 patients have conclusively proved that removing these secretions significantly reduces incidents of VAP.

These studies have all shown consistent, substantial reductions in VAP, ranging from 37.2% to 64.2% over control groups. None have reported significant adverse events with the use of subglottic secretion drainage. The results have been remarkably consistent, with an average reduction in VAP right around 50% and little difference between the different methods. Many studies have also shown a corresponding reduction in antibiotic usage, the amount of days spent on the ventilator, and/or the amount of days spent in the hospital[1-6] (see Fig. 8).

Table 1. Comparison of Traditional Modalities of SSD Treatment Versus Fully Automated System

	Traditional Approaches			Automated Approach
	Continuous	*Intermittent*	*Manual*	*Intermittent*
Method	Wall Suction or General Suction	Wall Suction or General Suction	Syringe	Specialized Suction Device
Pressure	-20 mmHg (may be too low to aspirate viscous secretion and increased above recommended guidelines)	-150 mmHg (high frequency aspiration – virtually continuous at a much higher pressure)	-580 to -720 mmHg (nearly 4-5 times higher than recommended)	Tailored by patient, -50 to -150 mmHg
Accuracy of Pressure Delivered	Not reliable	Not reliable	Always Higher than recommended Guidelines	Accurate/reliable
Frequency	Continuously, 24/7	Aspirating virtually continuously with short pauses (16 seconds), 24/7	Hourly (often less regularly)	Tailored by patient, Aspiration for 10 - 20 seconds and pause for 5 - 20 minutes, 24/7
Daily Aspirations	Non-Stop Aspiration	1,440 - 3,600 aspirations daily	24 aspirations daily	24 -144 aspirations daily
Noise Level	Highly Noisy	Highly Noisy	None	Quiet
Staff Time (per bed per day)	10 minutes	10 minutes	120 minutes	10 minutes
Volume of Secretions	10 - 30 ml	10 - 30 ml	30 ml	100 - 500 ml
FDA Cleared	No	No	No	Yes
Specifically Designed for SSD	No	No	No	Yes
Potential for Cross Contamination	Yes	Yes	Yes	Minimized

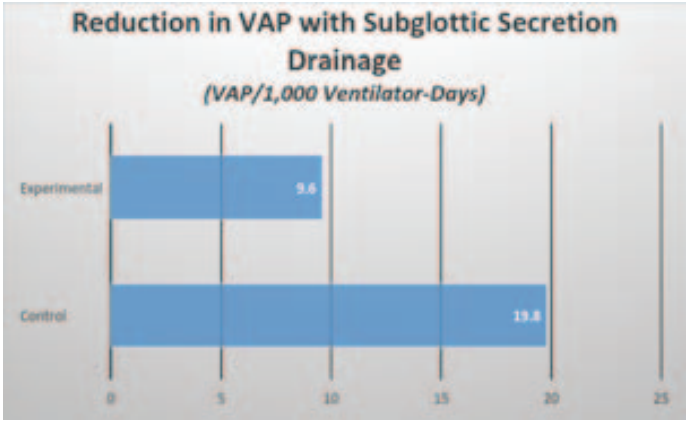

Figure 2. Damas P, Frippiat F, Ancion A, et al, Prevention of Ventilator-Associated Pneumonia and Ventilator-Associated Conditions: A Randomized Controlled Trial with Subglottic Secretion Suctioning, Critical Care Medicine Journal, 2015;43:1:22-301.[1]

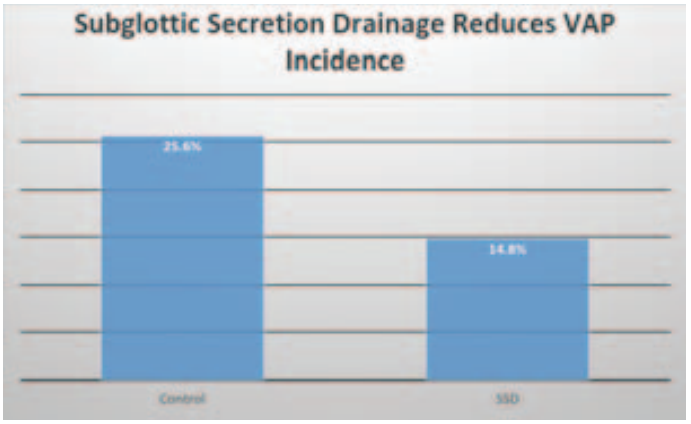

Figure 3. Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent Subglottic Secretion Drainage and Ventilator-associated Pneumonia: A Multicenter Trial. Am J Resp Crit Care Med. 2010;182:910-917.[2]

> "This study confirms the effectiveness of subglottic secretion suctioning in decreasing the rate of VAP even in ICUs with an operational VAP bundle."[1]

In this randomized, controlled clinical trial to assess the benefits of subglottic secretion drainage, the authors demonstrated a significant reduction in VAP and antibiotic use with SSD (see Fig. 2). A suction pump was set to -100 mmHg (within the -150 mmHg AARC Guideline), and operated for thirty seconds each minute. This would be considered an intermittent aspiration, with suction applied at least once a minute throughout the day, which is equivalent to 1440 aspirations daily.

A total of 352 patients were randomized into either the SSD group or the control group. In the control group 17.6% of patients acquired VAP, while only 8.8% of patients who received SSD acquired the nosocomial infection. Using SSD significantly ($p = 0.0076$) reduced the chance of VAP by 51.5% and also showed a significant reduction in antibiotic use. Patients who did not receive SSD were twice as likely to require antibiotics as patients who did.

> "The results of this randomized, multicenter study demonstrated that intermittent subglottic secretion drainage significantly reduces the incidence of microbiologically confirmed VAP, including late-onset VAP, without any noticeable adverse events. These results should encourage ICU physicians to progressively integrate SSD into their VAP preventative measures."[2]

The largest multi-site clinical study to evaluate the ability of SSD to prevent ventilator-associated pneumonia, this trial evaluated 333 patients at four different sites (see Fig. 3). Manual Intermittent Secretion Drainage was performed approximately every 90 minutes, a median of 18 times per day, utilizing a 10 ml syringe. An average of 14 ml of subglottic secretions were collected daily. The procedure was intended to occur every hour, though the staff was only able to perform it every 90 minutes.

The control group averaged a VAP rate of 25.6%, as opposed to 14.8% with manual intermittent subglottic secretion drainage. The authors demonstrated that incorporating SSD significantly ($p = 0.02$) reduced the incidence of VAP by 42%. The study also showed that SSD was effective in reducing VAP in both early-onset (80% reduction, $p = 0.02$) and late-onset (43.6%, $p = 0.01$).

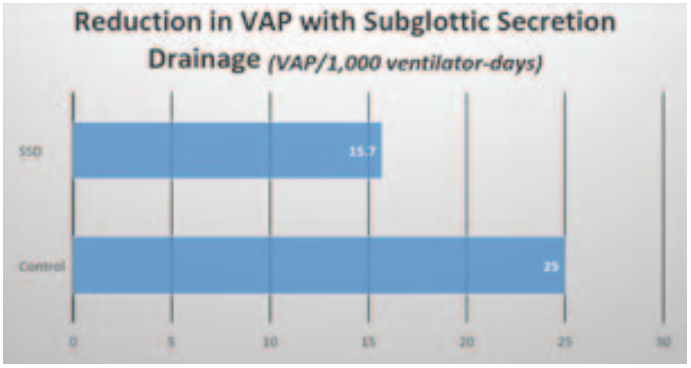

Figure 4. Juneja D, Javeri Y, Singh O, Nasa P, Pandey R, Uniyal B. Comparing influence of intermittent subglottic secretions drainage with/without close suction systems on the incidence of ventilator associated pneumonia. Indian Journal of Critical Care Medicine. 2011;15:3:168-172.[3]

> "We would emphasize the fact that the use of intermittent subglottic secretion drainage is beneficial in preventing VAP."[3]

In this controlled clinical trial of 311 patients, SSD was performed utilizing a subglottic endotracheal tube with a traditional intermittent suction device (see Fig. 4). VAP was shown to be significantly (p = 0.04) reduced with the use of intermittent subglottic secretion drainage. The VAP rate was 25.0 / 1,000 ventilator-days in the control group compared to 15.7 with secretion drainage, a 37.2% reduction.

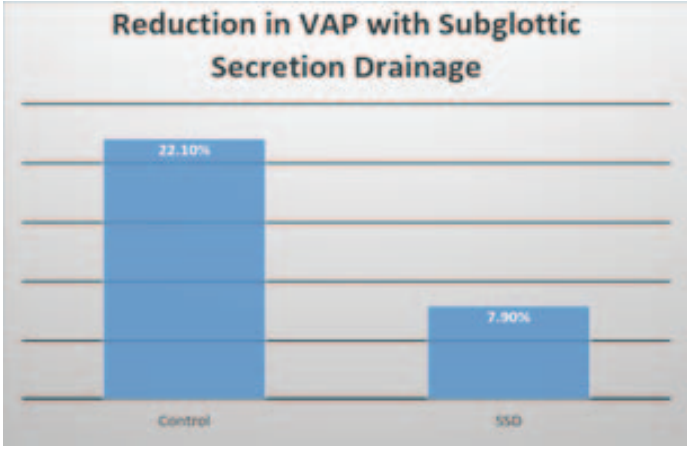

Figure 5. Lorente L, Lecuona M, Jimenez A, Mora M, Sierra A. Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. Am J Resp Crit Care Med. 2007;176:1079-1083.[4]

> "The main contribution of our study is the finding that [SSD], besides preventing early-onset VAP, also prevents late-onset VAP."[4]

In this randomized clinical trial, intermittent aspiration was performed at one hour cycles utilizing a 10 ml syringe (see Fig. 5). Subglottic drainage by intermittent aspiration was used because continuous subglottic drainage was found to be injurious to the tracheal mucosa in some studies.[14,21] In this trial conducted with 280 patients in a 24-bed ICU, intermittent subglottic secretion drainage was shown to reduce the incidence of VAP from 22.1% to 7.9% (p = 0.001), a 64.2% reduction. SSD was shown to significantly reduce the risk of both early-onset (p = 0.02) and late-onset (p = 0.01) VAP.

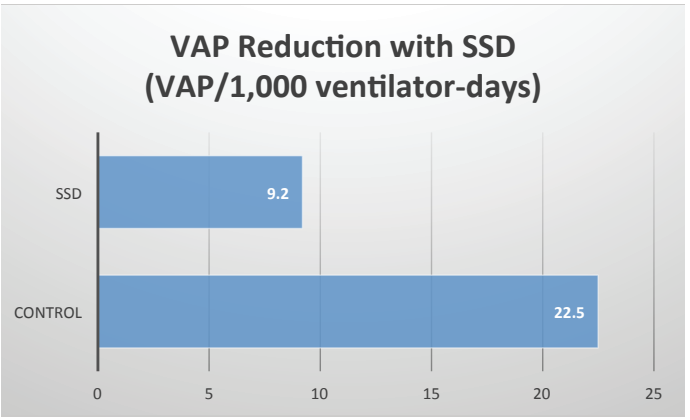

Figure 6. Smulders K, van der Hoeven H, Weers-Pothoff I, Vandenbroucke-Grauls C. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. Chest. 2002;121:3:858-862.[19]

> "Intermittent subglottic secretion drainage reduces the incidence of VAP in patients receiving mechanical ventilation"[19]

In this randomized, controlled clinical trial with 150 ICU patients, intermittent subglottic secretion drainage was shown to significantly (p = 0.001) reduce the incidence of VAP (see Fig. 6). In the control group, patients acquired VAP at a rate of 16%, while in the SSD group the rate was 4%. The wall suction regulator was used. Overall the authors saw a 59% reduction in incidence of VAP with subglottic secretion drainage. Because of the lower pressure guidelines for continuous suction, the authors used intermittent suctioning at -100mmHg, with 8-seconds on at intervals of 20 seconds. This is equivalent to over 3000 aspirations daily at -100mmHg pressure.

It is important to note that this study also required respiratory therapists to perform endotracheal secretion drainage procedures every four (4) hours, which was not performed in any of the other studies and likely inflated the reduction in VAP demonstrated in this study. Repeated, scheduled endotracheal procedures are not standard practice in most facilities, although endotracheal drainage is often necessary in response to secretions draining into the lungs. Endotracheal aspirations take substantial staff time, are extremely invasive for the patient, and can be counter-productive by causing irritation to the airways which increases subglottic secretions and can damage the tracheal mucosa.

Table 2. Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. Am J Med. 2005;118:11-18.[6]

First Author (Reference)	Number of Patients in RCT	Methodology	% Reduction of VAP Rate
Mahul[16]	145	Hourly Aspiration using Syringe	53.5
Kollet[17]	343	Continuous Wall Suction	39
Valles[18]	190	Continuous Wall Suction	49.7
Smulders[19]	150	Intermittent Wall Suction	59.1
Bo[20]	68	Continuous Wall Suction	48.8

> "Subglottic secretion drainage appears to be an effective method to prevent ventilator-associated pneumonia, shorten the duration of mechanical ventilation, and shorten the length of ICU stay among patients expected to require mechanical ventilation for more than 72 hours."[6]

This meta-analysis of previous controlled, clinical trials to investigate the ability of secretion drainage to reduce VAP included five different trials totaling 896 patients (see Table 2). The results supported the ability of SSD to prevent VAP, as well as reduce the length of time on ventilation and the time in the ICU.

Subglottic secretion drainage appears to be an effective method to prevent ventilator-associated pneumonia, shorten the duration of mechanical ventilation, and shorten the length of ICU stay among patients expected to require mechanical ventilation for more than 72 hours.[6]

Current Limitations of SSD

Despite the proven benefits of subglottic secretion drainage for ventilated patients, there remain several significant challenges in providing the highest quality of care to patients.

1. Ensuring Frequent Secretion Drainage

> "Respiratory therapists are instructed to drain the secretions for each patient on ventilation every hour, which is often difficult to accomplish with the volume of patients and high patient to staff ratio."[7]

Current traditional protocols call for intermittent subglottic secretion drainage to occur every hour for every ventilated patient, which can be a huge challenge for the staff at hospitals. In the clinical trials conducted, the staff was unable to meet their required protocols. In one multisite study that evaluated the frequency of drainage, they determined that the staff was only able to conduct the procedure every 90 minutes, rather than every hour.[2] Assuming the procedure takes 5 minutes, the respiratory therapist would need 2 hours (24 procedures x 5 minutes each = 120 minutes) with every patient each day—time that is often not available with current staff to patient ratios.

The challenge of ensuring that each patient is seen hourly is fundamental to the effectiveness of subglottic secretion drainage. Each time the protocol is not followed, is a chance for the secretions to be aspirated into the lungs and causing VAP or bronchial aspiration. It is likely that many of the cases of VAP that are seen in the clinical studies in the SSD group were caused by too long a period between procedures, and could be reduced even further with more frequent procedures.

2. Ensuring Proper Suctioning Force Levels

> "Current methods for subglottic drainage put between 2 and 5 times more force on the airway than is recommended."[7]

The American Association for Respiratory Care (AARC) has very specific guidelines for the pressure that is to be put on the airway of the patient, a maximum of -150 mmHg in intermittent treatment.[8] Pressure higher than this can put too much force on the airway, cause irritation for the patient and produce inflammation which can actually increase the volume of secretions and damage delicate mucous membranes.

Interestingly, the two methods of intermittent subglottic secretion drainage currently available and widely used, wall suction regulators and syringes, both exert more force on the airway than is recommended by AARC. Studies have found that 97.7% of procedure utilizing these modalities exceeded recommended pressure levels.[9] With wall-mounted suction, the pressure was measured at 123% higher than recommended, and with a syringe it was even higher.

Figure 7. Pressure gauge used to measure actual pressure generated by 10 ml syringe.

Depending on size, a syringe puts -578 to -722 mmHg of force on the airway, nearly 4 and 5 times more pressure than is recommended by the AARC[7] (see Table 3).

Table 3. Test to measure peak vacuum pressure of syringes with different volumes

Volume of syringe	Vacuum/Pressure (mmHg)			
	1	2	3	Average
2 mL	-578	-578	-578	-578
5 mL	-671	-671	-671	-671
10 mL	-706	-706	-706	-706
20 mL	-722	-722	-722	-722

3. Low and Variable Amounts of Secretion Drainage

> "Large variations in the volume of retrieved subglottic secretions have been previously reported. In one observational study, secretions were retrieved in less than 50% of collection attempts with suctioned volume ranging from 0.3 to 15.0 ml. This variability was confirmed in our study."[2]

An issue that is noted in many of the clinical trials is the low

and variable amount of secretions collected.[2] Among the factors that play into this are secretion viscosity, the effectiveness of suctioning and appropriate pressure, difficulties in maintaining the suction line, and frequency of drainage.

It seems clear that with current protocols reporting only 0.3-15.0 ml being removed each day,[2,10] a substantial amount of secretions are being missed, which have the potential to drain into the lungs and cause infection. Even though all the clinical trials observed major improvements in VAP rate with the use of SSD, it is worth noting that overall VAP rates remained high. The data suggests that VAP rates could be further lowered with effective, targeted subglottic secretion drainage that increases the amount of secretions collected. Current techniques using wall suction or manual suction with a syringe are improvised solutions and not specifically designed for subglottic secretion drainage.

With the advent of new automated intermittent subglottic secretion devices it is now possible to increase the volume of secretions routinely collected by up to 10 times.

4. Risk of Contamination

> "In addition to identifying suction regulators as potential reservoirs for nosocomial pathogens, this study demonstrated that contaminants can spread from a suction regulator to the wall-side canister within 30 minutes and can also spread back to a simulated patient stomach within 24 hours. Thus, suction regulators might be contaminated by one patient and then transmit pathogens to the stomach of a subsequent patient."[11]

In a study of 11 ICUs and 470 wall-mounted suction devices, 37% (173) were found to be contaminated with pathogens, including *Staphylococcus aureus*, *Psuedomonas aeruginosa*, and *Enteroccocus faecium*. Five different types of regulators were included in the testing, demonstrating this is a universal concern with wall suction. One common misconception is that after "cleaning" a regulator after patient use, the regulator is free of contamination. Current manufacturers' protocols state that back-flushing a regulator with disinfectants can remove contamination; however, there exist no data to support the efficacy of this practice. In addition, the internal flow paths in suction regulators can be convoluted, and bacteria can become trapped and can be aerosolized back during the venting cycle. The most effective method to ensure that a contaminated regulator does not contain pathogens is to sterilize it, which is costly and is not the presently recommended practice. Most brands cannot be safely sterilized. Identifying the suction regulator as a potential source of infection is noteworthy, and additional investigation is needed to clarify the risk that contaminated regulators pose to patients and to indicate optimal methods and protocols for disinfection.[11]

5. Limitations of Continuous Secretion Drainage

Because it is applied to the patient continuously, the AARC guideline for continuous secretion drainage is only -20 mmHg (compared to -150 mmHg for intermittent SSD). This low pressure is often not strong enough to remove many secretions, particularly those with high viscosity. It is tempting for respiratory therapists to increase the pressure settings to remove more secretions, but it is important to keep the pressure level low because continuously higher pressure levels cause drying of the mucous membrane.[2,4,14,15] This can cause irritation and lead to increased secretions.

6. Limitations of Manual Intermittent Secretion Drainage

There are two primary limitations with regard to manual secretion drainage. The first is the force exerted by the syringe. Depending on the size of the syringe, pressure levels as high as -722 mmHg can be exerted, which is substantially higher than the AARC recommended guideline of -150 mmHg. This is unsafe and can lead to complications. The second stumbling block is the demands on staff time given average staff to patient ratios. It is difficult to ensure that each patient receives the manual procedure hourly, as recommended. In clinical trials, this one hour interval was often longer than recommended and resulted in patients not receiving the recommended number of secretion drainage procedures each day. The volume of secretions collected, using manual intermittent secretion drainage have been measured at 33 ml per day.

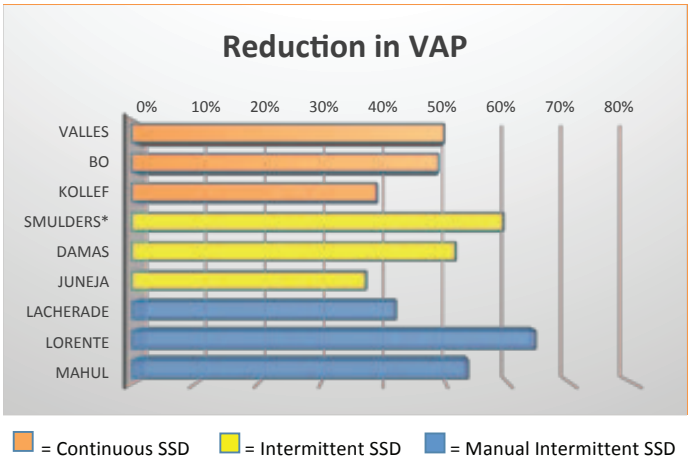

Figure 8. Reduction in VAP by Treatment Modality

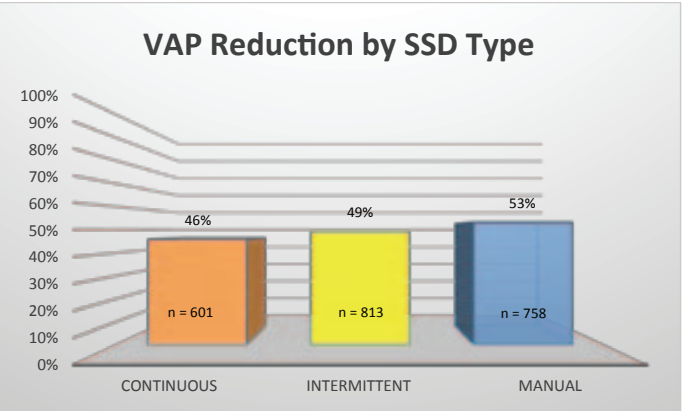

Figure 9. Average Reduction in VAP by Treatment Modality

Benefits of a Novel System in Addressing Limitations

With the FDA clearance of the SIMEX *cuff* Automated Intermittent Subglottic Secretion Drainage System, it is now possible to provide SSD in an optimal form, based on extensive research with specialty subglottic tracheal and endotracheal tubes.

1. Ensuring Frequent Secretion Drainage

With automatic intermittent SSD the frequency and pressure levels are preset according to patient needs. The recommended timeframe for aspiration ON time is 10-20 seconds and aspiration OFF/Pause time every 5 to 20 minutes, depending on the amount and type of secretion drainage. This can be customized to each

patient and reduces demands on the respiratory therapist to visit each patient every hour and ensures the frequency of drainage procedures.

The automated intermittent SSD device is electric and/or battery powered, is virtually silent and is designed to operate 24/7 at the patient's bedside. This ensures drainage is achieved at recommended intervals at reliably calibrated pressure levels. This allows for substantially more (up to 10 times more) secretions being removed compared to other methods. The secretions are removed from above the ballooned cuff and before they can reach the lungs to cause infection.

2. Ensuring Proper Suctioning Force Levels

The pressure level of the pump can be digitally set within the AARC guidelines for intermittent subglottic secretion drainage of -80 to -150 mmHg and can be customized according to patient needs. For example, thin secretions may allow for lower pressure levels than highly viscous secretions. Larger volumes of secretions may require decreasing the "OFF" time to allow for more frequent drainage. These customizable pressure levels, along with extended OFF times, significantly reduce excess strain on the airway of the patient, drying of tracheal mucosa and irritation of the airways. Additionally, in ongoing trials the amount of secretion collected averages up to 10 times more than with manual or continuous drainage.

3. Increasing Secretions Collected

"In our experience, the amount of material drained increases by up to 10 times over what we were seeing."[7]
—Dr. Markus Wolf, Asklepios Klinik, Hamburg, Germany

Figure 10. Patient with secretions of > 500 ml per day, E. coli, Pseudomonas, and Klebsiella. (Courtesy of Dr. Wolf)

By increasing the frequency of drainage and optimizing the pressure level for each patient, the optimal volumes of secretions can be collected and prevented from reaching the lungs. In trials with automated intermittent drainage, the amount of secretions collected was approximately 100-500 ml each day.[7,12] In the clinical trials with manual intermittent secretion drainage, the authors reported high variability and low volumes of secretions collected per day.[2,10] A recent study showed that switching from manual to automated intermittent drainage, the volume of secretions collected rose from 33 ml to 400 ml—a ten-fold increase. That is nearly 370 ml of infectious material that could have made its way into the lungs.[13]

Conclusion

The Promise of Automated Intermittent Subglottic Secretion Drainage

Based on the latest research, clinicians now have an innovative device to optimize treatments and outcomes to help reduce the incidence of VAP through true Intermittent SSD. Facilities that have adopted specialty subglottic tracheal and endotracheal tubes now have a state-of-the-art device to optimize their use as well.

When technology, driven by evidence-based research is fully engaged it can be used to design and engineer the breakthrough devices that will improve, optimize and change the way we administer proven therapies. The promise of the new SIMEX *cuff* device for Automated Intermittent SSD has been demonstrated in Europe in over 500 patients with no adverse events. Randomized control studies and multi-center trials are now underway in the US to further evaluate its efficacy.

We know that SSD can:

- Reduce the incidence of VAP in ventilator assisted patients by approximately 50% (37-64%)
- Reduce both early and late onset VAP
- Reduce the need for antibiotics
- Reduce the length of hospital stay

We know that the limitations of existing modalities of treatment include:

- Inability to accurately operate within AARC recommended pressure guidelines
- Exposing patients and clinicians to contaminants
- Limited volume of secretions collected
- Depending on modality, can require very low, ineffective pressure levels which limit the volume of secretions collected
- Are utilized at pressure levels that are too high and can injure the airways and tracheal mucosa
- Are dependent upon limited staff time due to high staff to patient ratios

And we know that Automated Intermittent SSD can:

- Be optimized to recommended pressure recommendations
- Be fully customized to individual patient needs
- Reduce staff time
- Reliably control pressure levels due to digital programming
- Run at optimal ON and OFF cycles to maximize secretion collection while minimizing injury to the airways and tracheal mucosa
- Collect up to 10X more secretions daily than other modalities
- Operate in virtual silence at the patient's bedside
- Significantly reduce cross contamination through use of an integrated, self-contained, disposable collection canister

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VAP Prevention Strategies in Long-term Mechanically Ventilated Patients: Clinical Experience and New Approaches Involving Subglottic Tracheostomy Tubes and Automated Removal of Subglottic Secretions

Jerry Gentile, BSRT, BSHA, MBA, EdD(c), RT, RRT, and Alphonso Quinones, DHA, MA, RT, RRT-NPS, RPFT, RPSGT, CCT, AE-C, FACHE

Abstract

Ventilator-Associated Pneumonia (VAP) is the most common nosocomial infection among mechanically ventilated patients. VAP is associated with high morbidity and mortality rates, increased hospital stays and time on mechanical ventilation, as well as increased costs to treat. Prevention strategies to mitigate the risk of VAP continue to evolve. The introduction of tracheostomy and endotracheal tubes with integrated suction lumen for subglottic suctioning are recent advances, but shortcomings in their designs and practical uses have been identified.

This paper focuses on the optimization of tracheostomy cuff pressure settings, and on suction portal design, and provides a summary of clinical experience in a long-term care setting with subglottic tracheostomy tubes and the removal of secretions from the subglottic space. An additional goal is to educate Respiratory Therapists and enhance their VAP prevention strategies. Interim results of a randomized, controlled clinical trial of an automated, intermittent subglottic secretion aspiration system are presented.

Keywords

Subglottic Secretion Drainage (SSD), Ventilator-Associated Pneumonia (VAP), Mechanical Ventilation, Tracheostomy Cuff Tubes, Cuff Pressure, Automated Intermittent Subglottic Secretion Drainage, Subglottic Suction Port

Background

Ventilator-Associated Pneumonia (VAP) is a nosocomial infection that develops 48 hours + post admission to the long-term ventilator unit. It develops in patients who are tracheostomized and on mechanical ventilation. VAP is the most common nosocomial infection among mechanically-ventilated patients (Davis KA, 2006). VAP rates are important in long-term ventilator units because ventilated patients that acquire VAP have close to a 45% increase in mortality rates (Ibrahim EH, et al 2001). These mortality rates are high primarily due to the patients' comorbidities and the virulence of the bacterium colonizing the lower airway. VAP is not just responsible for increased mortality rates, but also for increased discharges to the hospital ER, lost revenue, increased duration of mechanical ventilation, and costs exceeding $40,000 per incident (Guterl G, 2013).

The presentation of VAP/pneumonia is essentially the same in both non-ventilated and ventilated patients. Clinical symptoms include fever, tachycardia, tachypnea, increased volume and thickness of purulent secretions, and worsening hypoxemia (Bartlett JG, 2008). We currently use two methods for the diagnosis of VAP. One is a more clinically based or qualitative method called the Clinical Pulmonary Infection Score (CPIS). We examine clinical signs and symptoms to determine if the pulmonary infection is a true pneumonia. This method of diagnosis is not very accurate nor specific, primarily because the clinical presentation can mimic symptoms caused by other conditions (Chastre J, et al, 2002). The second and more definitive/quantitative method is the sputum sample for culture and sensitivity. This is a more invasive method to match clinical presentation to a known causative bacterium. By culturing the sputum and determining the specific organism, targeted antibiotic therapy can be initiated, decreasing the risk of further creating more drug resistant strains of organisms through the use of broad spectrum antibiotics (Davis KA, 2006).

The lower airways of the lung are normally sterile. When bacteria are introduced and colonize, VAP develops. The most common bacteria found in cultured sputum of ventilated patients include: gram negative-pseudomonas aeriginosa, klebsiella pneumoniae, and escherichia coli. Gram-positive bacteria include staphylococcus aureus. Tracheostomized and mechanically-ventilated patients are more at risk for acquiring these organisms because of the bypassing of the normal airway defenses. The longer the patient is both tracheostomized and mechanically ventilated, the greater the risk of developing VAP. Pseudomonas aeruginosa and staphylococcus aureus have become much more difficult to treat due to drug resistant strains. These strains result in higher numbers of VAP morbidity and mortality (Bartlett, 2006). Due to the placement of the tracheostomy tube, the normal defense mechanisms of the upper and lower airways are compromised (Pneumatikos IA, et al, 2009). If bacteria are introduced into the normally sterile lower airway, they allow for colonization and an infectious process. The tracheostomy tube disrupts the mucociliary escalator and impairs clearance. It also impairs the cough reflex and allows for a direct pathway to the lower airway. The tracheostomy tube not only disrupts normal airway defense mechanisms; it also injures the tracheal tissue.

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VAP is a two-step process that begins with the aspiration of contaminated secretions in the lower airway and the colonization of the bacteria. VAP on the long-term ventilator unit can develop at any time. In our facility we do not define VAP as early or late onset, however, we do distinguish between nosocomial and community acquired. If the patient is admitted to the unit from the hospital or other long-term care unit and spikes a fever within 48 hours, the patient is worked up for possible VAP. If sputum culture and sensitivity and chest radiograph confirm VAP, we consider this community acquired. If after 48 hours the patient spikes a fever and we confirm VAP, it is considered nosocomial.

Clinical Experience at Eastchester Rehabilitation and Healthcare Center

VAP rates in our 40-bed long-term ventilator unit have averaged between 12.5% to 20%. The transfer rate to the hospital for these patients has averaged 50%. Mortality rates for those transferred patients have averaged 20%. Therefore, preventing VAP in the long term ventilator unit has been a priority. One of the major problems that contributes to the level of VAP in long term care has been the tracheostomy tube itself. It directly interferes with normal respiratory defense systems and is an open gateway to the lower respiratory tract for bacterial colonization.

The tracheostomy tube cuff is used to seal the airway to provide positive pressure mechanical ventilation. This cuff also can provide a platform for secretions to pool and eventually leak around the cuff. Most Respiratory Therapists set cuff pressures to "minimal occluded volume," which is between 20 to 25 cmH2O. This prevents lymphatic flow obstruction (edema), venous flow of obstruction (congestion), and decreased venous-capillary blood flow (ischemia). However, our research is finding that these cuff pressures are too low to prevent leakage of contaminated secretions from around the cuff. Our preliminary research has found that cuff pressures at approximately 30.0 cmH2O (±5 cmH2O) are ideal for prevention of secretions from leaking around the tracheostomy cuff. Our results are similar to that of (Chendrasekhar A, et al, 2013). They concluded that ETT cuff pressures of 29.5 (±3.2 cmH2O) were needed to maintain secretions above the cuff.

The recommendations for cuff pressures of 20 to 25 cmH2O we feel inherently expose patients to a higher risk of VAP. We propose the concept that it is better for the Respiratory Therapist to implement pressures that are clinically ideal versus meeting a set number. Each patient's ideal cuff pressure will be different. The Respiratory Therapist may still use the minimal occluded volume technique, but use a pressure that is ideal for the individual patient. If the pressure necessary to seal the airway is 32 cmH2O, then use 32 cmH2O. This will further decrease the incidence of VAP in tracheostomized patients. Our new protocol for cuff pressures is between 25 to 35 cmH2O. Once the cuff has sealed the airway sufficiently to prevent leakage of contaminated secretions, the secretions then need to be removed from the airway. Otherwise, the subglottic secretions can be aspirated by the patient and bacterial colonization can occur (O'Keefe-McCarthy S, et al, 2008). The micro-aspiration of the subglottic secretions is a preventable factor in the development of VAP (Safdar N, et al, 2005).

The American Association for Respiratory Care (AARC), the American Thoracic Society (ATS), and the Centers for Disease Control and Prevention (CDC) all recognize the need and importance of removing secretions from the subglottic space as a measure to prevent VAP. There are, currently, a few long-term ventilator units that implement subglottic tracheostomy tubes and regular subglottic suction.

Switch to Tubes with Subglottic Ports

Once the patient is admitted, the Respiratory Therapist changes the standard tracheostomy tube to a subglottic suction version — we are currently using Portex Blue Line. This tracheostomy tube bypasses the upper airway, which eliminates air filtration, humidification, and mucociliary clearance. These normal airway defense mechanisms filter out contaminants in the air before they can reach the lower respiratory tract (Pneumatikos IA, et al, 2009). The tracheostomy cuff is the only separation between the contaminated upper airway and the sterile lower respiratory tract in mechanically ventilated patients. Without subglottic secretion aspiration, the subglottic space becomes a region of potentially infectious gram negative bacteria that can be micro aspirated by the patient.

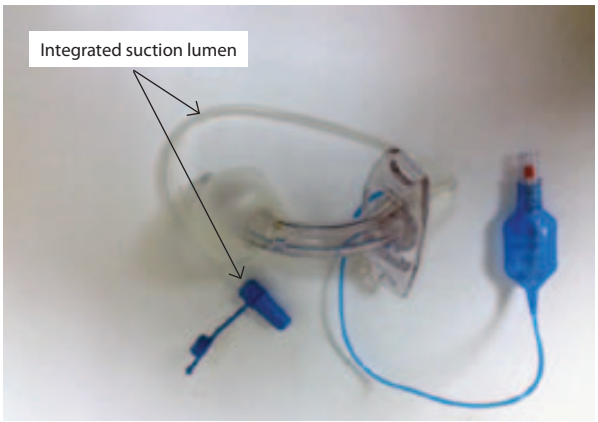

Figure 1. Subglottic Tracheostomy tube with integrated suction lumen

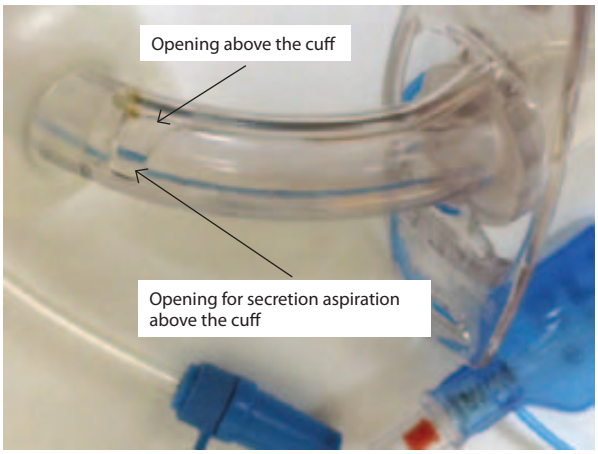

Figure 2.

VAP Risk Factors

In the long-term mechanically-ventilated patient, the presence of the tracheostomy tube places the patient at risk for development of VAP. There are, however, other factors that increase this risk. Comorbidities, such as COPD or decreased level of consciousness can be considered patient-related risk factors. Equipment-related risk factors could include suction tubing or ventilator circuits. Failure to maintain hand hygiene increases the risk of bacteria introduction into the ventilator circuit (ie, when changing HMEs) and is considered a personnel-related risk factor (Augustyn B, 2007).

VAP Prevention Strategies

The main goal in the prevention of VAP is decreasing the risk of bacterial contamination and colonization of the oropharynx and lower respiratory tract. Airway protection is decreasing the risk of micro aspiration of contaminated secretions around the tracheostomy cuff. Implementing new respiratory clinical practice guidelines and new preventive technologies will assist in reduction of VAP. We have developed a five-step VAP program that includes: (1) Head of bed 30 to 45°; (2) DVT prophylaxis; (3) proton pump inhibitor; (4) chlorohexidine 0.12% oral rinse; and (5) daily weaning from mechanical ventilation. (Efrati S, et al, 2010; O'Keefe-McCarthy S, et al, 2008). This had a small impact on our VAP rates, but did not significantly reduce our average of 16.25%. We were hopeful that implementation of subglottic suctioning would further reduce this rate.

Tracheostomy Cuffs and Ideal Subglottic Design

The objective of the tracheostomy cuff is to seal the airway for mechanical ventilation, as well as in preventing the aspiration of secretions entering the subglottic space. This can only be accomplished, however, if the cuff is inflated to form a good seal between the tracheostomy tube itself and the tracheal wall. If the cuff is improperly inflated and a good seal is not made, subglottic secretions will leak around the cuff. This enables contaminated secretions to enter the otherwise sterile lower airway. This leads to the development of VAP (Gentile MA, et al, 2010). With this in mind, attention has focused on the cuff material itself. Research has shown that polyvinyl material is not as effective at creating a good seal as silicone or polyurethane. Polyvinyl tends to be a thicker material and is prone to allow leakage around its seal (Deem S, et al, 2010). A study has found that polyurethane cuffs set to minimal occluded volume and use of subglottic suction has significantly reduced VAP rates when compared to a polyvinyl, non-subglottic group (Lorente L, et al, 2007). Polyurethane cuffs seem to trap subglottic aspirate more effectively than polyvinyl, which then allows it to be removed more efficiently. VAP prevention can only occur if the secretions are trapped above the cuff. The subglottic aspiration device can only be effective if there are secretions to be removed.

Throughout the randomized controlled clinical trial (RCT) we have used standard subglottic tracheostomy designs. Our research data has brought to light some potential issues with current subglottic tracheostomy aspiration port designs. Current models of subglottic tracheostomies have a small suction port located at the posterior section of the tube. This works well at lower angles (10-50 degrees). However, patients in long term ventilator units are sometimes sitting up in chairs or wheelchairs at angles from 70-90 degrees. Posterior suction ports are less effective at these angles. We are currently working on a new proprietary concept (patent pending) of a tracheostomy tube with 360 degree suction port design. This will allow for effective subglottic suctioning at any patient angle.

Early Clinical Results with an Automated Subglottic Aspiration System

The prevention of secretion accumulation in the subglottic space is key to the prevention of VAP. The goal is to eliminate aspiration of the pooled secretions above the tracheostomy cuff. In September, 2014, we switched all patients to subglottic suction tracheostomy tubes. The Respiratory Therapists were manually aspirating the subglottic ports 4x/day, which became labor-intensive. The subglottic ports would also frequently occlude, resulting in the Respiratory Therapist having to lavage ports, further increasing the risk of VAP. The average manual suction volume obtained by manual aspiration with a 20cc syringe was 30-40 ml/day. In March, 2015, we instituted a trial of five SIMEX Automated Subglottic Aspiration System devices. Trial suction pressures were started at -100 mmHg pressure/10 second duration/10 minute intervals. The Respiratory Therapist adjusted the settings based upon clinical presentation—patient comfort level, secretion volume, or evidence of tracheal tissue trauma. Over the course of the eight-month evaluation, we have had the SIMEX Subglottic Aspiration Device on 10 patients. The VAP rate on these 10 patients was zero during the evaluation period. Due to this promising outcome, we decided to perform a randomized controlled clinical trial. The RCT involves 25 study patients using SIMEX device and 15 control patients using a combination of conventional suction devices and manual aspiration.

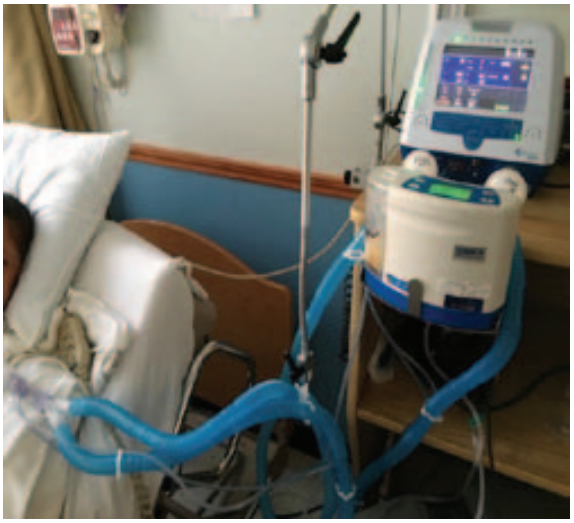

Figure 3. SIMEX device setup on a patient in facility

Figure 4. SIMEX subglottic aspiration container with subglottic secretions

Three months into the RCT, we have determined that optimal subglottic suction settings are -150 mmHg pressure/12 second

suction duration/10 minute suction intervals. We were initially collecting volumes between 70-200 ml/day. After we "redefined" tracheostomy cuff pressures and "ideal minimal occluded volume," our collection volumes ranged from 90 to 300 ml/day. This indicates that patient micro aspiration was previously occurring due to leakage around the tracheostomy cuff. As we increased the tracheostomy cuff pressures in both control and study patients, aspirate/secretion volume also increased.

Maceration of tissue surrounding the stoma has decreased significantly, resulting in less soiled clothing and less need to frequently change tracheostomy ties. Patients have reported that they have been very comfortable on the SIMEX subglottic aspiration device, with no reports of tracheal discomfort or signs of tracheal wall abrasion.

Figure 5. Subglottic tracheostomy tube that is connected to SIMEX device

Respiratory Therapists report that the SIMEX device is simple to program, monitor, and maintain. Suction collection canister changes are simple and contained. There have been no reports of spills or leaks.

Our current 4-month RCT study has 25 patients on the device and a 15 patient control group. We are 3 months into the trial and of the 25 patients on the device, we have had 2 confirmed cases of VAP (8%). We believe that 1 of these patients developed VAP through an emergent tracheostomy change due to cuff failure. Both patients were on the SIMEX device for 33 days. The control group of 15 patients has developed 5 confirmed cases of VAP (33%) since the start of the RCT. The SIMEX subglottic aspiration system, working in conjunction with our five-step VAP prevention program, has significantly decreased our VAP rates. The facility has saved a considerable amount of resources in VAP treatment, as well as decreased transfer rates to hospital ERs. We are looking forward to further researching the efficacy of the SIMEX subglottic aspiration system and its application in the prevention of ventilator-associated pneumonia.

Conclusion

The diagnosis of VAP is best accomplished by combining qualitative measures (such as CPIS), with the more definitive and quantitative, sputum sample for culture and sensitivity, which provides for targeted antibiotic therapy. Targeted antibiotic therapy decreases the risk of more drug resistant strains associated with the use of broad spectrum antibiotics.

Use of the SIMEX automated subglottic aspiration system provided for patient comfort and efficient removal of large secretion volumes, 90-300 ml/day, compared to previously-used manual suction via 20mm syringes where only 20-40ml/day of secretions were collected. The automated system also provided the means for measuring the effectiveness of various VAP prevention approaches, for example, the means for precise measurement and comparison of secretion volumes when cuff pressures were adjusted.

Three months into the planned 4-month randomized controlled clinical trial of the automated system, an interim VAP rate of 8% has been confirmed in the active SIMEX group of 25 patients. In contrast, an interim VAP rate of 33% has been confirmed in the control group of 15 patients. As a result, a considerable amount of center resources have been saved, and the rate of transfers of patients to hospital ERs has been greatly reduced.

Tracheostomy cuff pressures set at the commonly recommended pressures of 20-25 cmH2O (minimal occluded volume), have been shown not to provide an adequate seal, allowing for leakage of secretions past the cuff, and raising the risk of VAP. In conjunction with use of the SIMEX subglottic aspiration system in the RCT, cuff pressures were individualized for each patient, allowing for higher pressures if required to establish a good seal. In selected patients, higher "redefined" tracheostomy tube cuff pressures resulted in 30% increases in secretions collected.

As part of the RCT, a more effective tracheostomy tube design has been developed, one that has a 360-degree subglottic aspiration port. Future development of the new design holds promise for allowing decreased pooling volume and risk of leakage, and for more effective subglottic suctioning at greater patient angles in the range of 70-90 degrees, for patients in chairs or wheelchairs.

Since this RCT study represents the first trial of its type of the automated intermittent subglottic secretion system in the United States, additional trials will be needed to further define the efficacy and overall cost effectiveness of the novel system.

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Study Shows Use of ResMed myAir™ Patient Engagement Platform is Associated with High Adherence to CPAP Therapy

Chris Campbell

A ResMed retrospective descriptive study of myAir™ usage data demonstrated a connection between continuous positive airway pressure (CPAP) device usage, digital health applications and high compliance. According to the study of 2,343 de-identified patient records, researchers found 83.9% of new CPAP users who received standard care and used the ResMed myAir application achieved Medicare adherence in the first 90 days of their treatment. Equally impressive, 75.4% of users achieved adherence in 30 days, with a median time to achieve Medicare adherence of 23 days.

"The high level of CPAP adherence this study shows is evidence that myAir is a best practice for getting patients engaged in their care," said Raj Sodhi, president of ResMed's Healthcare Informatics Global Business Unit. "It reflects the potential for connected patient engagement tools to spur compliance in a cost- and resource-effective manner, for the benefit of providers, health systems, payers, and patients alike."

Consistent and ongoing adherence to CPAP therapy — considered the gold standard treatment for sleep apnea — is essential for the health benefits to be realized, and for home medical equipment providers (HMEs) to meet the strict compliance regulations required for them to receive reimbursement. With this in mind, ResMed developed myAir based on principles of behavior therapy. The free online support system allows patients to track their nightly sleep data, and through tailored coaching, empowers patients to stay engaged with therapy.

Study Design

Many adherence studies focus on the first three months of CPAP treatment, but because sustained benefits will only be achieved with consistent and ongoing adherence to therapy, usage beyond that point is equally important. Researchers for this study queried the myAir database for records created between October 2014 and March 2015 that had been activated, had at least 90 days of data, and had a realistic treatment start month. Two different categorizations of user experience were used: (1) brand new users (CPAP use for 0-30 days) vs. others (CPAP use for >30 days); (2) novice (CPAP use for 0-90 days), intermediate (CPAP use for >90 to 180 days), experienced (CPAP use for >180 days) and strugglers (defined as users who had 0-30 days experience using CPAP treatment prior to activating their myAir account and <2 hours average usage in the first 14 days on myAir).

Chris Campbell is the Senior Editor of Respiratory Therapy.

2,343 patient records met the inclusion criteria; 70% of patients were male, 29% were female, and 1% did not disclose gender. Novice (n=1,731), intermediate (n=37), and experienced (n=575) users had 16.2±21.7 days, 121.1±21.0 days and 7.9±4.6 years of experience using CPAP treatment prior to using myAir, respectively. 1,067 patients were identified as brand new users and 86 patients were classified as strugglers.

Study Results

The proportion of brand new users who achieved the criteria for Medicare adherence — defined as objective evidence of CPAP use for four or more hours per night on at least 70% of nights during a consecutive 30-day period anytime during the first three months of initial usage — in 90 days was 83.9%, and 75.4% within 30 days. The median time to achieve Medicare adherence was 23 days, and was similar in males and females. Of 86 strugglers, 19.8% went on to achieve Medicare adherence in 90 days; female strugglers took longer than males to achieve adherence.

The results compare favorably to a study that examined CPAP adherence over a 24-month period in 3,100 Mediterranean patients with newly-diagnosed moderate sleep apnea who received either standard care (ie, physician consultation where data were discussed) or high-touch intensive care (eg, education, role models, monitoring, regular follow-up, and other simultaneous strategies).[1] Use of labor-intensive approaches to maintain or improve adherence led to 79.8% of patients in the standard group and 92.8% of those in the high-intensive group using CPAP regularly for four or more hours per night on 70% of days.

About myAir™

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Altered Protease and Antiprotease Balance During a COPD Exacerbation Contributes to Mucus Obstruction

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Abstract

Background: Proteases have been shown to degrade airway mucin proteins and to damage the epithelium impairing mucociliary clearance. There are increased proteases in the COPD airway but changes in protease-antiprotease balance and mucin degradation have not been investigated during the course of a COPD exacerbation. We hypothesized that increased protease levels would lead to mucin degradation in acute COPD exacerbations.

Methods: We measured neutrophil elastase (NE) and alpha 1 protease inhibitor (A1-PI) levels using immunoblotting, and conducted protease inhibitor studies, zymograms, elastin substrate assays and cigarette smoke condensate experiments to evaluate the stability of the gel-forming mucins, MUC5AC and MUC5B, before and 5-6 weeks after an acute pulmonary exacerbation of COPD (n = 9 subjects).

Results: Unexpectedly, mucin concentration and mucin stability were highest at the start of the exacerbation and restored to baseline after 6 weeks. Consistent with these data, immunoblots and zymograms confirmed decreased NE concentration and activity and increased A1-PI at the start of the exacerbation. After recovery there was an increase in NE activity and a decrease in A1-PI levels. In vitro, protease inhibitor studies demonstrated that serine proteases played a key role in mucin degradation. Mucin stability was further enhanced upon treating with cigarette smoke condensate (CSC).

Conclusion: There appears to be rapid consumption of secreted proteases due to an increase in antiproteases, at the start of a COPD exacerbation. This leads to increased mucin gel stability which may be important in trapping and clearing infectious and inflammatory mediators, but this may also contribute acutely to mucus retention.

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Introduction

Proteases play a major role in bacterial entrapment [5], pathogen phagocytosis [16], mucin hypersecretion and mucociliary clearance [9]. In COPD there is a deficiency and decreased activity of anti-proteases [21, 30], contributing to emphysema [1] and mucus hypersecretion [4]. This protease and anti-protease imbalance has been suggested to result from neutrophil infiltration in the lung [3, 28]. These neutrophils release proteases including neutrophil elastase (NE), cathepsin-G (CG), and proteinase 3 (PR3).

Mucins are linearly linked core proteins encoded by mucin (MUC) genes. The principal airway gel-forming mucins are MUC5AC and MUC5B [24]. Several lines of evidence show that mucus is hypersecreted in COPD [30]. Studies performed on surgically isolated lung tissues from COPD patients have shown that mucus containing inflammatory exudate accumulates in small airways and is associated with disease progression [11]. In biopsies from COPD patients with severe lung disease, mucus occupies about 15 % of the total luminal area of small airways; whereas, in "healthy" smokers, it is limited to less than 5 % of the luminal area [13]. The amount of small airway mucus is strongly associated with mortality in patients with COPD [12]. We have shown that increased secretion of serine proteases in cystic fibrosis (CF) can degrade the gel-forming mucins during the time of transport from peripheral airways to central airways [9]. However the effect of serine proteases on mucin in COPD subjects has not been well characterized.

In this study, we investigated the role of proteases and anti-proteases on COPD mucin stability and degradation during the course of an infectious and inflammatory exacerbation of COPD. As in subjects with CF, we hypothesized that that there would be an acute increase in proteases during exacerbation leading to mucin degradation.

Methods

Subject details and sample collection

Nine subjects were included in the study, with a mean age of 59.9 years. They had been hospitalized or evaluated in the outpatient clinic of the Department of Pulmonary Medicine, Philipps-University Marburg, because of an acute pulmonary exacerbation of COPD defined by the Anthonisen criteria of

Table 1 Study summary

	Time	Procedures
Visit 1	day 1; week 1 (within 7 days after start of exacerbation)	Sputum collection, pulmonary function test, chest x-ray, blood sample, physical examination
Visit 2	days 40–46, week 5–6	Sputum collection, pulmonary function test, blood sample

increased dyspnea and cough, increased sputum volume and change in sputum color [2]. Subjects were included if they had at least 2 of symptoms with an onset within 7 days before the start of the study. We included only subjects in GOLD group II or III (FEV1/VC < 70 %, FEV1 30-80 %) [31]. Criteria for exclusion were signs of bacterial infection with fever >38.5 °C, CRP-elevation >30 mg/L or procalcitonin elevation > 5 µg/L, suspected or known pneumonia with infiltrate on chest x-ray, Pseudomonas aeruginosa in sputum cultures, pre-admission antibiotic treatment, or suspected or known asthma. At the first day of the reported pulmonary exacerbation symptoms, sputum was collected. All subjects were followed up 5-6 weeks after the onset of the exacerbation and another sputum sample was collected (Table 1). At visit 1 the subjects were grouped as "COPD with exacerbation" and after 5-6 weeks (visit 2) as "COPD without exacerbation". All subjects were treated with oral steroids (40 mg once daily) for total of 10 days, and inhalation therapy with long-acting muscarinic antagonists and short- and long-acting beta2-agonists. Five of the 9 subjects were current smokers and 4 were former smokers. Antibiotic treatment was not necessary for any of the subjects and all of them recovered from the exacerbation within the observed time. Clinical characteristics and demographics of the COPD subjects are given in Table 2. Sputum collection was approved by the Philipps-University Marburg Institutional Review Board.

Control mucus collection

As a control group we collected mucus coating the endotracheal tubes (ETT) of subjects who had no lung disease and required non-thoracic surgery under general anesthesia. When the subject was extubated, the ETT was removed from the airway and mucus was removed by gently scraping the ETT [25, 26]. Collected ETT mucus was placed in a small O-ring container to prevent dehydration, labeled as to date of collection with no subject identifiers, and sent to Philipps-University Marburg on dry ice. ETT mucus collection was approved by the Virginia Commonwealth University Institutional Review Board and signed consent, and assent when appropriate, was obtained.

Protease inhibitors and antibodies

NE and cathepsin G were purchased from Merck Chemical, Nottingham, UK. Serine protease inhibitors diisopropyl fluorophosphates (DFP), phenylmethyl sulfonyl fluoride (PMSF), and 1-chloro-3-tosylamido-7-amino-2-heptanone HCl (TLCK), metalloprotease (EDTA and GM6001) and cysteine proteases (leupeptin and E64) were purchased from Sigma (Saint Louis, MO). Alpha-1 protease inhibitor (A1-PI) was obtained as Prolastin (Grifols Therapeutics Inc. Frankfurt, Germany) and was used at a final concentration of 0.3 µg/mL. DFP (final concentration 2 mM); PMSF (final concentration 2 mM); TLCK (final concentration 10 mM); EDTA (final concentration 100 mM); E64 (final concentration 500 ng/mL) or Merck Chemical (Nottingham, UK): GM6001 (final concentration 40 µM) and leupeptin (final concentration 40 µM) were used. Polyclonal anti-MUC5AC and anti-MUC5B antibodies were generated as previously described [10]. The antibodies were characterized and specificity was ascertained by pre-absorption studies using increasing concentrations of the antigenic peptides [25]. Specificity of these antibodies was verified using immunoblotting against MUC5AC and MUC5B from whole cell lysates, secretions from normal human tracheobronchial epithelial (NHBE) cells (passage 2) (Clonetics Corp., La Jolla, CA, USA), and human mucus. The blots were analyzed with antisera for MUC5AC and MUC5B and the pre-immune sera of the same rabbit. We

Table 2 Demographic data of the COPD patients included the study

subject	age	Pack years	smoking status		chest x-ray (infiltrations?)	CRP in mg/l	leucocytes in G/l (normal: 4.3–10)	Procalcitonin in µg/l	FEV1 (%)	VC (%)	FEV1/ VC (%)	color of sputum
01	51	80	current smoker	Visit 1	no	<5	6.24	*	49	95	47	clear
				Visit 2		<5	7.05	*	58	94	55	clear
02	61	80	former smoker	Visit 1	no	<5	8.28	0.22	63	95	66	clear/slightly yellow
				Visit 2		14	8.14	0.17	67	95	70	clear
03	74	20	former smoker	Visit 1	unkown	31	7.25	*	67	95	70	clear
				Visit 2		18	6.64	*	81	95	75	clear
04	67	20	former smoker	Visit 1	no	11	10.7	<0.1	48	89	53	clear/slightly yellow
				Visit 2		*	*	*	42	98	43	clear
05	65	30	former smoker	Visit 1	no	18	3.92	<0.1	68	98	69	clear
				Visit 2		<5	5.21	<0.1	95	98	97	clear
06	52	50	current smoker	Visit 1	no	11	13	*	32	93	34	clear
				Visit 2		<5	9.15	*	74	98	75	clear
07	57	35	current smoker	Visit 1	no	<5	5.89	*	37	91	41	clear
				Visit 2		*	*	*	58	90	64	clear
08	50	50	current smoker	Visit 1	no	14	15.3	<0.1	36	93	39	clear
				Visit 2		24	15.3	<0.1	51	92	55	clear
09	62	70	current smoker	Visit 1	no	7	8.5	*	56	89	63	clear/slightly yellow
				Visit 2		<5	6.15	*	67	89	75	clear

*Data not collected

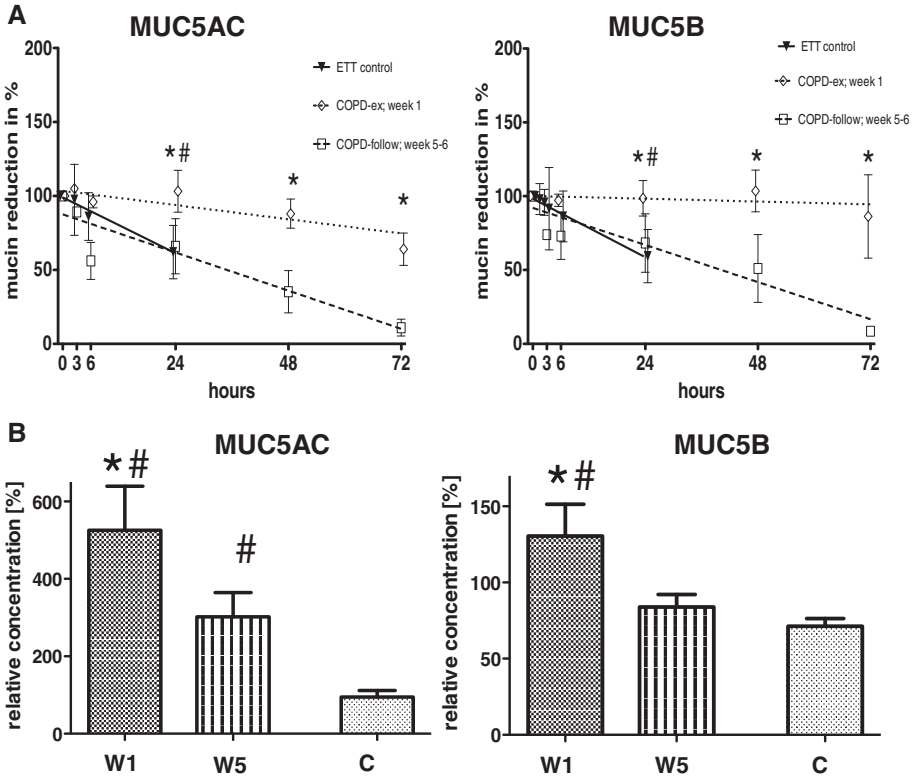

Figure 1. Sputum collection and mucin quantification from COPD subjects. Quantification of mucin in sputum obtained from 9 subjects with COPD. a Sputum was collected at the start of an exacerbation of COPD (COPD-ex; week 1) and again 5–6 weeks later (COPD-follow; week 5–6) from the same subjects. Results were compared to mucin concentration in mucus from 11 ETT control mucus samples (control). b The results are shown as mean density of individual samples related to the internal control (=100 % relative concentration). * = significant to "COPD-follow; week 5-6" (t-Test, $p < 0.05$); # = significant to "control" (Mann Whitney test, $p < 0.05$).

found one well-defined band of high molecular weight with the antisera. To increase the specificity of the antibodies and reduce nonspecific binding, affinity purification of the antipeptide antibody was performed from the whole serum using the immobilized amino acid sequences of interest (SulfoLink-Kit, Pierce). An internal control for mucin was collected from a voluminous sputum sample from a single patient undergoing lung transplantation for non-CF bronchiectasis [10]. Mucin signals obtained from COPD sputum and normal controls were normalized to this internal control, which was set to 100 %.

Agarose wet western blotting for MUC5AC and MUC5B

Sputum and internal control samples were diluted 1:10 with PBS and denatured using Laemmli buffer (125 mM Tris pH 6.8; 4 % SDS; 20 % glycerol; 0.001 % bromophenol blue, 20 mM DTT) and separated using 1 % agarose gels (15 × 15 cm), prepared in running buffer (25 mM Tris, 250 mM glycine, 0.1 % SDS). Electrophoresis was performed in a horizontal gel apparatus at 60 V at room temperature for the first 30 min, and then voltage was set to 100 V for the rest of the time. To identify small proteins that remained in the gel, the gel was stopped when the dye front was 2/3 of the distance from the wells. Proteins were transferred to nitrocellulose membranes using vertical wet electroblotting apparatus, LKB bromma at (300 mA) for 3 h at 4 °C. Membranes were blocked with 10 % nonfat skimmed milk in PBS for 1 h and subsequently incubated with primary antibodies (1:100 MUC5AC and 1:100 MUC5B) for 18 h in 1 % nonfat skimmed milk in PBS at 4 °C. Blots were washed 3 times in PBS for 10 min, and incubated with the secondary HRP-labeled goat-anti-rabbit antibody (1:1000) (Jackson-Immuno) in 1 % nonfat skimmed milk in PBS for 1 h. Blots were washed in PBS for 10 min 3 times and developed using the Pico-Developer-Kit (Pierce). Exposures were taken on CL-XPosure film (Pierce) at equal exposure times. The films were scanned and band intensities were determined by densitometry using NIH Image software (http://rsbweb.nih.gov/nih-image/).

SDS PAGE western blotting for alpha-1-protease inhibitor (A1-PI) NE

Sputum and internal control samples were diluted (1:100 for A1-PI and 1:20 for NE) with PBS and homogenized using a syringe. As a positive control, human A1-PI (Prolastin) and a control subject sample known to contain NE were used. Upon denaturation, the samples were separated by SDS-PAGE (7.5 % for A1-PI and 10 % for HNE) before blotting onto PVDF membranes. The membranes were blocked with 5 % nonfat skimmed milk in TBST for 1 h at room temperature and incubated with primary antibodies anti- A1-PI (Sigma Aldrich) HNE- (Abcam) over night at 4 °C. Membranes were washed three times in TBST for 15 min, and incubated with the HRP-labeled secondary antibodies dissolved in TBST containing 5 % milk, for 1 h at room temperature. Membranes were developed using ImmunoCruz Luminol agent (Santa Cruz). Exposures were taken on CL-XPosure film (Pierce) at equal exposure times. The film was scanned and band densities were determined by densitometry using NIH Image software (http://rsbweb.nih.gov/nih-image/).

Analyzing NE activity with specific substrates

To analyze free NE activity in the sputum we used the substrate

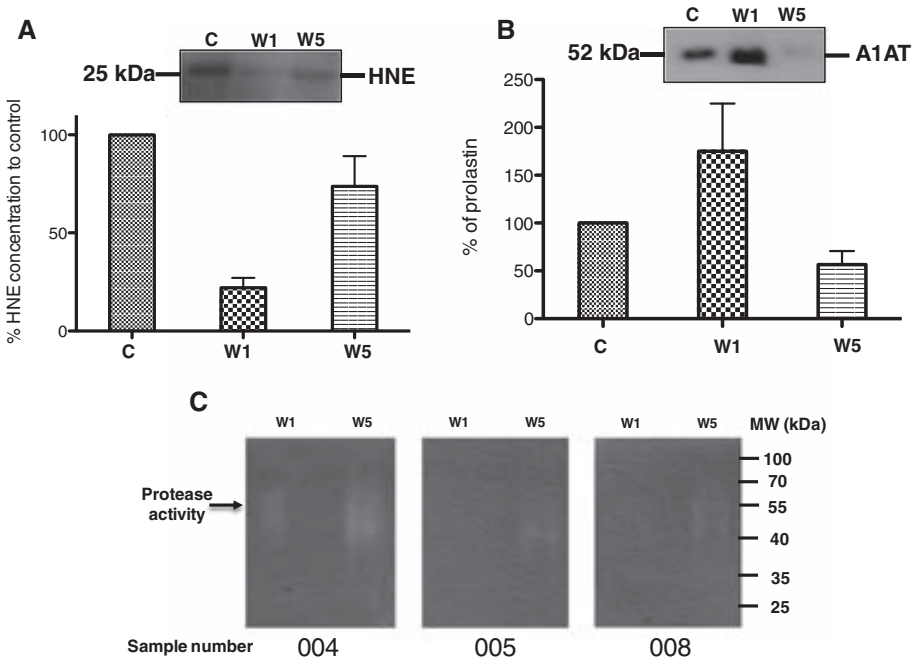

Figure 2. Altered NE and A1-PI in COPD sputum samples. a Representative western blot analysis for NE from 3 COPD subjects (003, 005, 007) during the course of exacerbation. C = Control, W1 = week 1, W5 = week 5–6. To compare the results graphically western blots were analyzed by densitometry and compared to an internal control sputum sample, which was set to 100 %. b Representative western blot for A1-PI from 3 COPD subjects (003, 005, 007) C = control; W1 = week 1 and W5 = week 5–6. To compare the results graphically western blots were analyzed by densitometry and compared to an internal control sputum sample, which was set to 100. c Analysis of sputum protease activity by zymogram. Sputum was obtained from 3 COPD subjects with an acute exacerbation within the first week (COPD-ex; week 1) and from the same subjects 5–6 weeks later (COPD-follow; week 5–6) n = 3.

N-Methoxysucuccinyl -ALA-ALA-PRO -VAL P-Nitroanilide (Sigma Aldrich, Saint Louis, MO). According to the manufacturer, the substrate is specifically hydrolyzed by HNE and cannot be hydrolyzed by cathepsin G. To get comparable results, we used a test volume set at 1000 µL, consisting of 900 µL substrate solution and 5 µL of patient sputum samples with added buffer, adding the enzymatically active compound at last. The test solution was thoroughly mixed and the analysis was started immediately. As an internal control we used triplets of each sample in dilution steps of 1:10, 1:20 and 1:40 in PBS. As an external control 3 µL of purified NE (Calbiochem, product no. 324681) was used. The degradation of the substrate was analyzed at a wavelength of 410 nm over 30 min in a Nicolet Evolution 100 UV–vis Spectrophotometer. The results were documented via VISIONlife software.

Analysis of protease activity using zymograms

NOVEX 4-16 % zymogram blue casein gels (Life Technologies) were used to detect NE enzymatic activity in sputum samples. Mucin samples were homogenized using a sterile Filtropur syringe filter (0.20 µm pore size). Equal volumes of homogenized sputum samples were loaded on a gel and separated using electrophoresis at 125 V for 2 h. The gel was run in Tris/glycine SDS running buffer under nondenaturing conditions. The separated proteins were renatured using a buffer containing a non-ionic detergent (Novex Zymogram Renaturing Buffer). Gels were washed twice for 15 min in PBS and equilibrated using a developing buffer (Novex Zymogram Developing Buffer) containing divalent metal cations for 30 min as described in the manufacturer's protocol. The gel was then incubated at 37 °C for 20 h in fresh developing buffer for enhanced digestion. Enzymatic activity was visualized as a clear band against a dark background of stained casein. ETT mucus from healthy subjects was used as a positive control. The gels were scanned using a Canon ScanLide 50 scanner and activity was measured by quantification of digested area using Image-J densitometry software.

Preparation of cigarette smoke condensate (CSC)

Cigarettes were smoked in a smoking chamber for 5 min and smoke was suctioned using a vacuum pump into a Falcon tube containing 37 °C pre-warmed 10 mL PBS. Care was taken to maintain constant temperature (37 °C) and continuous stirring to allow the smoke to dissolve fully in PBS. One cigarette in 10 mL PBS is referred to as CSC10, which was considered to be 10 %.

Inhibition of NE-activity by CSC

Inhibition studies of NE were performed spectrophotometrically using specific NE-substrate (Merck Chemicals) as described in the manufacturer protocols (Elastin). Different concentrations of CSC (CSC5, CSC10) were used to inhibit pure NE (final concentration 0.33 µg/ml). Activity of NE was measured at 410 nm.

Data analysis

All analyses were performed at least in triplicate. Results are presented as mean values ± standard error. The mucin concentration of the sputum samples was normally distributed within all groups (Skewness < ± 2). The mucin concentration is shown as % to an internal control. To compare sputum samples from the same group (COPD week 1 and week 5-6) we used the paired t-Test. To compare sputum samples of the different groups we used the Mann–Whitney U-Test. After post hoc correction for multiple comparisons, a probability of $p < 0.05$ was considered

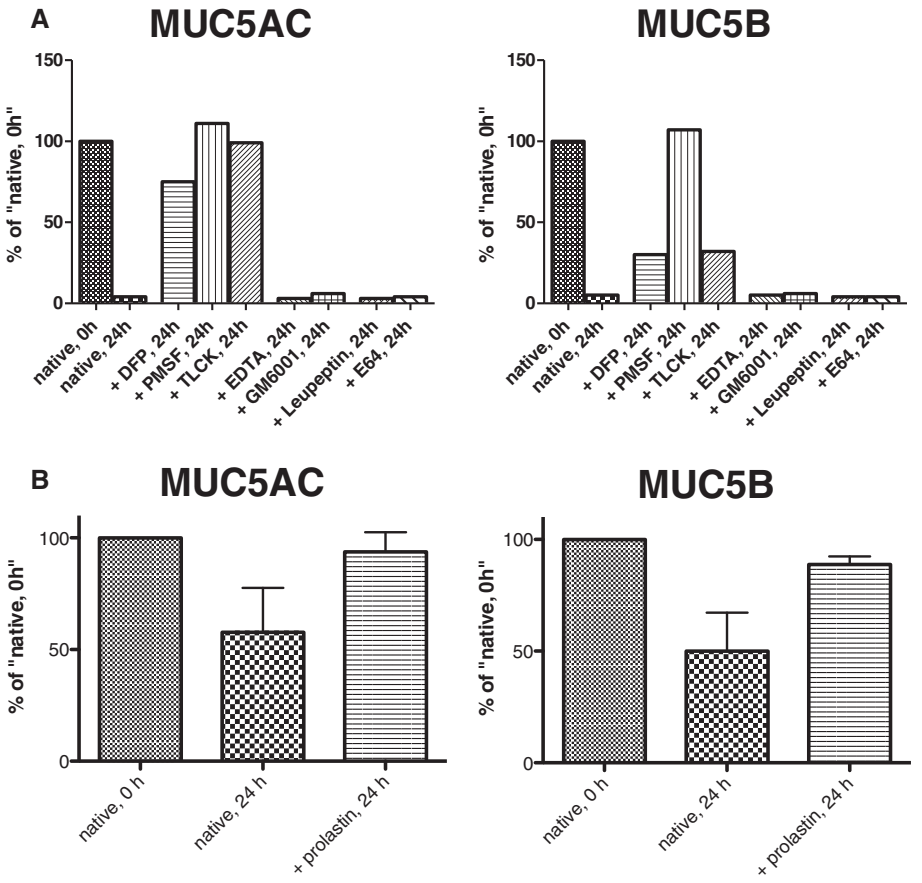

Figure 3. Serine proteases inhibit mucin degradation. Analysis of sputum MUC5AC and MUC5B by western blot after incubation at 37 °C over 24 h with or without of protease inhibitors. Sputum was obtained from a COPD subject 5–6 weeks after an acute exacerbation. Mucin concentration of the native control without incubation over 24 h was set to 100 %. a We used the serine protease inhibitors DFP, PMSF and TLCK, the metalloprotease inhibitors EDTA and GM6001 and the cysteine protease inhibitors leupeptin and E64. Analysis was performed in triplicate. b Incubation of COPD sputa (5–6 weeks after the onset) with A1-PI (n = 4) and compared with control sputa.

significant. All analyses were performed by means of GraphPad Prism 5 software (San Diego, CA). Descriptive statistics were used to summarize subject demographics.

Results

Increase in mucins concentration before exacerbation

Sputa were collected at the onset of a COPD exacerbation and 5-6 weeks later and compared with ETT mucus obtained from healthy subjects. Mucin stability in samples was analyzed in vitro after incubation at 37 °C for 24 h. In comparison to ETT mucus, there was a 5-fold increase in MUC5AC and 2-fold increase in MUC5B at the start of an exacerbation. Five to 6 weeks later, MUC5AC was about 3-fold higher in comparison to ETT control mucus or 2-fold lower than at the start of the exacerbation. MUC5B concentration decreased to ETT mucin levels at 5-6 weeks (Fig 1a, b). Results obtained from immunoblot densitometry showed about a 40 % degradation of sputa from COPD patients at 5-6 weeks with almost no degradation seen at the start of an exacerbation. These observations suggest that there was dramatically (and unexpectedly) increased antiprotease activity or decreased NE activity at the start of the exacerbation, but by week 5, protease and antiprotease activity returns to baseline.

A1-PI and free NE concentration in sputum

In order to understand the reasons for increased mucin stability at the start of an exacerbation, we quantified NE and A1-PI in sputum samples using an immunoblot and found that the NE concentration in the sputum of the COPD patients at the onset was 3.5 times lower than at 5-6 weeks after the onset of the exacerbation (Fig 2a). Additionally, we analyzed nonspecific protease activity in sputa from 3 subjects with COPD at the start of an exacerbation and compared it to sputa from the same subjects 5-6 weeks later using zymograms (Fig. 2c). Dornase alfa was added to the sputum to release proteases trapped in DNA. The strongest signal for nonspecific enzyme activity was detected only in the sputum samples obtained 5-6 weeks after the onset. We found that A1-PI concentration in the sputum of the COPD patients at the beginning of the exacerbation was 3 times higher when compared with sputum 5-6 weeks after the onset of the exacerbation (Fig. 2b). Thus at the start of a COPD exacerbation it appears that protease activity is low which as well correlates to increased A1-PI.

Increase in A1-PI at the start of an exacerbation inhibits mucin degradation

To verify the role of non-specific proteases in COPD mucin degradation 5-6 weeks after the onset of an exacerbation, we incubated the mucus with different protease inhibitors at 37 °C for 24 h. Results obtained from immunoblots revealed that without protease inhibitors, MUC5AC concentration decreased by 96 % and MUC5B by 95 % of the initial concentration, whereas incubation with the protease inhibitors DFP, PMSF and TLCK inhibited mucin degradation. However, incubation with the

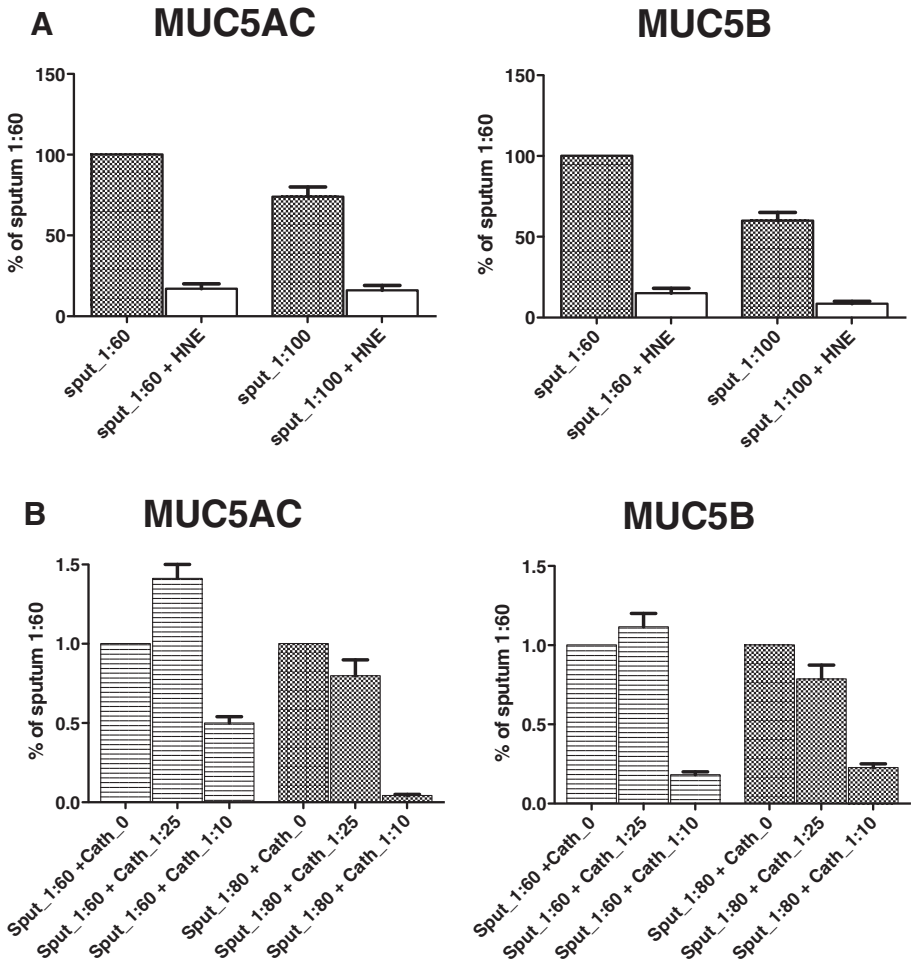

Figure 4. Mucus hydration increases mucin degradation. a Sputum was obtained at the onset of a COPD exacerbation and diluted 1:60 and 1:100. Mucin degradation was measured after incubation for 6 h at 37 °C with or without NE 0.02 mg/mL. Mucin concentration of the control at 1:60 was set to 100 %. b Sputum was obtained at the onset of a COPD exacerbation and diluted 1:60 and 1:80. Mucin degradation was measured after incubation for 6 h at 37 °C with cathepsin G 100 µU/µL diluted 1:25 and 1:10. Mucin concentration of the control was set at 1:60 and 1:80 was set to 100 %.

metalloprotease inhibitors, EDTA and GM6001, and cysteine protease inhibitors, Leupeptin and E64, did not inhibit the mucin degradation (Fig. 3a). We also tested if A1-PI could decrease mucin degradation. We incubated COPD sputa from 4 subjects at week 5-6 after exacerbation, with and without A1-PI and inhibited the degradation of MUC5AC to just 6 % (SEM ± 9) and MUC5B to 11 % (SEM ± 3) of the native mucin concentration (Fig. 3b).

Inaccessibility of NE decreases mucin degradation

Serial dilutions of mucus identified that a 1:60 to 1:100 dilution of mucus is most effective for measuring protease activity (Fig. 4a). We then incubated COPD sputum from the start of an exacerbation at dilutions of 1:60 and 1:80 with synthetic proteases, NE 0.02 mg/mL, and cathepsin G 100µU/µL and incubated at 37 °C for 6 h. Both MUC5AC and MUC5B mucins were degraded by NE and cathepsin G in a concentration dependent manner (Fig. 4b).

Cigarette smoke condensate (CSC) decreases mucin degradation and inhibits protease activity

To analyze the role of CSC on mucin degradation, COPD sputum was incubated with different CSC concentrations (5-40 %) for 0, 24 and 36 h. COPD sputa without CSC, MUC5AC and MUC5B mucins were significantly degraded after 24 and 36 h. A dose dependent inhibition of mucin degradation was observed with COPD sputum incubated with increasing concentrations of CSC (Fig. 5a). To elucidate the role of CSC in inhibiting mucin degradation, we incubated HNE (0.33 µg/mL) with different concentrations (5-10 %) of CSC and analyzed the activity of NE using a HNE specific substrate (5-methoxy-Ala-Ala-Pro-Val). To conclude, CSC directly interfered with protease activity in a dose dependent manner (Fig. 5b).

Discussion

We had anticipated that with an acute exacerbation of COPD, there would be increased inflammation and increased proteases with subsequent degradation of mucins, Thus we were surprised to discover that at the start of a COPD exacerbation there was consistently decreased proteases, increased anti-proteases, and increased mucin stability. A possible explanation for this is that although we evaluated subjects and collected sputa at the start of symptoms of an exacerbation, it is likely that the inciting infection and inflammation had been present for several days. These data might reflect the natural host immune response to decrease the initially observed increased protease activity. Although this is entirely speculative, it would explain these paradoxical results.

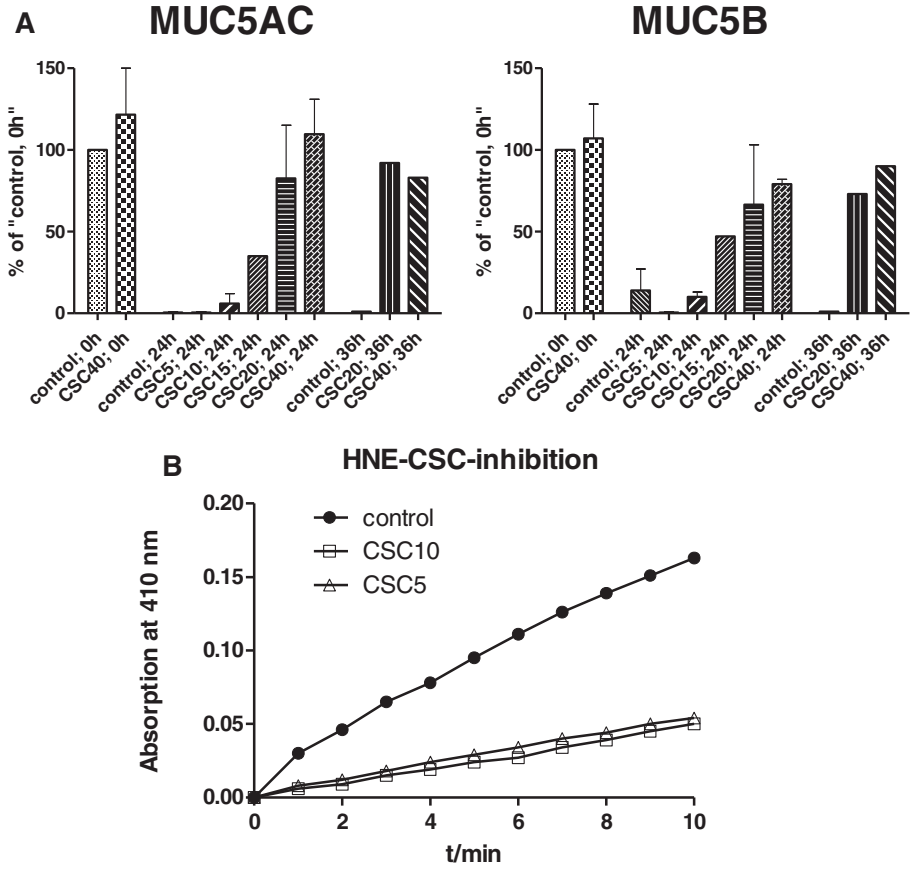

Figure 5. Cigarette smoke extract inhibits NE and increases mucus accumulation. a Quantification of COPD mucin degradation after incubation at 37 °C with increasing concentrations of CSC (5–40 mg/mL) for 0, 24 and 36 h. b Substrate specific activity of NE 0.33 µg/mL with and without CSC (5–40 mg/mL) . Mucin concentration of the native control was set to 100 %.

One consequence of inhibiting mucin degradation might be increased mucus obstruction, which is considered a hallmark of a COPD exacerbation. It has been reported that persons with COPD have increased mucus synthesis and secretion, and decreased mucus clearance [19, 20, 22]. We have reported that in CF sputum, serine proteases degrade mucins after secretion [9]. Bacterial or host inflammatory cell proteases in CF sputum may further contribute to mucin degradation [23]. Delayed mucin degradation in COPD could well be caused by this protease-anti protease imbalance. We report a 5-fold increase in MUC5AC and a 2 fold increase in MUC5B at the onset of symptoms and even 5-6 weeks later, MUC5AC was 3 times greater in COPD sputa compared to mucus from healthy controls (Fig. 1a, b).

COPD is an inflammatory disease of small airways with increased neutrophil infiltration and NE [14, 30]. Studies performed by other groups suggested that in mucoid COPD sputum no NE was found (NE nM 0.0) [8, 27]. These observations are similar to our findings, where little or no NE activity was observed in mucoid sputa of COPD subjects at the onset of an exacerbation (Fig. 2a, c). In CF, sputum NE is predominantly bound by DNA and this inhibits proteolytic activity [17]. Much of the DNA in CF sputum originates from neutrophil extracellular traps (NETs). It is speculated that NE-NET formations are reservoirs of active proteases for a possible later release [6]. In CF and COPD sputa the DNA concentration is higher than in normal airway secretions, therefore this NE that is bound to DNA is not available for mucin degradation [9, 10, 18]. A1-PI is increased during infection and inflammation and its primary role is to inhibit NE. Consistent with our results (Fig. 2b), during an acute exacerbation of COPD, A1-PI is elevated in sputum [29], serum [7] and in exhaled breath condensate [15]. We did not detect increased NE concentrations or protease activity during an acute COPD exacerbation, which is in agreement with previous studies [8, 27, 32].

We also show that CSC can inhibit mucin degradation in a dose dependent manner by inhibiting the activity of NE (Fig. 5b). Thus tobacco smoke and increased DNA might contribute to mucus retention in COPD.

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Role of Bronchoalveolar Lavage in the Diagnosis of Acute Exacerbations of Idiopathic Pulmonary Fibrosis: a Retrospective Study

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Abstract

Background: It has been recognized that despite previous stability some patients with idiopathic pulmonary fibrosis (IPF) experience acute clinical deteriorations called acute exacerbations of idiopathic pulmonary fibrosis (AEX-IPF). We hypothesized that pulmonary infection can be excluded based on clinical and laboratory data and that bronchoscopy with BAL is not mandatory in the diagnostic work-up of suspected AEX-IPF.

Methods: In this retrospective study we identified patients with acute respiratory failure who were evaluated for AEX-IPF at the Cleveland Clinic between January 2002 and December 2011. Univariate and multivariate analysis were performed with predefined risk factors and final diagnosis of AEX-IPF and pulmonary infection. All tests were performed at a significance level of 0.05.

Results: A total of 77 patients met the study inclusion criteria. Of these patients 47 (61 %) were diagnosed with AEX-IPF. Bronchoscopy was more likely to be performed in patients who were on cytotoxic medications ($p < 0.05$). In most cases the diagnosis of AEX-IPF versus pulmonary infection was based on combination of other microbiological, clinical, radiologic data and clinical judgment. A total of 10 patients out of 14 (71 %) with a final diagnosis of pulmonary infection were on steroids on admission versus 21 out of 63 patients (33 %) with other final diagnosis ($p = 0.024$, OR 7.817, 95 % CI 1.31–46.64).

Conclusions: Exclusion of infection in our IPF patient cohort was mostly based on factors other than diagnostic bronchoscopy with BAL. Based on our results we suggested an algorithm for management of IPF patients presenting with acute respiratory failure.

Background

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia. It has been recognized that some patients with IPF experience acute clinical deteriorations, despite previous stability. Most of these deteriorations are idiopathic; others are secondary to infection, left heart failure, pulmonary embolism, pneumothorax and other identifiable causes of acute lung injury. These episodes of idiopathic acute deteriorations have been termed acute exacerbations of IPF (AEX-IPF). Diagnostic consensus criteria for AEX-IPF were suggested by Collard et al. in 2007 [1] and include: previous or concurrent diagnosis of IPF, unexplained worsening or development of dyspnea within the past 30 days, specific high resolution chest computed tomography (CT) pattern and no evidence of infection in the absence of alternative causes that are specifically mentioned in the consensus statement.

According to these criteria, AEX-IPF can only be diagnosed if there is no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage (BAL). Evaluation of samples should include studies for routine bacterial organisms, opportunistic pathogens such as pneumocystis jiroveci (PJP), and common viral pathogens including influenza A and B, parainfluenza 1–4, respiratory syncytial virus A and B, human metapneumovirus, adenovirus and coronaviruses. Those patients who have no endotracheal aspirate or BAL available are classified as having "suspected acute exacerbation of IPF".

A study by Wootton et al. [2] did not detect viral infection in most cases of AEX-IPF. In this study four of 43 BAL samples from AEX-IPF patients were positive for respiratory viruses and 15 for non-respiratory viruses compared to no viral detection in stable IPF controls. This study suggested that isolation of these viruses has no proven clinical significance, so BAL viral

Table 1 Table represents final diagnosis in IPF patients admitted with acute respiratory failure. Two most common final diagnosis were AEX-IPF and pulmonary infection

Final diagnosis	
AEX-IPF	47
Pulmonary infection	14
IPF progression	5
Acute CHF	2
NSIP flare	2
Hypoglycemia and respiratory failure	1
COPD exacerbation	1
Pulmonary embolism	1
Transtracheal oxygen catheter related problem	1
Pneumomediastinum	1
Ischemic heart disease	1
Bronchogenic carcinoma	1
Total number of cases	77

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Table 2 Table represents association between IPF patient characteristics on hospital admission and performance of bronchoscopy with BAL. Two patients with missing data on BAL performance were excluded

	Bronchoscopy with BAL done			
Factor	No (*N* = 46)	Yes (*N* = 29)	Total (*N* = 75)	*P*-value
Gender				0.97[a]
Female	22 (47.8 %)	14 (48.3 %)	36 (48.0 %)	
Male	24 (52.2 %)	15 (51.7 %)	39 (52.0 %)	
Tobacco exposure				0.28[a]
Yes	23 (48.9 %)	15 (62.5 %)	37 (53.6 %)	
No	23 (51.1 %)	9 (37.5 %)	32 (46.4 %)	
Prior steroid use				0.85[a]
No	26 (56.5 %)	13 (54.2 %)	39 (55.7 %)	
Yes	20 (43.5 %)	11 (45.8 %)	31 (44.3 %)	
Prior cytotoxic agents				<0.001[b]
No	46 (100.0 %)	17 (73.9 %)	63 (91.3 %)	
Yes	0 (0.0 %)	6 (26.1 %)	6 (8.7 %)	
Antibiotics on admission				0.46[a]
No	35 (76.1 %)	17 (68.0 %)	52 (73.2 %)	
Yes	11 (23.9 %)	8 (32.0 %)	19 (26.8 %)	
Fever on admission				0.99[b]
No	43 (92.5 %)	23 (95.8 %)	60 (93.8 %)	
Yes	3 (7.5 %)	1 (4.2 %)	4 (6.3 %)	
Tachycardia on admission				0.95[a]
No	36 (74.4 %)	18 (75.0 %)	47 (74.6 %)	
Yes	10 (25.6 %)	6 (25.0 %)	16 (25.4 %)	
Tachypnea on admission				0.37[a]
No	16 (23.1 %)	8 (33.3 %)	17 (27.0 %)	
Yes	30 (76.9 %)	16 (66.7 %)	46 (73.0 %)	
ICU care				0.70[a]
No	29 (63.0 %)	17 (58.6 %)	46 (61.3 %)	
Yes	17 (37.0 %)	12 (41.4 %)	29 (38.7 %)	
Procalcitonin				0.60[c]
Mean (SD)	0.4 (0.8)	0.7 (0.6)	0.6 (0.7)	
Range	(0.1–1.6)	(0.1–1.7)	(0.1–1.7)	

[a]Chi-Square
[b]Fisher Exact
[c]*T*-Test

studies might not be helpful in management of these patients [2]. AEX-IPF cases occur more commonly in winter and spring, suggesting that some of them might have unidentified infections etiology, even despite extensive microbiological workup [3]. On the other hand, some patients with suspected AEX-IPF have microbiological evidence of infection but also have clinical and imaging characteristics of AEX-IPF [4]. Completing the course of broad spectrum antibiotics might be reasonable even if there is a low suspicion of pulmonary infection and AEX-IPF is the working diagnosis especially if there is clinical improvement. Procalcitonin guided antibiotic use has been tested in various respiratory infections, including IPF, and was shown to reduce the antibiotic exposure in AEX-IPF patients [5]. This strategy is not routinely recommended and should be further explored.

In a recent proposal by Johannson and Collard, authors also question the mandatory role of BAL in the diagnostic workup of AEX-IPF patients, considering poor sensitivity of microbiological tests and the risk of worsening hypoxemia with bronchoscopy in non-intubated patients with baseline high oxygen requirements [6]. Some risk factors favor the diagnosis of AEX-IPF, such as obesity, subacutely worsening dyspnea, decline in forced vital capacity and pulmonary hypertension [7,8]. Identified risk factors should be incorporated into clinical decision tools and treatment algorithms.

Table 3 Table represents microbiologic data obtained in the study patients with IPF presenting with acute respiratory failure and the positivity rate of the cultures

Type of culture	Total (*N* = 77)	
	No	Yes
Tracheal aspirate obtained	71 (92.1 %)	6 (7.9 %)
Growth on tracheal aspirate	76 (98.7 %)	1 (1.3 %)
Sputum culture obtained	51 (65.3 %)	26 (34.7 %)
Sputum culture positive for infection	75 (97.4 %)	2 (2.6 %)
Blood cultures obtained	27 (34.2 %)	50 (65.8 %)
Blood culture positive	75 (97.4 %)	2 (2.6 %)

In this study, we hypothesize that pulmonary infection can be excluded based on clinical and laboratory data and that bronchoscopy with BAL is not mandatory in the diagnostic work-up of patient with suspected AEX-IPF. We also looked for risk factors and patient characteristics that might help to guide treatment decisions.

Methods

This retrospective study identified patients with idiopathic pulmonary fibrosis and acute respiratory failure who were evaluated for AEX-IPF at the Cleveland Clinic between January 2002 and December 2011. Study claims compliance with Helsinki Declaration. Cleveland Clinic institutional board review approved the study protocol and determined that it meets criteria for waiver for consent.

Inclusion criteria

Adult patients with known history of IPF who presented with possible AEX-IPF or new patients that eventually were diagnosed to have AEX-IPF as an initial manifestation of the disease and patients with full predefined information available in the electronic medical records at the Cleveland Clinic for the following diagnoses: idiopathic pulmonary fibrosis and acute exacerbation of idiopathic pulmonary fibrosis.

Exclusion criteria

Patients with missing information in the medical records, and patients status post lung transplant.

Statistical methods used

Continuous measures were described as means, standard deviations, and percentiles. Categorical measures were summarized using frequencies and percentiles. The Pearson's chi-square test or Fisher's exact test was used to assess the associations between the binary groups and categorical measures. The two sample T-test were used to evaluate the relationship between binary groups and continuous measures. All tests were performed at a significance level of 0.05. SAS 9.3 software (SAS Institute, Cary, NC) was used for all analyses.

Results

A total of 77 patients met the study inclusion criteria, of which

Table 4 Multivariable association between final diagnosis of AEX-IPF and patient risk factors. No statistically significant association was revealed

Effect	Odds ratio	95 % CI		*P*-value
Steroids on admission: No vs Yes	2.998	0.881	10.206	0.079
Cytotoxic agents on admission: No vs Yes	1.054	0.156	7.117	0.96
Antibiotics on admission: No vs Yes	1.372	0.352	5.344	0.65
Sputum culture positive: No vs Yes	4.007	0.235	68.279	0.34
Elevated WBC on admission: No vs Yes	1.22	0.37	4.022	0.74
Fever on admission: Yes vs No	1.112	0.086	14.313	0.94
Tachycardia on admission: No vs Yes	1.454	0.396	5.331	0.57
Tachypnea on admission: Yes vs No	1.814	0.472	6.978	0.39

37 were females and 40 were males. Of these patients, 47 (61 %) were diagnosed with AEX-IPF (Table 1). Bronchoscopy with BAL was done in 38 % of all patients (29 procedures), as well as 38 % in the subgroup of patients eventually diagnosed with AEX-IPF (18 procedures). In 6 of these 29 procedures, bronchoscopy was performed prior to administration of antibiotics.

Bronchoscopy was more likely to be performed in patients who were on cytotoxic medications, but it did not depend on gender, smoking history, prior steroid therapy or any other patient characteristics (Table 2). Diagnosis of infection was made when BAL, tracheal aspirate, sputum culture or blood culture was found positive and not considered to be a contaminant. Of the 14 patients who were diagnosed with pulmonary infections, two had fever on admission ($p = 0.15$), and 12 had white blood count greater than 11.0 k/ul ($p = 0.17$) and a total of 57 out of 77 patients were started on broad spectrum antibiotics. Six patients had a BAL performed, but with only one identified case of infection. In this one patient, BAL was positive both for PJP and cytomegalovirus and blood culture was positive for vancomycine resistant enterococcus (VRE). An additional patient had a BAL performed which grew methicillin sensitive staphylococcus aureus (MSSA), but the final diagnosis was AEX-IPF. Both of these patients were treated with antibiotics prior to BAL being performed. Tracheal aspirate cultures were done for six patients (four of them had BAL done with no growth), and one patient was positive for influenza A virus. Sputum culture was performed in 26 patients, and two patients grew Stenotrophomonas maltophilia (judged to be contaminant) and Klebsiella pneumoniae respectively. Blood cultures were done in 50 patients, and two patients grew VRE and staphylococcus hominis respectively (latter was judged to be contaminant, Table 3). Of the three patients who had BAL and sputum cultures done at the same time, only one sputum culture was positive for growth (Klebsiella pneumoniae) while the BAL did not show evidence of infection. Mycoplasma IgM, urine streptococcus pneumonia antigen and urine Legionella antigen were checked in six, four, and twelve patients respectively and were negative in all patients.

Univariate and multivariate analysis were performed with predefined risk factors and final diagnosis of AEX-IPF and pulmonary infection (Tables 4 and 5). Only prior to admission steroid use, which was defined ad daily prednisone intake 10–60 mg, was found to be significantly associated with developing a pulmonary infection, where 10 out of 14 patients (71 %) on steroids were found to have an infection versus only 21 out of 63 patients (33 %) patients who were not on steroids ($p = 0.024$, OR 7.817, 95 % CI 1.31–46.64). Overall mortality in our population cohort was 28.6 %, and this was not significantly different amongst AEX-IPF patients (29.8 %), patients with pulmonary infection (28.5 %) and patients with respiratory failure due to other causes (25 %).

Discussion

Today, BAL technique is standardized [9] and it is often used in the workup of AEX-IPF. Pesci et al. [10] recommended that BAL should be considered in all IPF patients with suspected infection, malignancy or AEX-IPF. Papanikolaou et al. [11], as well as Wuyts et al. [12] state that BAL should be performed if the patient can tolerate the procedure (DLCO > 30 % and PaO2 > 75 mmHg on supplemental oxygen). The official ATS/ERS/JRS/ALAT statement on pulmonary fibrosis does not give clear recommendations on the diagnostic workup for AEX-IPF [13]. Overall BAL is widely considered a part of the diagnostic workup of a patient with IPF presenting with acute respiratory failure, and is performed for nearly every evaluated patient that can tolerate it, although the predictive usefulness and safety of the procedure has not been fully elucidated.

Several other potentially useful roles of the BAL were recently entertained. It has been shown that BAL samples from some AEX-IPF patients have increased level of pepsin [14] and that treatment with proton pomp inhibitors might have a role in the

Table 5 Multivariable association between final diagnosis of pulmonary infection and patient risk factors

Effect	Odds ratio	95 % CI		*P*-value
Steroids on admission: Yes vs No	7.817	1.31	46.64	0.024*
Cytotoxic agents on admission: No vs Yes	2.407	0.196	29.524	0.49
Antibiotics on admission: Yes vs No	2.051	0.308	13.65	0.46
Sputum culture positive: Yes vs No	2.427	0.148	39.718	0.53
Elevated WBC on admission: Yes vs No	1.474	0.268	8.094	0.66
Fever on admission: Yes vs No	1.651	0.109	25.021	0.72
Tachycardia on admission: No vs Yes	1.552	0.201	11.956	0.67
Tachypnea on admission: Yes vs No	1.088	0.142	8.362	0.94

*Patients who were on steroids on admission were more likely diagnosed with pulmonary infection then patients who were not on steroids ($p = 0.024$)

prevention of exacerbations in these selected patients [15]. This suggests that some IPF exacerbations might be triggered by silent aspiration and those patients do not need treatment with broad spectrum antibiotics. Song et al. showed that measuring percentage of neutrophils in the BAL fluid can be a useful tool to discriminate between pulmonary infection and AEX-IPF but this practice has not been routinely recommended and needs further investigation [16]. If clinical suspicion for drug induced alveolitis or other specific etiology, BAL can be performed tailored to that specific diagnoses, in case the BAL fluid differential count would change the management. For AEX-IPF or infection, no such strong data is available, and one should not base treatment decisions on BAL fluid differential count. In addition, the percentage of neutrophils in the BAL fluid is increased during the AEX-IPF episodes compared to stable patients with IPF and controls, which makes this data less reliable to exclude infectious process [17, 18]. It has also been shown that BAL is not a benign procedure and in fact, is an independent risk factor for IPF exacerbation [19–22]. In a retrospective study it was shown that the risk of AEX-IPF is elevated within 30 days after BAL (RR 4.12; 95 % CI 1.03–12.2), moreover the relative risk of developing AEX-IPF after second or later BAL procedures was estimated to be considerably higher (RR 9.10; 95 % CI 2.27–26.98). In a recent review of the utility of BAL in diffuse parenchymal lung diseases, the role of BAL was critical in the diagnosis of opportunistic infections in patients treated with immunosuppressive therapy [23], but is not necessary in all patients.

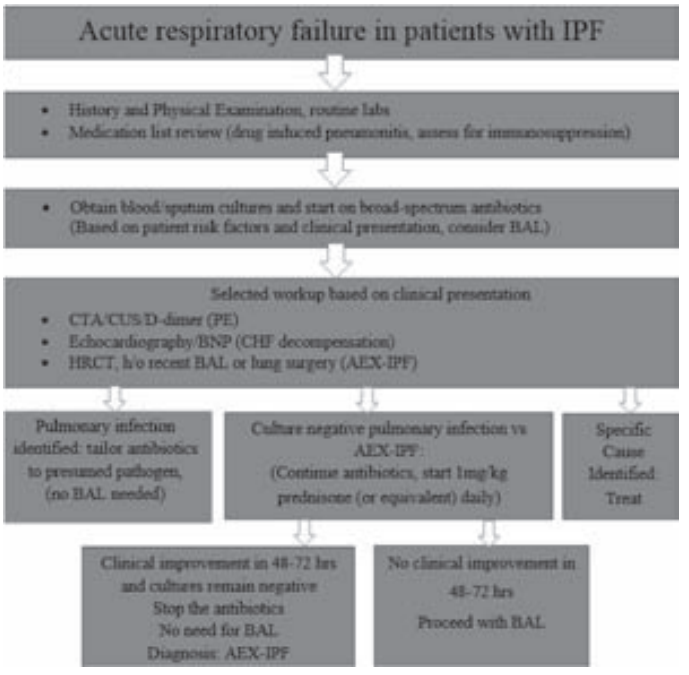

Figure 1. Suggested algorithm for the management of patients with IPF who present with acute respiratory failure. IPF-idiopathic pulmonary fibrosis, BAL-bronchoalveolar lavage, CTA-computer tomographic angiography, CUS-compression ultrasonography, PE-pulmonary embolism, BNP-brain natriuretic peptide, CHF-congested heart failure, AEX-IPF-acute exacerbation of idiopathic pulmonary fibrosis.

In this retrospective study to assess the diagnostic value of bronchoscopy and BAL performed in the work up for suspected AEX-IPF cases we identified patients with a known history of IPF, who presented with acute respiratory failure and were being evaluated for AEX-IPF. AEX-IPF and pulmonary infection were the two most common final diagnoses and a minority of patients were found to have other cardiovascular and pulmonary conditions as a cause of their acute decompensation. The diagnosis of AEX-IPF was not associated with any of the predefined patient characteristics or measurable factors (such as gender, tobacco exposure or vital signs on admission). 38 % of patients had a bronchoscopy with BAL performed as a part of the diagnostic workup and it was more likely to be performed in patients receiving cytotoxic agents. One can only speculate that these patients were considered high risk for pulmonary infection and BAL was done due to high pretest probability. There was no other significant difference between two groups, which allowed further statistical analysis.

It is worth noting that in our cohort only three of 14 patients who had a final diagnosis of pulmonary infection had microbiological confirmation, one each from BAL and blood culture, tracheal aspirate culture and sputum culture. Only prior to admission steroid use was associated with a final diagnosis of pulmonary infection. In most cases, diagnosis of infection was made on the basis of physical examination, clinical history, laboratory/imaging data and clinician judgment. It seems BAL is most helpful when performed in patients with high pretest probability such as patients on steroids or immunosuppressive agents.

Most of our patients were started on broad spectrum antibiotics on admission prior to BAL and completed the course despite negative microbiological workup. We believe this is a common scenario in other centers too and shows that BAL fluid analysis does not change the treatment strategy. In our cohort bronchoscopy with BAL had little influence on the management of the patients which might suggest that patients who present with possible AEP-IPF versus pulmonary infection should be empirically treated with broad spectrum antibiotics and that bronchoscopy with BAL should be performed in selected cases only based on clinical judgment and case scenario, such as current use of steroids or other immunosuppressive agents.

Limitations of our study include relatively small sample size, single center participation and the retrospective nature of the study. Treatment selection biases as well as reliance on expert opinion in many cases for final diagnosis should be considered as well. Cleveland Clinic is a tertiary care center and a patient selection bias also could not be excluded. Our practice is not to use immunosuppressants for maintenance treatment of IFP patients, so our findings may not be translatable in other institutions who have not adopted this practice. Most of our patients were started on antibiotics before BAL could be performed and our conclusions may not be generalized to patient in whom BAL with fluid differential and cultures are done first.

Therefore, based on our findings in this study, we propose the following algorithm in the management of IPF patients presenting with acute respiratory failure (Fig. 1). IPF patients presenting with acute respiratory failure should first be evaluated for identifiable causes for their deterioration including but not limited to pulmonary infection, congestive heart failure decompensation, aspiration, pulmonary embolism, drug induced complications, and AEX-IPF based on clinical presentation. We suggest that all patients should be initiated on broad spectrum antibiotics upon presentation (including coverage for PJP if clinically indicated), ideally after blood, sputum and, in select cases, BAL cultures are obtained. One should not wait for culture results to initiate antibacterial therapy, but it should be used for de-escalation strategy. If BAL cultures are routinely

obtained after initiation of antibiotic therapy, false negative results are likely and make further decisions for de-escalation a guess. Accordingly, we do not suggest BAL for all patients. If BAL can be safely obtained before the antibiotics are given, the diagnostic workup might be different and not reflected by our algorithm as most of our patients did get antibiotics before the BAL. If a non-infectious cause is identified, such as pulmonary embolism or pneumothorax, then antibiotics can be safely discontinued. Bronchoscopy with BAL should be performed in immunocompromised patients on steroids and other cytotoxic drugs, but also for selected patients with worsening respiratory failure despite broad spectrum antibiotics and inconclusive or unrevealing workup. In a retrospective study by Song et al., BAL and/or endotracheal aspiration were performed in 52.8 % of 461 patients highlighting the fact that in real life scenarios BAL is not performed for various reasons despite the universal recommendation and that our algorithm will be suitable for these cases [16]. It is based on small sample size, retrospective data and single center experience and should be used with these limitations in mind.

Conclusions

Our data support that the decision regarding performance of BAL should be used in conjunction with other historical and clinical data, and in select cases clinician should be able to forego bronchoscopy. Exclusion of infection in our IPF patient cohort was mostly based on factors other than diagnostic bronchoscopy with BAL. Prior to admission steroid use was associated with a final diagnosis of pulmonary infection. Based on our results we suggested an algorithm for management of IPF patients presenting with acute respiratory failure.

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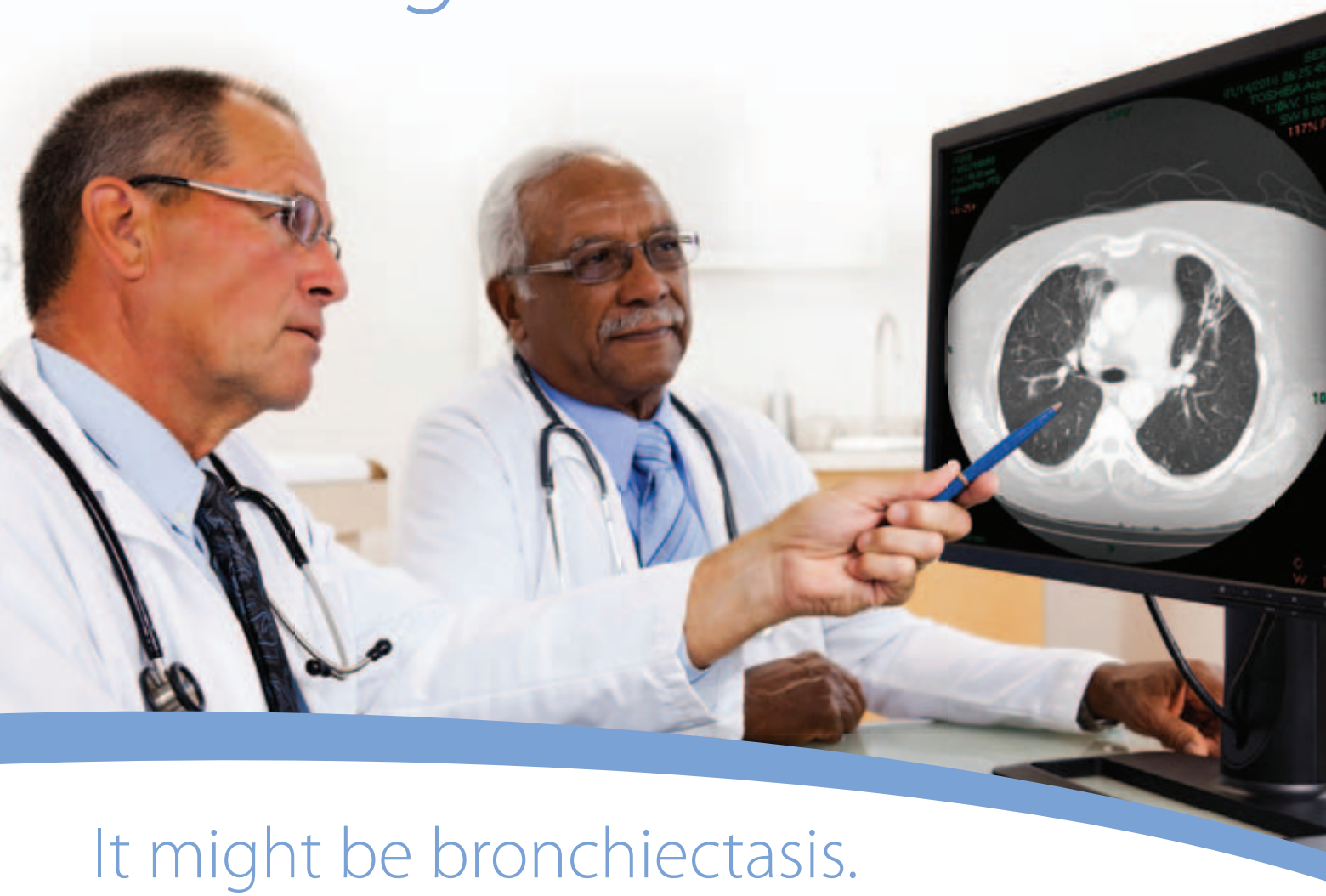

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