Volume 15 Number 2 Spring 2020

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The Journal of Pulmonary Technique

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News

■ Spring 2020

CORONAVIRUS IN THE NEWS

Co-workers Contract Coronavirus

Four people who work at the same company in southern Germany have been infected with the coronavirus, and one of them contracted it from a colleague visiting their workplace in China. The cases raise concerns about the spread of the flu-like virus that broke out in the central Chinese city of Wuhan at the end of last year and has killed 106 people and infected more than 2,800 people. It spreads in droplets from coughs and sneezes and has an incubation period of up to 14 days. In one of the first cases of person-to-person transmission outside China, a 33-year-old man apparently contracted the virus during a training session with a Chinese colleague, the ministry said. The three additional patients were being monitored in isolation at a clinic in Munich. "A total of around 40 employees at the company have been identified as potential close contacts. As a precaution, the people concerned are to be tested on Wednesday," Bavaria's Health Minister Melanie Huml said in a statement. German car parts supplier Webasto said an employee at its headquarters in Stockdorf, Bavaria, had become infected following the visit of an employee from China. A day earlier it said an employee from Shanghai tested positive for the virus upon returning to China. Confirmation of any sustained human-to-human spread of the virus outside of China, as well as any documented deaths, would bolster the case for reconvening the World Health Organisation's Emergency Committee to consider again whether to declare a public health emergency of international concern. The independent panel last week twice declined to declare an international emergency. Outside of China there have now been 45 confirmed cases in 13 countries, with no deaths so far, the WHO's spokesman Christian Lindmeier told a briefing in Geneva. The WHO said a case in Vietnam involved human-to-human transmission outside China and a Japanese official has said there was a suspected case of human-to-human transmission there too.

Suspected Chinese Coronavirus Patient Gives Birth to Baby by Cesarean

Chinese doctors safely delivered a baby boy from a Chinese woman suspected of being infected with the new coronavirus through a caesarean section in the city of Wuhan, the epicentre of the outbreak. The doctor who performed the cesarean said the 27-year-old mother's condition had been deteriorating and the baby was putting too much pressure on her. At the same time, the woman could not get proper treatment for her illness while carrying the baby. But the surgery was extremely dangerous as the mother had a fever and was coughing non-stop while the doctors faced the risk of infection with the coronavirus, state television reported. The doctor who performed the operation, Zhao Yin, deputy director at the obstetrics and gynecology department at Wuhan Union Hospital, wore two protective suits, a face mask and goggles during the one-hour surgery. "I could barely see or hear anything," Zhao told state television. "And I was soaked with sweat." The virus has killed 106 people and infected more than 4,500 across China. The mother, identified only as Xiaoyan, was 37 weeks pregnant when she was suspected of being infected by the coronavirus in early January. Her infection has not been confirmed, state television said. The 3.1 kg (6.8 lb) baby boy was sent home as quickly as possible to avoid the danger of it being exposed to the virus in hospital, state television said. "I just want my baby to be healthy," Xiaoyan told state television.

Countries Evacuating Nationals From China Virus Areas

Countries around the world are planning to evacuate diplomatic staff and private citizens from Chinese areas hit by the new coronavirus, which is spreading quickly. Wuhan, a city of 11 million in the province of Hubei and the epicentre of the outbreak is in virtual lockdown and much of Hubei, home to nearly 60 million people, is under some kind of travel curb. Following are some countries' evacuation plans, and how they are planning to manage the health risk from those who are returning.

- Germany will evacuate 90 citizens living in China's Wuhan region.
- Morocco will evacuate 100 citizens, mostly students, from the Wuhan area.
- France expects to repatriate up to a few hundred of its 800 citizens living in the Wuhan area. Evacuees will have to spend

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DEPARTMENTS

ARTICLES

14 days in quarantine to avoid spreading the virus in France.

- Japan is expected to arrange charter flights as early as Tuesday for any of its citizens who wish to return from Wuhan, two sources familiar with the matter said. Foreign Minister Toshimitsu Motegi said about 430 Japanese nationals have been confirmed to be in Hubei province.
- Spain's government is working with China and the European Union to repatriate Spanish nationals from the Wuhan area, Foreign Minister Arancha Gonzalez Laya said.
- The US State Department said it will evacuate personnel from its Wuhan consulate to the United States and offer a limited number of seats to private US citizens on a flight. Some private citizens will be able to board the "single flight" leaving Wuhan on Jan. 28 for San Francisco, it said.
- Britain is talking to international partners to find solutions to help British and other foreign nationals leave Wuhan, a spokesman for Prime Minister Boris Johnson said.
- Canada has about 167 nationals in the Wuhan area, Foreign Minister Francois-Philippe Champagne said on Monday, and eight people have sought consular assistance, which is being provided. While the minister did not rule out possible evacuations, he did not indicate there were any planned at the moment, adding that each consular request would be evaluated on a "case by case basis."
- Russia has been in talks with China about evacuating its nationals from Wuhan and Hubei province, Russia's embassy in China said.
- The Dutch government is assessing ways to evacuate 20 Dutch citizens from Wuhan, press agency ANP reported.
- Authorities in Myanmar said they had cancelled a planned evacuation of 60 students from Mandalay who were studying in Wuhan. Kyaw Yin Myint, a spokesman for the Mandalay municipal government, told Reuters that a "final decision" had been made to send them back after 14 days, once the virus' incubation period had passed.

In Virus-Hit 'Ghost Town,' Stranded Thai Med Student Waits for Help

When Thai medical student Badeephak Kaosala dares to leave his rented apartment in the central Chinese city of Wuhan, he puts on a mask, gloves, a hat and layers of clothing to try to avoid infection with the coronavirus that has the city on lockdown. "Anywhere you go, you are always self-conscious of touching someone or you always have to keep in mind that you have to keep a distance from the person you're walking next to - when he sneezes, when he coughs, even when he breathes," said the 23-year-old student at Wuhan's Tongji Medical College. Lately, he has had trouble finding basic supplies such as milk and eggs in the city of 11 million since it became the epicentre of the coronavirus outbreak that has killed 81 and infected 2,740 people in China. "There's a shortage. Everyone wants to stock up, but it is already too late," Badeephak said. "There are no vehicles on the road except private vehicles, which I only see going to pharmacies and hospitals," he added. Badeephak wants to go home to Thailand, he has little choice but to wait. The Thai government put a military plane on standby for a possible evacuation of its citizens, but Prime Minister Prayuth Chan-ocha said they do not yet have Beijing's permission for the airlift. Most commercial flights out of Wuhan were halted last week to try to contain the virus. "At the moment the Chinese authorities have said the situation is still under control, so we have prepared a plan…Once it's time we will seek permission to fly in," Prayuth said.

Swiss Seek Access to EU Early-Warning System as Coronavirus Spreads

Switzerland needs access to a European Union early-warning system for health crises to shore up its defenses against the new coronavirus in China, Swiss health officials said. Under the EU's Early Warning and Response System (EWRS), member states share information to try to prevent or control cross-border threats to health. But Switzerland is not a member of the EU, so it is not part of the EWRS. With the coronavirus's emergence, Bern has sought temporary access to the system and expects Brussels eventually to agree to its request, as it did during a recent Ebola outbreak. But permanent access to the EWRS is hindered by an impasse in protracted talks with the EU because of disagreement over a treaty that foresees Switzerland routinely adopting single-market rules, among other things, to preserve favored-trading status. The situation could serve as a warning to Britain as it prepares to leave the EU while keeping trade ties to the bloc. "It's very difficult for us to know exactly what is going on in our neighboring countries, especially which measures they are taking," Daniel Koch, head of the communicable diseases unit at the Swiss

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- ☑ 37 minute reduction in ED median length of stay[4]

compared to a traditional small volume nebulizer.

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1. Dugernier J, Hesse M, Vanbever R, Depoortere V, Roeseler J, Michotte JB, Laterre PF, Jamar F and Reychler G. SPECT-CT Comparison of Lung Deposition using a System combining a Vibrating-mesh Nebulizer with a Valved Holding Chamber and a Conventional Jet Nebulizer: a Randomized Cross-over Study. Pharmaceutical research. 2017;34:290-300 2. Hickin S, Mac Loughlin R, Sweeney L, Tatham A, Gidwani S. Comparison of mesh nebuliser versus jet nebuliser in simulated adults with chronic obstructive pulmonary disease. Poster at the College of Emergency Medicine Clinical Excellence Conference. 2014 3. Cushen B, McCormack N, Hennigan K, Sulaiman I, Costello RW and Deering B. A pilot study to monitor changes in spirometry and lung volume, following an exacerbation of Chronic Obstructive Pulmonary Disease (COPD), as part of a supported discharge program. Respiratory medicine. 2016;119:55-62 4. Compared to a SVN : Dunne R et al. Aerosol dose matters in the Emergency Department: A comparison of impact of bronchodilator administration with two nebulizer systems. Poster at the American Association for Respiratory Care. 2016

ZENITH AWARD 2016 · European Business Awards RSM Winner 2015/16 · IAIR Awards 2014 & 2015 Best Company Innovation & Leadership · Irish Exporters Association 2014 WINNER Irish Exporter of the Year · Irish Medical Devices Association

PM315

Federal Department of Health, said. "What it shows now is that when a crisis starts, it's a little bit late to put us in, it takes too much time."

IN OTHER RT NEWS

VERO Biotech Receives US FDA Approval

Biotech LLC, an Atlanta, Georgia-based biotechnology company focused on saving lives, alleviating suffering and improving the health economics of care, announced it has received US Food and Drug Administration approval of GENOSYL (nitric oxide) gas, for inhalation. GENOSYL is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents. GENOSYL is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood. VERO Biotech's GENOSYL Delivery System (DS) is a compact and user-friendly nitric oxide delivery system, that will not only enable hospitals to reduce logistical burden as compared to the cumbersome tank-based systems currently available, but could provide greater patient access to this potentially life-saving drug. "FDA approval is a major milestone for VERO Biotech and represents an alternative technology within the inhaled nitric oxide market," said Brent V. Furse, President and Chief Executive Officer. "We look forward to making GENOSYL DS available to the critical care community and patients who may benefit from treatment. This is the first step towards VERO Biotech executing on its vision to bring innovative, patient-centric therapeutic solutions to market." VERO Biotech anticipates launching GENOSYL DS in US hospitals in early 2020.

More News continued on Page 54....

BLOODGAS ROUNDTABLE

Instrumentation Laboratory

Tell us about your oximetry products currently available.

Instrumentation Laboratory's (IL) GEM® Premier™ 5000 analyzer with integrated CO-Oximetry panel is a revolutionary analyzer for point-of-care and centralized laboratory testing, offering Arterial Blood Gas (ABG), Electrolytes, Glu, Lac, Hct, tHb, O_2Hb, COHb, HHb, MetHb, sO_2, tBili, from a single sample. Self-contained GEM PAK cartridges incorporate all components for patient testing and are maintenance-free. Enhanced Intelligent Quality Management 2 (iQM®2) on the GEM Premier 5000 system is an active quality process control program designed to provide continuous monitoring of the analytical process; before, during, and after each sample measurement with real-time, automatic error detection, automatic correction and automatic documentation of all corrective actions.

Hemoglobin monitoring with CO-Oximetry provides complete oxygenation monitoring status and supports lung-protective strategies for the management of oxygenation therapy in acutely ill patients. Measuring tHb directly vs. calculating Hct can reduce red blood cell transfusions, hospital length-of-stay, comorbidities and mortality.[1] Measurement of tHb is performed by CO-Oximetry using multi-wavelength spectrophotometry in the GEM Premier 5000 analyzer, which is not affected by dilution of blood proteins and results in more consistent measurements of hemodilution during cardiopulmonary bypass.[2,3]

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2. Myers G, Browne J. Point of care hematocrit and hemoglobin in cardiac surgery: a review. *Perfusion*. 2007;22(3):179–83.
3. Maslow A, Bert A, Singh A, Sweeney J. Point-of-Care Hemoglobin/Hematocrit Testing: Comparison of Methodology and Technology. *J Cardiothorac Vasc Anesth*. 2016;30(2):352–62.

Discuss the range of your oximetry products' applications.

IL's CO-Oximetry products have three main applications — supporting patient blood management with measured tHb in the Cardiovascular Operating Room (CVOR), supporting lung-protective strategies in intensive care patients on mechanical ventilation and detecting dyshemoglobinemia (elevated carboxyhemoglobin and methemoglobin).

Effective patient blood management is critical to optimizing patient care in the CVOR. Unnecessary transfusions increase risk of infection and ischemic complications, and can contribute to costly, prolonged hospital stays. Studies have demonstrated that the precision in hemoglobin measurement is critical; a difference of only 1 g/dL can impact the decision to transfuse. Up to 57% of transfusions are likely 'unnecessary' and initiated based on poor or inaccurate test results.[1] The GEM Premier 5000 system supports transfusion management with precise, measured tHb in the CVOR.

Oxygen therapy is one of the most common and beneficial interventions in medicine. It can promote significant improvements in quality of life and reduce morbidity and mortality in the treatment of critically ill patients.[2,3] Maintaining adequate oxygen delivery to vital organs often requires the administration of supplemental oxygen, sometimes at high concentrations. At these levels, oxygen therapy can be harmful, particularly when administered for prolonged periods.[4] ABGs and a measured CO-Oximetry (not affected by dyshemoglobins like pulse-oximetry) offered on the GEM Premier 5000, align with guidelines and clinical best practices in providing safe and effective diagnostics and ensuring optimal patient management of oxygen therapy.

Additionally, CO-Oximetry on the GEM Premier 5000 system can detect carboxyhemoglobin (COHb) and Methemoglobin (MetHb). Elevation of these dysfunctional hemoglobin derivatives can profoundly affect tissue oxygenation. These conditions are not detectable with blood gas analysis alone. Accurate and measured tHb, rather than a calculated value derived from Hct or using pulse oximetry, is the gold standard methodology for detecting dysfunctional hemoglobins.

Further, IL also offers the Avoximeter™ 4000 CO-Oximeter, providing rapid, accurate assessment of oxygenation status in less than 10 seconds. Patented state-of-the-art optics ensure accurate determinations of: O_2Hb, HHb, MetHb, COHb, tHb, O_2Ct, SO_2, O_2Cap, from a single, whole-blood

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sample. A comprehensive and complete evaluation enables critical decisions and treatments, essential during Cardiac Catheterization, where timing is critical. Another IL system, the Avoximeter 1000E Oximeter is ideally suited for quantitative measurements to aid in the diagnosis and detection of intracardiac and great-vessel shunts. With no sample preparation needed, Avoximeter systems are fast and simple to use. The two-step test method, using easy-to-fill, room-temperature disposable cartridges, minimizes waste.

Additional applications for IL's CO-Oximetry products include: MetHb for nitric oxide (NO) in the Neonatal Intensive Care Unit, and COHb for CO poisoning in the Emergency Department.

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What oximetry products do you have in development?
All GEM Premier systems today and in the future are designed to address the critical clinical applications that benefit from lab-quality, measured CO-Oximetry.

What type of customer assistance and training do you offer?
iQM/iQM2 on the GEM Premier systems automatically detect, correct and document errors, eliminating the need for manual maintenance and troubleshooting. And, all GEM Premier systems feature the GEM PAK, the only all-in-one, multi-use cartridge on the market today. With all components for critical testing contained in the cartridge itself, there is virtually no need for maintenance or technical support, and thus training is minimal. A single GEM PAK, stored at room temperature at any testing site, is simply installed when needed.

IL offers Technical Support staff in the field for customers to ensure optimal product performance and customer satisfaction. In addition, the IL Technical Support group is available by phone, 24 hours a day, 7 days a week.

To assist customers with regulatory compliance, IL also offers a comprehensive document outlining how GEM Premier systems meet the regulatory requirement of each regulatory agency. Additionally, IL conducts educational seminars throughout the year at customer hospitals and at national conferences. These seminars include experts in diagnostics, quality control and clinical practice, and provide Continuing Education Units (CEU) for attendees.

Masimo

Designed for a variety of clinical scenarios, we offer RD SET sensors for all patient populations as well as specialty sensors, which are designed specifically to meet the needs of trauma, neonatal, infant, and pediatric patients.

To date, several studies have demonstrated the clinical benefits of Masimo SET® across various care areas.[1] For example, when Masimo SET® was coupled with changes in clinical practice, it led to a significant reduction in rates of severe retinopathy of prematurity (ROP).[2] Additionally, in a study of 122,738 infants, critical congenital heart disease (CCHD) screening sensitivity increased from 77% to 93% with the combined use of Masimo SET® and clinical assessment.[3]

Alongside SET® pulse oximetry, offering SpO_2, pulse rate, and perfusion index, advanced Masimo rainbow® measurements enable clinicians to gain an array of additional insights into patient status in real time. These noninvasive measurements include pleth variability index (PVi®), total hemoglobin (SpHb®), carboxyhemoglobin (SpCO®), methemoglobin (SpMet®), oxygen content (SpOC™), and acoustic respiration rate (RRa®). With more information at their fingertips, clinicians can make better informed care decisions.

We help clinicians manage this important patient data with the Root® Patient Monitoring and Connectivity Platform. Root's advanced connectivity capabilities aggregate and display data from other Masimo and even third-party devices. With the assistance of Masimo Iris Gateway® or Patient SafetyNet™, that data can be automatically transferred into hospital electronic medical records (EMRs) and displayed at central view stations and on UniView™, which intelligently visualizes data and alarms to help reduce cognitive overload and streamline care team

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workflows. Root is compatible with both third-party devices and our expanded portfolio of noninvasive monitoring technologies and devices, which includes brain monitoring (Next Generation SedLine® and O3® Regional Oximetry) and ventilation monitoring solutions (NomoLine® Capnography and rainbow Acoustic Monitoring®).

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2. Castillo et al. *Acta Paediatr*. 2011;100(2):188-92.
3. Zhao et al. *Lancet*. 2014;384(9945):747-54.

What oximetry products do you have in development?
At Masimo, we're always looking for new and innovative ways to help improve patient outcomes through advanced monitoring technologies and systems. It is also our goal to help provide clinicians with the tools they need to better manage the data generated by our technologies—freeing them up to spend more time delivering bedside care.

Recently, we released the Radius PPG™ tetherless pulse oximetry solution in the US and plan to release it globally in the future. Radius PPG provides continuous SET® pulse oximetry monitoring without the need for a cabled connection to a monitor. Lightweight and comfortable to wear, Radius PPG gives patients freedom of movement without compromising safety—providing uninterrupted continuous pulse oximetry monitoring no matter where they go. It's easy to pair Radius PPG with other Masimo products and third-party devices.

What type of customer assistance and training do you offer?
Masimo takes pride in offering the best education solutions for customers. Expert clinical specialists, including trained nurses and respiratory therapists, work hand-in-hand with the hospital's clinical educator(s) to build an education plan that meets the needs of hospital staff.

To help clinicians maximize the utility of our products, we've created three phases of customer training—modeled after Adult Learning Theory—that provide engaging, effective educational content. These phases include self-directed eLearning via our learning portal (MasimoU), on-site demonstration, and "super-user" training geared toward in-house clinical champions in various care areas. Through these trainings, customers learn the fundamentals of pulse oximetry, SET® technology, key physiological and laboratory concepts, advanced troubleshooting, proper sensor placement, and much more.

Tell us about your oximetry products currently available.
We offer a wide range of pulse oximetry products, including both continuous and spot-check monitoring solutions with Masimo SET® pulse oximetry.

Over 30 years ago, Masimo founder and CEO Joe Kiani was convinced that the use of adaptive signal processing could solve the long-time patient monitoring concerns clinicians faced by separating true arterial signal from sources of noise. With this insight, Masimo SET® Measure-through Motion and Low Perfusion™ pulse oximetry was born—empowering clinicians with accurate, real-time patient oxygenation data even during periods of motion and low perfusion.

Masimo SET® pulse oximetry is available on various monitoring devices, including the Radical-7® Pulse CO-Oximeter® and the Rad-67™ Pulse CO-Oximeter. Radical-7 is a continuous monitoring solution designed to provide a variety of important patient parameters in a versatile, upgradeable monitor—for handheld use, use at the bedside, or during transport. For monitoring on the go, the Rad-67 spot-check monitoring device provides noninvasive total hemoglobin and SET® pulse oximetry in a light, handheld format. With its intuitive touchscreen and fast, on-demand results, Rad-67 makes an ideal mobile monitoring solution in clinical and non-clinical settings, such as emergency rooms, pre- and post-surgery settings, and physician offices. SET® can also be integrated into third-party monitors. For use with these devices, we offer a variety of sensors designed for patient comfort and ease of use, including RD SET® sensors and specialty sensors.

In clinical settings, Masimo SET® has demonstrated fewer false alarms and more true alarms than conventional pulse oximeters,[1] and over 100 studies have shown that SET® outperforms other pulse oximetry technologies.[2] At Masimo, we never put innovation on hold—and our proven SET® technology is no exception. We are excited to announce a significant improvement in our SpO_2 accuracy specification with the latest RD SET sensors, from 3% to 1.5% A_{RMS} during motion, in all patient populations.

Today, Masimo SET® is estimated to be used on more than 100 million patients in leading hospitals and other healthcare settings around the world and is the primary pulse oximetry at 9 of the top 10 hospitals according to the 2019-20 US News and World Report Best Hospitals Honor Roll.

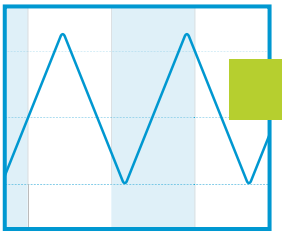
1. Shah et al. J Clin Anesth. 2012;24(5):385-91.
2. Masimo. Clinical Evidence. https://www.masimo.com/evidence/featured-studies/feature/

Discuss the range of your oximetry products' applications.
Our pulse oximetry solutions are versatile, customizable, and transportable. Whether it's continuous pulse oximetry monitoring in critical care areas or spot-check patient monitoring during vital signs checking, SET® technology can be used anywhere pulse oximetry is needed—in pre-hospital, acute, and post-acute care settings.

Chronic respiratory patients getting treatment but not feeling better?

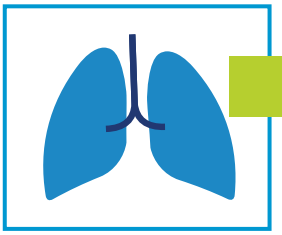
Three great reasons to try the Philips InCourage system:

1 The Philips InCourage system triangle waveform technology **clears more mucus than** competing technology[1]



Triangle waveform

2 RespirTech bronchiectasis patients reported **62% reduction in hospitalizations** and a **14% reduction in antibiotic use** one year after initiating Philips InCourage vest therapy[2]

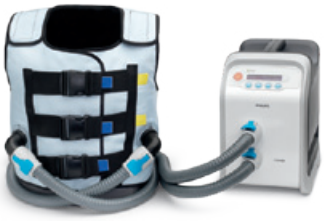


Outcomes

3 "I was on antibiotics every month of the year for the last 40 years... **Since I've had the InCourage machine, I haven't had to take antibiotics* in over a year**..."
-Marjorie M., CA
*Individual results may vary.

Patient results

For chronic respiratory patients with excess secretions, consider the Philips InCourage system (high-frequency chest wall oscillation) to help clear their airways. Since 2004, RespirTech has helped thousands of people like Marjorie—patients with bronchiectasis, COPD, cystic fibrosis, neuromotor conditions and more.



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1. Milla CE, Hansen LG, Weber A, Warwick WJ. High frequency chest compression: effect of the third generation waveform. Biomed Instrum Technol 2004; 38:322-328. Note: 8 CF comparing triangular waveform vs. sine waveform technology.
2. Data from RespirTech's bronchiectasis patient outcomes program. Methodology: As of 6/30/19, self-reported data from over 16,000 bronchiectasis patients.

Intentional Breathing

Janet Tompkins, RRT

Being an in home Pulmonary Rehab RT gives me a unique look into my patients lives on a daily basis. I treasure this look as it provides me the opportunity to better serve my patients individual needs. As Respiratory Therapists, we have many tools in our pockets to help our patients live more active and productive lives. When I put both of these together, I have a responsibility to my patients to provide them with the tools they need on an individual basis depending on those needs.

One of the tools we use as RT's is pursed lip breathing. When I am in the home and we are on the subject of breathing techniques, triggers and infection control, I spend time in conversation with each patient to determine what makes them short of breath. Some may find this a waste of time, I however, find it very helpful. All too often, we do not stop and think about these things when we see them in the hospital one more time and are administering one more breathing treatment. We should try to find out what caused this latest exacerbation.

Each person has one or more activities that cause them to become more short of breath then usual. For one person it could be a simple as bending down to pick something up, for another it could be mopping the kitchen floor and yet for another it could be going to the mailbox to retrieve the days mail.

Most of the time I will have the patient demonstrate for me the action that is causing them to become short of breath. During this time, I use another tool we have as RT's and do not use too often being in the hospital setting or even in the out patient based Pulmonary Rehab—observation. This has become a powerful tool for me. I stop and observe what the patient is doing, how they are doing it and how they are breathing as they do this task.

Pursed lip breathing is easy to explain to the patient, in through the nose and out through the mouth. Smell the roses and blow out the candles. Do we though, stop and give them the reason behind what they are doing? Do we explain how this forces the gases in their alveoli to be exchanged allowing the next breath to better fill those alveoli with good clean oxygen?

Do we stop and have them put this breathing into the action that is causing them to be short of breath? This takes practice and time. This is not a technique that they will just pick up and never forget. For this reason, I take the time to go over this with them at each and every visit thereafter to show them how important it is. Many of them say "shouldn't my body just know how to breath?" Truth be told, no. Their bodies have gone through physiological changes that have changed how they breathe. For this reason, I call it "Intentional Breathing".

Intentional breathing is a way for them to concentrate on how to breath through their activity, using pursed lip breathing, in order to keep them from becoming short of breath. With practice, this has worked time and time again. One example of this "intentional breathing" looks like this:

Problem: The patient complains of getting short of breath when they bend over to pick things up. RT observes this task and realizes that the patient (like most of them) is holding their breath until that object is picked up and they are standing back upright. Due to the breath hold, they are now short shallow breathing to try and "catch their breath".

Solution: RT instructs the patient to take a deep breath in before they bend over, then bend over and grab the object, and last exhale through those pursed lips as they stand back up.

This keeps the patient from holding in CO2 and will keep them from the short shallow breaths which in reality cause more CO2 build up.

We can use this when walking as well. The patient takes a breath in as they take two or three steps and exhale through pursed lips as they take 4-5 more steps and repeat. This has also been a proven technique with multiple patients I have seen over the past 3 years.

As we see, assess and observe our patients, we also need to be asking pertinent questions about their lives at home and find possible interventions to keep them at home.

Try putting some of these techniques into your daily routine with your patients to help them have a better quality of life!

Janet Tompkins has been a Therapist since 2002 and has found passion for Respiratory in Home Care—the one place she thought she would never go. She began her career in NE Ohio and in 2008 moved to NC where she resides today.

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Lung Volume Recruitment: A Novel Method that Maximizes the Therapeutic Impact from MI-E Devices

Jon Nilsestuen PhD, RRT, FAARC, David Troxell

Abstract

Neuromuscular disease (NMD) refers to a group of diseases (motor neuron diseases, muscular dystrophies) that are collectively associated with progressive respiratory muscle weakness that ultimately result in a decline in vital capacity, a decrease in chest wall and lung compliance, atelectasis, an increase in work of breathing, and an impaired ability to cough. As a result, progressive neuromuscular diseases carry an increased risk of respiratory infection, respiratory failure, and mortality.[1] Non-invasive ventilation (NIV), mechanical insufflation-exsufflation (MI-E), and lung volume recruitment (LVR) have been repeatedly discussed in literature and clinical studies as critical elements of the respiratory support strategy for patients with NMD.[2,3]

This article will briefly summarize NIV's and MI-E's respective role in the respiratory support strategy for NMD and explore both the physiological evidence and clinical benefit for providing LVR. Additionally the article will discuss the primary application technique for LVR, namely breath-stacking, and analyze how this technique has been mistakenly applied to MI-E devices that operate using a pressure control (PC) mode of therapy. The article will explain why the "breath-stacking" technique does not work when attempted with a MI-E device using a PC mode. Finally the article will conclude with a comprehensive explanation of a novel approach for providing effective LVR that is based on the PC mode of operation and has sound physiologic backing.

The ultimate goal of this article is to promote use of MI-E devices in a way that facilitates the delivery of both mechanically-assisted coughing as well as effective LVR to a broad scope of patients thereby maximizing the therapeutic impact from a single home airway clearance (ACT) device.

Key Points

- Lung Volume Recruitment is used to enhance the clinical outcomes and quality of life for neuromuscular patients with respiratory insufficiency.
- A common practice is to deliver LVR using a "breath-stacking" approach with a resuscitation bag + one-way valve or a volume ventilator.
- "Breath-stacking" is unlikely to be effective when using a MI-E device with a PC mode, instead consider using the Long Slow Deep technique described in this paper.

Discussion

Ventilatory support has become a standard of care for both rapidly (ALS, SMA) and relatively rapidly (DMD) progressing neuromuscular disease as well as for chronic NMD conditions (e.g. other myopathies). For chronic NMD conditions, long term mechanical ventilation (LTMV) is the primary intervention to support respiratory muscle function extending survivability as well as improving health related quality of life.[1] NIV may provide clinical benefit by the reduction of nocturnal hypoventilation as well as the compounding effects of sleep disordered breathing (SDB) on NMD. Using NIV in addition to MI-E may delay mortality and is thought to have cardio-protective benefits in the Duchenne Muscular Dystrophy (DMD) patient population.[3] Mellies et al determined that NIV had a favorable long term effect on both nocturnal and diurnal gas exchange in patients with NMD. For non-DMD patients, NIV was associated with an improvement in vital capacity.[4]

NIV can be delivered in the form of simple bi-level therapy or using more sophisticated ventilators capable of features such as volume-targeted variable pressure support modes and mouthpiece ventilation (MPV); also termed sip and puff, for daytime ventilatory support. Volume targeted modes vary the pressure support to achieve an average tidal volume which is designed to adapt to the patient's changing ventilatory support needs over time.

For all patients, an effective cough maneuver (PCF 360-840 lpm)[5] is an essential protective mechanism against respiratory tract infections. MI-E is a mechanically-assisted therapeutic intervention designed to decrease the risk of respiratory infections that are exacerbated by progressively weakened respiratory muscles and decreased peak cough flow (PCF) values. Current clinical consensus is that PCFs <160 lpm are ineffective for cough clearance and that when peak cough flows (PCF) reach a threshold of 270 lpm in the NMD patient population, mechanical insufflation exsufflation is indicated.[6,7] MI-E therapy utilizes positive pressure to help a patient achieve a large lung volume; targeting maximum inspiratory capacity,

Jon O Nilsestuen is Professor Emeritus at the University of Texas Medical Branch at Galveston, and is a consultant to Philips. David Troxell is Senior Global Product Manager for Sleep & Respiratory Care (SRC) Philips.

followed by a rapid shift to negative pressure creating a large pressure gradient that raises expiratory flow rates to a level required to clear irritants, microbes, and secretions from the central airways.

MI-E therapy can be associated with a raise in peak cough flows of more than four times that of an unassisted cough[8] and has been shown to decrease recurrent respiratory infections.[2] In addition, MI-E therapy has been shown to prevent the need for tracheostomy.[9] Several studies have shown MI-E to decrease hospitalizations,[9,10] as well to increase survivability.[2,11,12,13] MI-E is better tolerated/preferred over suctioning and patients find MI-E therapy less irritating, less painful, less tiring and more comfortable as compared to invasive suctioning.[14]

Background on Lung Volume Recruitment

Clinical Evidence

LVR is an important therapeutic intervention. When properly administrated, LVR is associated with the mitigation and or reversal of alveolar atelectasis, improvement in lung and chest wall compliance, and aids in the assisted cough effort aimed at avoiding respiratory infections. Excerpts from clinical studies regarding LVR are summarized below:

- Implementation of LVR twice daily in a cohort of DMD patients helped maintain respiratory system compliance despite a loss in vital capacity (VC) associated with a progression of their disease.
- LVR implementation sharply attenuated the rate of VC decline from 4.5% decline per year to 0.5% decline per year and assisted PCF stability was maintained within a therapeutic range.[15]
- In the cited study, the attenuated decline in VC was observed up to 10 years while the stability in PCF was maintained for up to 8 years.
- Bach and colleagues have described a decrease in daytime ventilator use when the cohort of patients regularly used LVR (air stacking) as part of their respiratory support strategy.[16]
- Bach and associates concluded that "Noninvasive respiratory management including NIV and mechanically assisted cough (MAC) can be used to avoid respiratory failure, hospitalizations, and tracheotomy for patients with NMDs and spinal cord injury (SCI) who have functioning bulbar musculature and can be used to extubate and decannulate patients."[17]

Physiology of LVR

Animal and human studies have provided complimentary and consistent information about the physiologic mechanisms behind alveolar recruitment. Albert and colleagues performed compelling research on alveolar recruitment by creating an animal model with anesthetized and ventilated rats.[18] Both gross alveolar recruitment and microscopic alveolar recruitment were evaluated at three recruitment pressure settings: 20 cmH_2O, 30 cmH_2O, and 40cmH_2O respectively. The impact of time on alveolar recruitment was then evaluated at each recruitment pressure beginning at the baseline collapsed level at 0 seconds and extending exposure to the inflating pressure up to a maximum of 40 seconds. The majority of recruitment occurred at the recruitment pressure of 40 cmH_2O (78% gross, 85% microscopic) within the first 2 seconds of pressure delivery. Significantly less recruitment was achieved at the lower pressures of 30 cmH_2O (56% gross, 78% microscopic) and the least amount of recruitment occurred at a pressure of 20 cmH_2O (36% gross, 52% microscopic).

Breath Stacking Examples

Breath-Stacking with a Resuscitation Bag. Our resuscitation bag has a total volume capacity of 2 liters with a one-handed squeeze technique yielding an average of approximately 800 mL. Subtracting the average leak around the interface or mouthpiece during inhalation leaves us with an estimated volume delivery per bag squeeze at 500 mL. Assuming the patient can synchronize glottis opening and closing with each breath, the first breath would yield a lung volume of approximately 500 mL, while the second breath would conceptually add to the initial breath yielding a cumulative lung volume of approximately 1000 mL assuming there is no additional leak. The cumulative volume is larger than the volume of the first breath dependent upon the total amount of volume the patient could accept with the second breath ≤2 L.

Breath-Stacking with MI-E in PC Mode. By comparison, a PC mode is only set to deliver and maintain a target inhale pressure. Opening and closing the glottis in between each manual pressure delivery does not result in the set pressure being increased in each subsequent manual pressure delivery rather it will simply add or "stack" inhalation time. Increasing the amount of time spent at a target inhale pressure during the inhale phase may increase the net lung volume achieved, however a "time stacked" technique is both inefficient and limiting in its application. By requiring the patient to open and close their glottis, the technique would be limited to patients who have intact glottis control and exclude patients with bulbar weakness. Secondly regarding efficiency of the technique: multiple, manually delivered, "time-stacked" breaths are not necessary to achieve alveolar recruitment. This technique may be potentially tiring for the patients given the active inhale effort that is required, and may lead to less than optimal results when time spent at set/optimal pressure is carefully scrutinized (see Figure 1).

In 1993 Rothen et al[19] studied alveolar recruitment on anesthetized humans with healthy lungs. The study procedure started by ventilating the anesthetized patient using 40 cmH_2O, alveolar atelectasis was then established by introducing -15 cmH_2O. CT scans were used to quantify baseline atelectasis as well as alveolar recruitment following a stepwise recruitment pressure application (10, 20, 30, 40 cmH_2O) with a breath hold time of 15 seconds. 10 cmH_2O was determined to be equivalent to the subjects tidal volume, a sigh breath (VT x 2) or 20 cmH_2O sustained for 15 seconds did not significantly reduce atelectasis on CT scans. In both groups, inflation to Vital Capacity; at an inflation pressure of 40 cmH_2O, virtually eliminated any residual atelectasis; lower pressure settings did not alleviate the atelectasis.

In 1999 Rothen and associates[20] revisited the vital capacity maneuver (inflation to 40 cmH_2O) in a subsequent clinical study to evaluate the efficacy of recruitment levels and pulmonary shunting using a reduced time at recruitment pressure. In this updated study, the authors concluded that similar results could be obtained, that is virtual abolishment of atelectasis, using a pressure delivery time of only 7-8 seconds. The reduction in pressure delivery time was aimed at reducing the risk of adverse cardiovascular effects while applying the VC maneuver. This

new study confirms key facts regarding LVR with the following two points: 1) 40 cmH_2O was the target inhale pressure used for the VC inflation maneuver; applying a lesser pressure for a prolonged time does not necessarily result in re-opening of more lung units, and 2) CT scans indicated nearly complete resolution of atelectasis after only 3.5 seconds.

Bach and associates[21] have described passive LVR techniques using pressure ventilators and MI-E devices, however the target inhale pressure was 50 cmH_2O or greater. It is worth considering that 40 cmH_2O represents a minimal target inhale pressure and that based on Dr Bach's work, higher target inhale pressures may be indicated in the NMD patient population.

LVR Application Techniques

LVR can be separated into two primary application techniques. The more commonly known technique is often termed "breath-stacking" associated with volume delivery whereas the second technique utilizes a pressure control mode. Breath-stacking may be delivered in its most simple construct utilizing a resuscitation bag combined with an integrated one-way valve, however breath-stacking may also be achieved using a mechanical ventilator.

1. **Breath-Stacking Techniques**

   In the resuscitation bag technique, the integration of a one way valve prevents the patient from exhaling while facilitating stacking of successive inhalation breaths; one on top of the other, thereby increasing the net lung volume achieved. The equipment is inexpensive, and the technique is relatively simple as the one way valve does not require the patient to have glottis control in order to prevent exhalation during the procedure. This technique does require that the patient is able to create a lip seal and have upper or lower limb mobility to squeeze the bag if performed autonomously, otherwise caregiver assistance and training on an effective technique would be indicated.

   An alternate method used to facilitate breath stacking is the use of a volume ventilator set to provide on demand inspiratory support while configured to avoid nuisance alarms. Breath-stacking with a volume ventilator in the home setting would require the patient to have glottis control and the ability to create a lip seal. Several home ventilators (LTV, Trilogy) are compatible with mouthpiece ventilation (MPV) where a user can be trained to breath-stack in a volume mode. Toussaint and associates[22] concluded that "air-stacking" via resuscitation bag was as effective as the same technique performed with a home mechanical ventilator.

   Regardless of the equipment used, it should be noted that the "breath-stacking" LVR technique is dependent upon the ability to deliver a fixed volume with each breath that the patient receives. In addition to glottis control, the ability to control leak, limb mobility, caregiver assistance and training are all considerations when evaluating the appropriateness of selecting breath-stacking as the choice in LVR technique.

2. **Alternative LVR Delivery Technique: Pressure Control**

   The second and possibly less commonly known method for delivering effective LVR utilizes a pressure control mode of therapy with a uniquely different technique. A pressure control (PC) mode of therapy can be found in both mechanical ventilators as well as certain MI-E devices.

   The concept of utilizing a MI-E device; such as the Philips CoughAssist 70-series, may not be completely novel to some clinicians, however the technique when using the PC mode often is. Clinicians, recognizing the value of LVR, have attempted to use a MI-E device to perform LVR by simulating the "breath-stacking" technique. In this scenario the clinician will set the MI-E device to a manual mode, set a target inhale pressure setting, and then use the toggle/foot pedal to manually deliver sequential, time variable, positive only pressures (usually three), during the inhale phase. This technique is often combined with the patient being instructed (if able) to close their glottis at the end of each manually delivered positive pressure period, then subsequently open their glottis with the start of the next manually delivered inhale phase. Unfortunately, breath-stacking in a pressure control mode is simply impossible based on the mode's mechanism of operation. While it is true that an individual with glottis control may feel as if they have achieved a large lung volume at the end of multiple, manually delivered, positive pressure phases, they simply are not stacking breaths as they would with a volume ventilator or resuscitation bag with an integrated one-way valve. In reality since the device is being used in a pressure control mode the set target inspiratory pressure does not change, and thus prevents true breath stacking.

To illustrate, we will use the resuscitation bag and one-way valve to examine first the breath-stacking technique, next we will compare that to the same technique applied to the CoughAssist MI-E device (*see Box on* ***Page 17 Breath Stacking*** *examples*), and finally we will explore a novel method for performing LVR with the CoughAssist MI-E device.

A New Proposal: The Long Slow Deep (LSD) Technique

A novel technique for LVR with a MI-E device has been developed by taking into consideration both the physiologic requirements for effective alveolar recruitment as well as the mechanism of operation when using a pressure control mode of therapy. We propose the term long, slow, deep (LSD) to describe this passive inhalation recruitment technique.

True "breath-stacking" requires a device with a preset volume delivery, glottis control or the integration of a one-way valve to prevent exhalation during the multiple inhale efforts. The LSD technique by contrast is a single, completely passive breath that is delivered using a target inhale pressure set greater or equal to critical alveolar opening pressure (40 cmH_2O)[18,19,20] and for an extended pressure delivery inhalation time period of 3-3.5 seconds[18,20] for the average adult. The LSD technique may offer several advantages for a patient that already has a MI-E device prescribed for cough therapy namely:

- No additional equipment or devices are required
- No active patient effort is required, the LSD technique is completely passive making it comfortable and not tiring for most patients
- No glottis control is required making the LSD technique an option for a broad spectrum of patients including bulbar ALS patients
- Little coordination or technique training is necessary. When combined with a triggering feature a patient simply has to be coached to completely relax (relinquishing control of the inhale phase to the MI-E device) so that target pressure may be achieved for the inhale time required for optimal LVR therapy
- At the end of the breath patients may be coached to passively

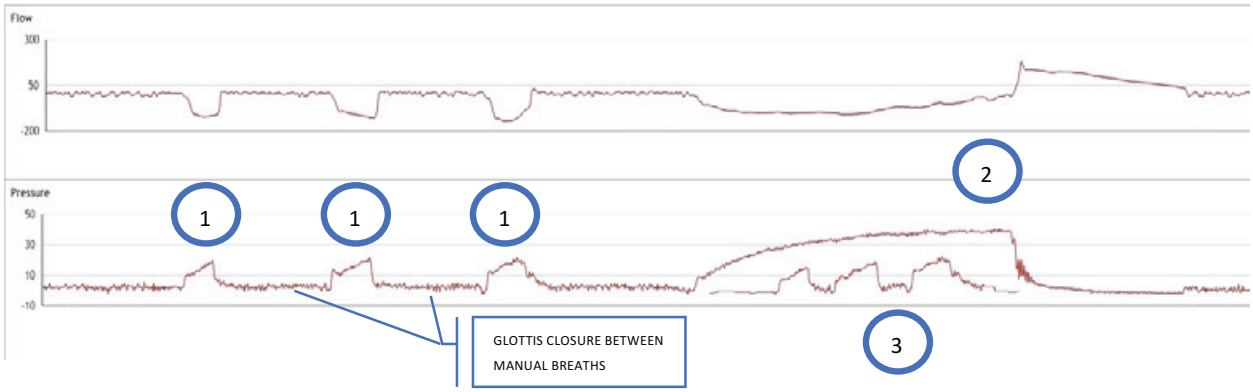

Figure 1. The pressure and flow waveforms for this model were obtained via SD card download from a CoughAssist 70-series device. The composite graphic demonstrates use of both the manual time-stacked technique (1) and followed by the single, passive inhale effort, LSD technique (2). Both techniques used a target inhale pressure setting of 40 cmH_2O and a low flow setting. Technique 1 was associated with manually delivered, variable inhale times (T_I) with each of the 3 delivered breaths, whereas technique 2 utilized a single breath with a 3.5 second T_I. Close examination of the pressure trace with technique 1 reveals failure for the manual breaths to reach target pressure — in part because each manual breath is associated with a rise time to reach the target inhale pressure setting. Technique 2 reached and maintained the target inhale pressure as illustrated by 3 where the manually assisted breaths are superimposed within the single passive breath.

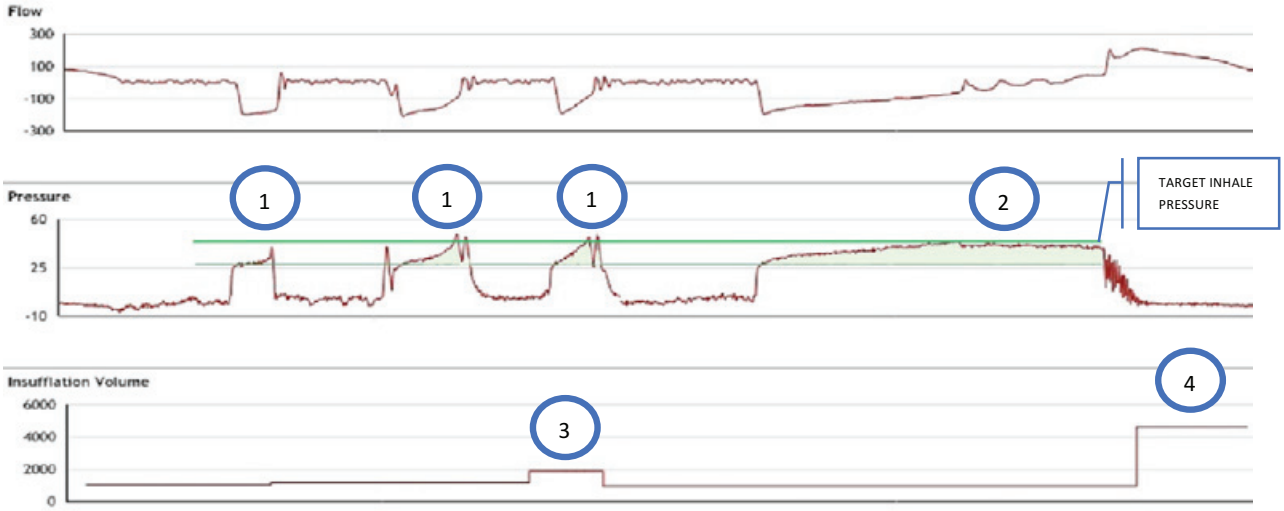

Figure 2. As with Figure 1, the pressure and flow waveforms for this model were obtained via SD card download from a CoughAssist 70-series device. The composite graphic demonstrates use of both the manual time-stacked technique (1) and followed by the single, passive inhale effort, LSD technique (2). Both techniques used a target inhale pressure setting of 40 cmH_2O, however given that the manual technique in Figure 1 failed to achieve target inhale pressure, the flow setting was changed to High. As with Figure 1, technique 1 was associated with manually delivered, variable inhale times (T_I) with each of the 3 delivered breaths, whereas technique 2 utilized a single breath with a 3.5 second T_I. In this model the manually delivered breaths did achieve the target inhale pressure setting of 40 cmH_2O. When compared to the single, passive, LSD breath (2) considerably less time was spent at critical alveolar opening pressure with the manual technique as indicated by the green lines and light green shaded area (1), (2). In addition, when comparing the device-reported VT_I trend the VT_I for the manual technique (3) was 2 L compared to 4.3L for the LSD technique (4) which equals less than half of the trended insufflation volume achieved with the single, passive LSD technique.

exhale and take a short rest period prior to performing subsequent LVR efforts (up to five) ideally repeated 2-3 times per day.

Two models were set up to graphically illustrate the differences in the two LVR techniques that utilize an MI-E device (PC mode) and underscore the advantages associated with the passive LSD technique. (See Figures 1 and 2.)

Conclusion

In this article we have briefly discussed some of the clinical benefits associated with LVR in the NMD patient population and described two different techniques for achieving LVR. The first technique involves true breath stacking with a resuscitation bag or a mechanical ventilator. This technique while useful, may require glottis control (volume ventilator) on the part of the patient and frequently requires a caregiver to squeeze the bag or manage the ventilator. The second technique relies on the use of a Pressure Control mode where both a target inspiratory pressure and an inspiratory time are set. This can be implemented using a mechanical ventilator, but very importantly can be also be initiated using a MI-E device with a pressure control mode.

The two key physiologic factors to consider when implementing LVR using the pressure control mode are:

1. target inhale pressure set at or **above** alveolar critical opening pressure of 40 cmH_2O (Bach et al ≥50 cmH_2O in NMD

subjects)
2. inhale time set in the range of 3.5 seconds (adult)

This later technique involves a single, extended, passive inflation that we have described as long, slow, deep (LSD) and should be considered by the healthcare team when a patient already has access to a MI-E device to maximize the therapeutic impact from a single home ACT device. The distinctive advantage of this technique is that the maneuver is passive and does not require patient effort other than to trigger the breath and requires minimal caregiver assistance other than to help maintain mask seal. The passive LSD technique should also be considered due to the broad patient population that may benefit from this technique including bulbar ALS patients with loss of glottis control as well as other NMD patients with intact glottis control but progressive muscle weakness.

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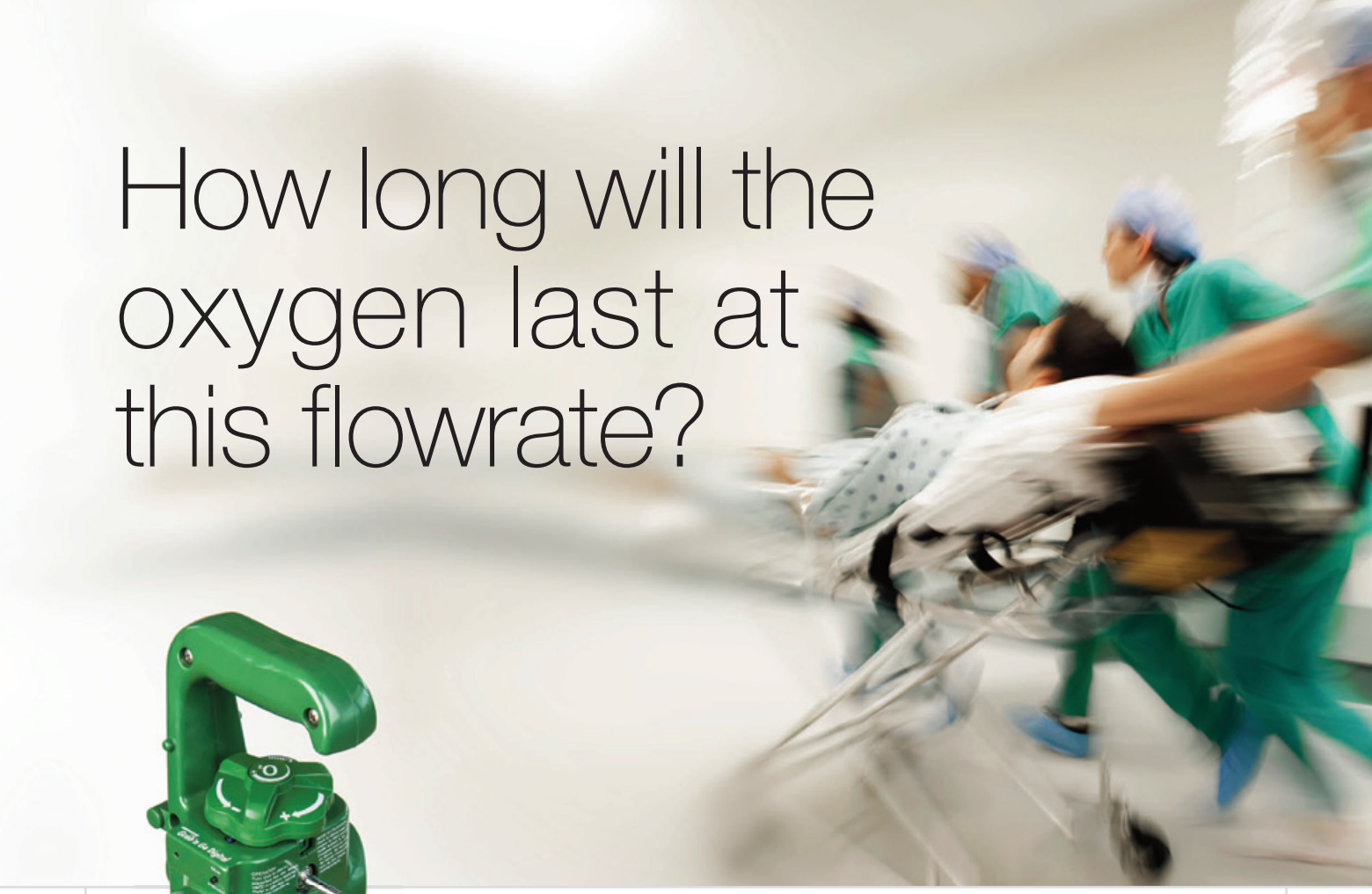

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HEALTHCARE SERVICES

Study Examines Pulse Oximetry Diagnostic Performance in the Emergency Department

Chris Campbell

Medical professionals are always looking for as many options as possible when it comes to treating patients in distress.

This is even more important when it comes to an Emergency Department — where time is always in short supply.

That's why a team out of the University of Vermont examined the diagnostic performance of carbon monoxide testing by pulse oximetry in the ED.

The team looked at alternatives to standard measurements when it comes to carbon monoxide exposure in their study, Diagnostic Performance of Carbon Monoxide Testing by Pulse Oximetry in the Emergency Department. The study — by Nuria Villalba, Zachary T Osborn, Pamela R Derickson, Chelsea T Manning, Robert R Herrington, David A Kaminsky and Kalev Freeman from the Department of Surgery, Larner College of Medicine, University of Vermont — wanted to see the performance of one such alternative method.

"Carbon monoxide (CO) exposure causes roughly 40,000 emergency department (ED) visits annually and is commonly misdiagnosed," the authors said. "Whereas the standard method of carboxyhemoglobin (HbCO) measurement utilizes blood gas analysis, a noninvasive, FDA-cleared alternative exists. We evaluated the performance of pulse oximetry (S_pCO) for identification of CO exposure in ED patients."

Study Methods

The study authors wrote about how it compared pulse oximetry to blood HbCO levels by the use of a prospective observational study of adult and pediatric subjects recruited from the ED.

"Nurses screened a convenience sample of patients and referred those with S_pCO ≥10% to research staff," the authors wrote. "Researchers also approached individuals who presented with signs and symptoms of CO toxicity. We determined diagnostic performance with a Bland-Altman analysis and calculated sensitivity and specificity for detection of elevated HbCO at thresholds of ≥10% and ≥15%. To optimize the potential sensitivity of S_pCO for detection of CO toxicity, research technicians performed 3 S_pCO readings within 5 min of the blood draw for laboratory measurement. A positive S_pCO test was defined as any S_pCO ≥10%."

Study Results

The authors screened a large number of patients — 42,000 in all, with 212 evaluated, and 126 subjects eventually enrolled.

"Median HbCO level was 6% (range 1.6-21.9%)," the authors wrote. "Limits of agreement were -10.3% and 8.1%. Of 23 individuals with elevated HbCO ≥10%, 13 were not suspected based on clinical assessment. Critically elevated HbCO was present in 6 individuals. Based on our a priori threshold of 10% for a positive test, pulse oximetry identified 14 of 23 subjects with HbCO ≥10%, with a sensitivity of 61% (95% CI 39-80%) and a specificity of 86% (95% CI 78-92%), and 5 of 6 subjects with HbCO ≥15%, with a sensitivity of 83% (95% CI 36-100%) and a specificity of 81% (95% CI 73-87%)."

Study Conclusions

"Pulse oximetry underestimated HbCO and produced false negative results (ie, S_pCO <10% for all three measurements) in 17% of ED subjects with elevated HbCO ≥15%. Triage screening with pulse oximetry detected cases of elevated HbCO that were not suspected by the clinical provider."

Chris Campbell is the Senior Editor of Respiratory Therapy.

A Challenge to the Recommendation of Using Asymmetrical Pressures During MI-E

Jon Nilsestuen PhD, RRT, FAARC, David Troxell, Rob Chase[3]

Abstract

The aim of this article is to challenge the current recommendation of using asymmetrical pressures, defined as greater exhale as compared to inhale pressure, during mechanical insufflation exsufflation (MI-E) therapy. Asymmetrical pressure settings, as a suggested standard of practice when delivering MI-E therapy, have notably appeared in two recent clinical journals: Chatwin M, Simonds A, Long-Term Mechanical Insufflation-Exsufflation Cough Assistance in Neuromuscular Disease: Patterns of Use and Lessons for Application, Respir Care 2019[1]: and, the Expert Panel Recommendations for Airway Clearance Techniques published in 2018.[2]

The objective of challenging the recommendation is to discuss the significant clinical evidence that contradicts the support for use of asymmetrical settings. We believe that it is critical that clinicians are informed of these considerations so as to shape MI-E clinical practice in a way that promotes maximal peak cough flow rates (PCF) required for effective therapy while considering patient comfort and adherence.

Key Points

- The potential for upper airway collapse has been well established in clinical literature including: healthy non-OSA subjects, in NMD, during laryngoscopy, using CT scans, and using spirometric flow-volume loops. Finally upper airway collapse has also been identified with a novel method that utilizes MI-E device generated pressure and flow traces.
- Using asymmetrical pressure settings in the bulbar ALS patient population increases the risk of upper airway collapse.
- Using higher negative pressure settings in our bench model resulted in lower PCF rates as compared to the same pressure gradient with the inhale pressure being the larger of the two settings.

Discussion

One of the major findings in the 2020 Chatwin article[1] that we wish to address is the authors' conclusion that "Greater exsufflation pressures than insufflation pressures" were used. While this is a true statement based on the authors' protocol for MI-E settings, it is not a scientific result based on the measurement of clinical outcomes such as peak cough flow (PCF) or lung volumes to guide the adjustment of MI-E settings. Rather, use of higher negative exhale pressure settings is specifically tied to the treatment protocol (Fig 2 of their article) where the titration protocol states, "Set the negative pressure to be at least 5 cmH_2O more negative than the insufflation pressure". As such, the finding, while appropriate in a sub-population of patients with rigid airways**,** is not suitable for the large majority of patients with neuromuscular disease that use MI-E via a face mask and have a potentially collapsible upper airway. In addition it should be noted that cough audibility was used as a subjective feedback mechanism intended to guide the adjustment of the negative exhale pressure setting.

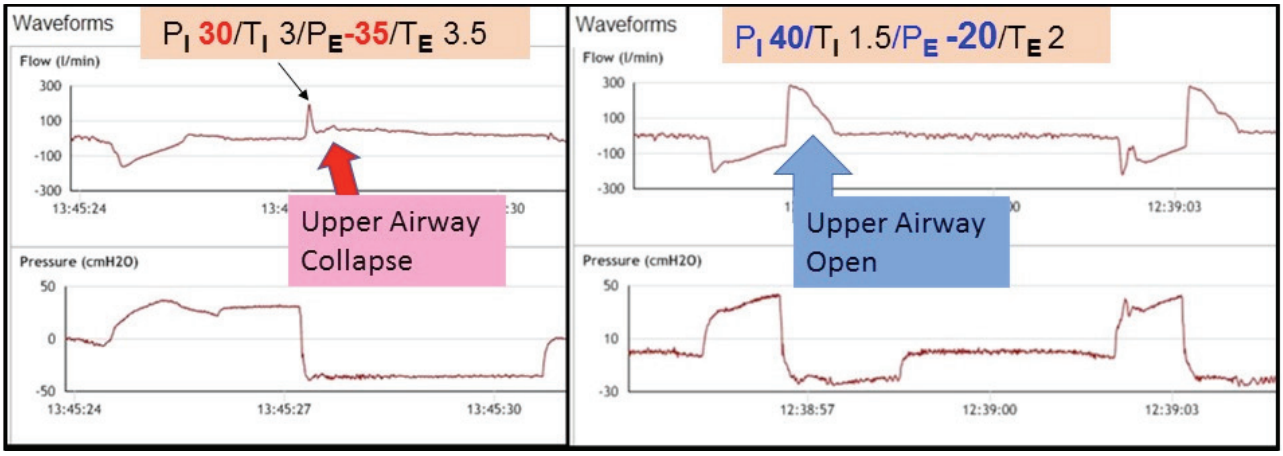
The reason given was that the MI-E device used in the study (*Nippy Clearway®*, *Breas Medical*) did not display or report PCF values. Cough audibility is not likely a very sensitive way to guide exhale pressure adjustments and in fact may encourage use of excessive negative pressure resulting in airway compression, which, in turn, could increase the audibility of the patients exhale flow until complete airway closure is created.

The protocol approach to setting target pressures on the MI-E devices appears to based on the Expert Panel Recommendations for ACT published in 2018.[2] In this report the Expert Panel recommended that the MI-E pressure settings should be set to reflect higher expiratory pressures than inspiratory pressures (*asymmetrical pressures*).

A limitation of the asymmetrical pressure recommendation is that support for the recommendation to use higher negative pressure settings is based solely on the results of one pediatric bench study.[3] The bench model was performed using a pediatric lung model with attached infant tracheostomy tubes. A tracheostomy tube (or endotracheal tube) is a rigid airway that prevents the negative pressure from collapsing the airway. It is reasonable to assume in this model, and in clinical application to patients where the MI-E device is connected to a rigid tube, that greater exsufflation pressure would have a more substantial impact on mean expiratory flow. This is a mechanical result of the how the device works in that the target pressure at

[1]Jon O Nilsestuen is Professor Emeritus at the University of Texas Medical Branch at Galveston, and is a consultant to Philips. [2]David Troxell is a Senior Global Product Manager for Sleep & Respiratory Care, Philips. [3]Rob Chase is a Clinical Manager Home Ventilation, Sleep & Respiratory Care, Philips UK & Ireland.

Figure 1. Titration of MI-E pressure settings to prevent upper airway collapse.



Adjusting Negative Pressure. The graphic illustrates the result of adjusting the pressure settings on a bulbar ALS subject that was experiencing upper airway collapse during expiration. The collapse is indicated by the thick red arrow in the left-hand panel; the thin black arrow is the gas decompression spike. On the right-hand panel, after increasing the target pressure from 30 to 40 cmH2O to support positive lung recoil and reducing the magnitude of the negative pressure from -35 to -20 cmH2O the collapse was alleviated, and the peak expiratory flow increased to almost 300 L/min.

end inspiration only lasts for a fleeting moment as lung recoil declines when the device transitions from the inspiratory phase to the expiratory phase (a function of the time constant); whereas the negative pressure is applied continuously during the expiratory time.

In contrast to a rigid airway, the natural upper airway is not protected from the forces imposed by negative pressure. As such, the application of greater negative pressure could result in narrowing of the airway, and frequently, in complete collapse of the upper airway.

The evidence supporting that the upper airway collapses when exposed to increasing amounts of negative pressure is strongly reinforced by several different scientific approaches. These include both clinical studies in OSA and non-OSA subjects, in neuromuscular patients using very diverse approaches, clinical studies reporting data from ALS and bulbar type patients, our own clinical evidence in bulbar subjects (presented at the 2017 ALS/MND Conference in Boston), and our own bench study using a collapsible upper airway model. These different approaches are outlined below in steps 1 through 5.

1. **Upper Airway Collapsibility in Healthy Subjects, OSA, and NMD**
   Passive Pharyngeal Critical Closing Pressure (Pcrit) testing in healthy versus OSA subjects: The pharyngeal critical closing pressure (Pcrit) testing methodology has established that a relatively low amount of negative pressure (≤ -5cmH_2O) can collapse an airway in healthy, non-OSA subjects with normal upper airway anatomy.[4]

   Upper Airway Collapse in Neuromuscular Disease and Healthy Subjects: Airway collapse is a critical concept and provides the foundation for this correspondence, it is worth reinforcing that several scientific articles have noted the relative ease with which the upper airway collapses even in normal subjects when exposed to negative pressure.[6,7,8,9,10] This tendency for upper airway collapse is further accentuated in Bulbar Type ALS patients. In these patients the loss or upper airway control predisposes the airway to collapse and renders MI-E therapy much less effective.[11,12,13,14]

Pharyngeal Airway Anatomy

The pharyngeal airway is largely unsupported by rigid (bony) structures making it inherently susceptible to collapse with even the negative pressure generated during inspiration. Upper airway dilation is a protective mechanism that is associated with a number of muscles that surround the pharyngeal airway and influence its patency, the largest being the genioglossal muscle. Genioglossal muscle activity increases during inspiration whereas genioglossal activity drops during expiration. The drop in genioglossal muscle activity during expiration alone exacerbates the risk for upper airway closure.[5]

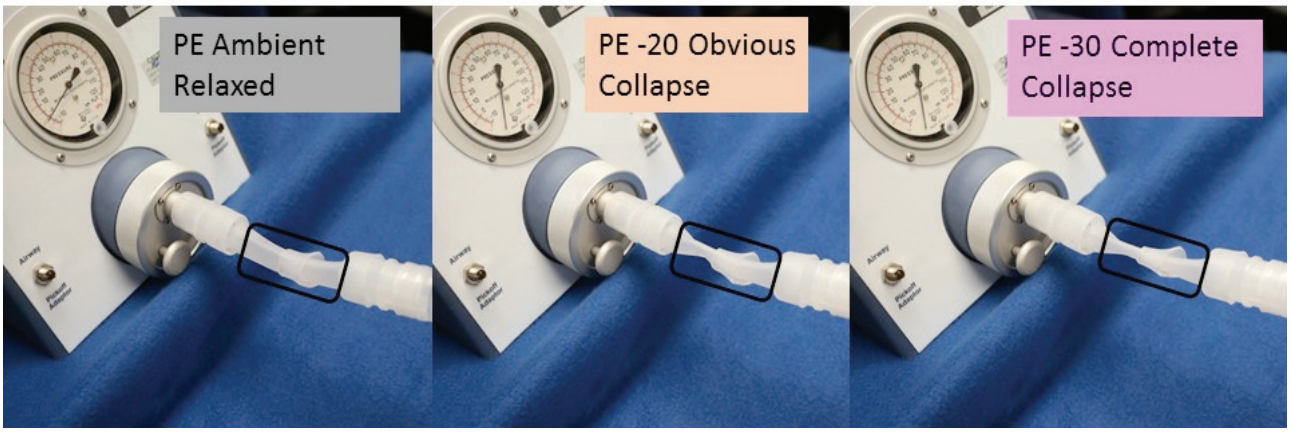
2. **Imaging: Videography using Trans-nasal Fiber-optic Laryngoscopy**
   Application of negative pressure results in airway narrowing in both normal subjects[6,7] and ALS patients.[7] Hypopharyngeal constriction during exsufflation was observed in all subjects both healthy controls and ALS subjects, and occurred most prominently in subjects with bulbar symptoms.[7]

3. **Imaging: Computed Tomography**
   CT Scans in bulbar patients showing the collapsed upper airway when exposed to negative pressure. Sancho.[14]

4. **Using a Spirometric Device to Measure Flow-Volume Loops**
   This recent study was performed by adding an in-line spirometer to the cough assist circuit. The results confirmed that expiratory collapse occurs in bulbar subjects when using MI-E with negative pressure settings.[15]

5. **Flow and Pressure Graphic Curves**
   Flow and Pressure waveforms that can be downloaded from the CoughAssist 70-series platform and viewed using DirectView software (Philips). The upper airway collapse can be prevented by using a proprietary titration protocol that includes a step-wise approach to reduce the magnitude of the negative pressure until the airway no-longer collapses along with other potential settings modifications (see Figure 1).

Figure 2. Flexible airway collapse when exposed to negative pressure.



Progression of airway narrowing and eventual collapse when applying negative pressure to flexible airway. The bench model used was an Adult Michigan Instruments Training Test Lung (TTL). A flexible upper airway was created using a section of the Philips DreamWear® interface. CoughAssist settings included a target inspiratory pressure set at 40 cmH2O, flow set to medium; TI set to 2 seconds, TE set to 2 seconds, target expiratory pressure in sequence: O cmH2O, -20 cmH2O, -30 cmH2O.

6. Our own Bench Model

Bench level studies using a Michigan Instruments adult test lung and a collapsible upper airway created by using a flexible tubing section taken from the Philips Dream Wear headset. Results: in every case where the asymmetrical pressures were flipped so the inspiratory pressure was greater than the expiratory pressure the PCF improved significantly. When using the asymmetrical pressure settings the airway narrows as a result of the negative pressure and the PCF is reduced. This collapse can also be seen visually during the test procedure (see Figure 2).

Our findings from the bench model indicate that in every combination of positive and negative pressures from +20 to +50, and -20 to -50 (tested in increments of 10 cmH_2O); that whenever the negative pressures are greater in magnitude than the positive pressures -asymmetric pressure settings (eg +20/-30 or +30/-40 see Figure 3) that the resulting PCF is less than the corresponding opposite pair.

For example:

- PCF for +20/-30 is less that the opposite pair +30/-20
- PCF for +30/-40 is less than the opposite +40/-30
- The pressure difference (PI -PE) or magnitude of the driving pressure in each of the example pairs is the same

We postulate that the lower flows obtained by the asymmetric pressure combinations (see Figure 4) are a result of the influence that greater negative pressure has in narrowing the collapsible airway which in essence creates high expiratory resistance to flow or even completely collapsing the airway during exhalation.

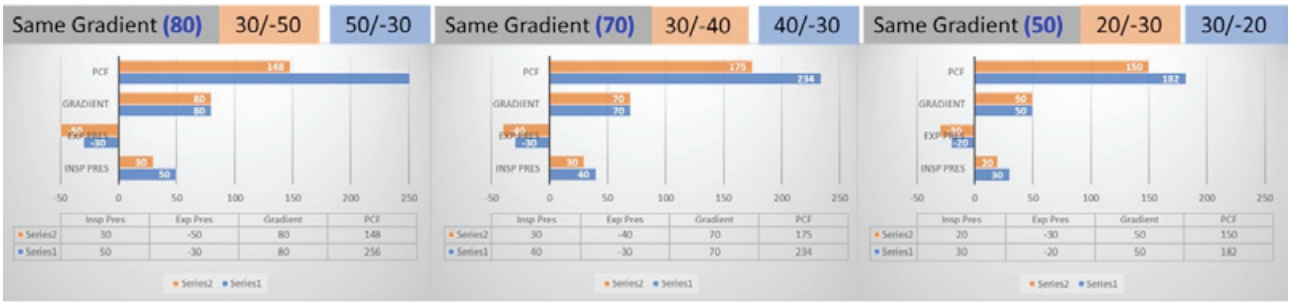
The bench study also supports our CoughAssist graphic findings (noted in Figure 1) that indicate if we maximize the inspiratory positive pressure on bulbar subjects and then titrate the negative pressure towards ambient in stepwise increments, that the luminal pressure in the upper airway at some point moves towards a positive value and the collapse is prevented. This is also supported by studies in bulbar subjects in which a timed abdominal thrust at the beginning of exsufflation creates positive luminal pressure and reduces exsufflation airway narrowing or collapse and improved peak expiratory flow.[16]

The fact that multiple studies using widely different techniques all support the same finding; namely that negative pressure causes upper airway narrowing and collapse provides the strongest possible scientific validation.

Conclusion

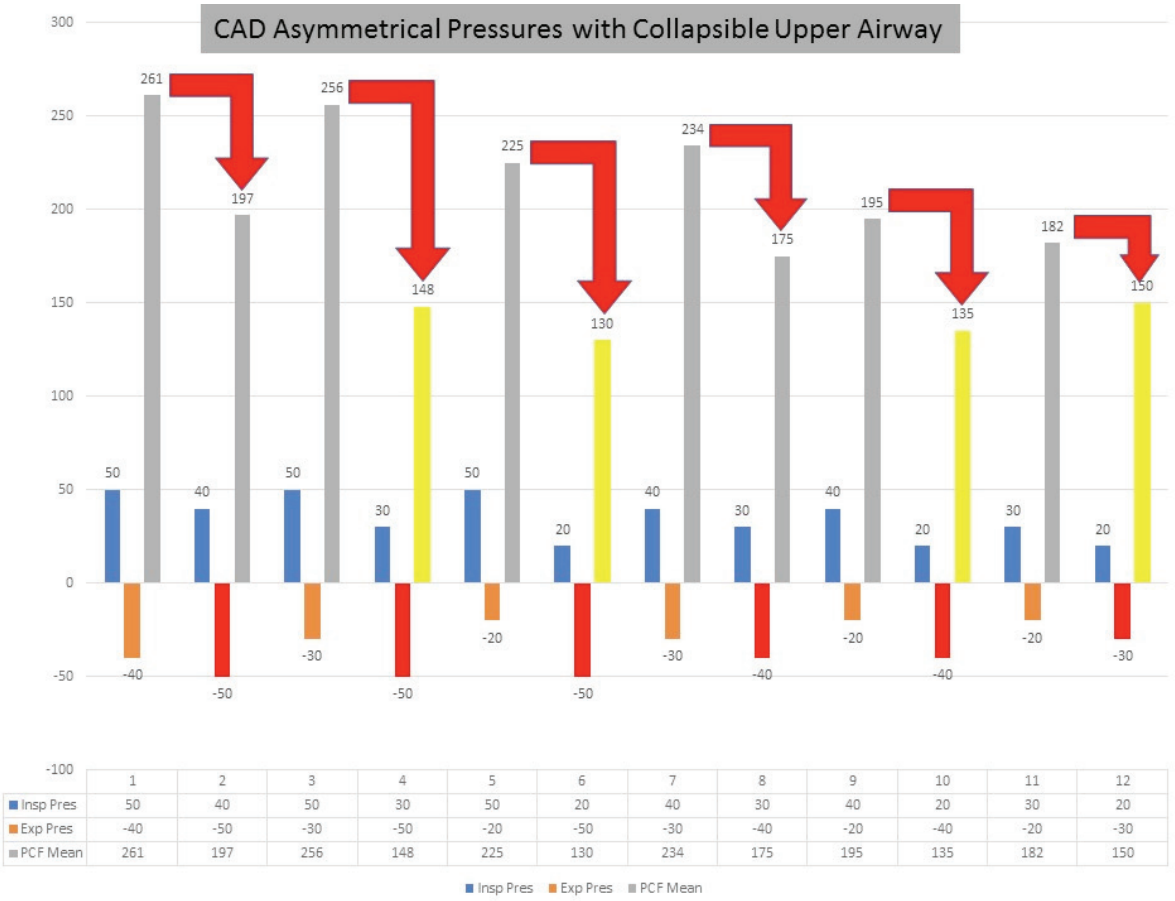
Based on the available evidence it would be an oversight to generalize that all patients receiving assistance with clearance from a MI-E device should use pressure settings with larger

Figure 3. Sample PCF data using different asymmetrical pressures.



Bar charts representing mean PCF data from 20 sequential breaths. Orange bars show data when larger negative pressure is used, and blue bars indicate data resulting from the matched reversed settings with larger inspiratory pressure than expiratory pressure. All three matched pairs of data have the same driving pressure or gradient from peak inspiratory pressure to the negative pressure setting. The three bar charts in sequence representing a gradient of 80 cmH2O, a gradient of 70 cmH2O, and a gradient of 50 cmH2O.

Figure 4. Composite PCF data from six pairs of matched asymmetrical pressures.



Mean PCF data from six pairs of asymmetrical pressure settings. Each asymmetrical pair is represented in sequence by the: Blue Bar = Target Insp Pressure setting, followed by the orange or red bar = negative pressure setting, followed by the grey bar with the resulting mean PCF. Note that for every matched pair when the greater pressure is set on the negative phase of the CAD that the resulting PCF is less; This drop in PCF as a result of the larger negative pressure setting is indicated by the Red arrows. Also in four of the matched pairs when the negative pressure was greater than the positive press the resulting PCF was less than the 160 L/min reported as the minimum to support clearance. In the graphic above the yellow bars are PCF values below the 160 threshold for clearance. It is interesting that the Settings of PI=20, PE=-50 a difference of 70 cmH2O and the subsequent pair of PI=+30, PE=-40 also a difference of 70 cmH20 produced a different result. When there was greater negative pressure (PE=-50 vs PE=-40) the PCF was less suggesting that even though the driving pressure was the same the large negative pressure caused greater narrowing or collapse of the airway model.

negative pressures. While that recommendation may be relevant for patients with rigid airways (tracheostomy or endotracheal tubes), multiple research techniques (noted above) support that this may not be the best approach when dealing with the majority of neuromuscular patients that use the MI-E with a mask interface. The asymmetrical settings approach to negative pressure would seem to be especially contraindicated for those patients (Bulbar Type ALS patients) who have upper airways that are highly susceptible to collapse and have lost the ability to close their glottis when attempting to cough.

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Evaluation of Precision Performance on the GEM® Premier™ 5000 System at CHR de la Citadelle (Belgium)

A Randazzo, J De Marchin, and J Cervera

Abstract

The GEM Premier 5000 is a new blood gas analyzer for rapid analysis of heparinized, whole blood samples at the point of care or in a central laboratory. This analyzer contains a single, multi-use cartridge PAK to provide quantitative measurements of pH, *p*CO2, *p*O2, sodium, potassium, chloride, ionized calcium, glucose, lactate, hematocrit, total bilirubin and CO-Oximetry (tHb, O_2Hb, COHb, MetHb, HHb, sO_2) parameters. These measurements (and derived parameters) aid in the diagnosis of a patient's acid/base status, electrolyte and metabolite balance and oxygen delivery capacity.

Introduction

Clinical performance of the GEM Premier 5000 system was evaluated at the CHR Citadelle Hospital. Analytical performance was compared, in the clinical environment, to three blood gas analyzers from different manufacturers: the GEM Premier 4000 (IL), ABL 90 (Radiometer) and RapidPoint 405 (Siemens).

Method comparison and regression analysis was performed for each reference analyzer, according to Clinical Laboratory Standards Institute (CLSI) EP09- A3**.**

Methods and Materials

Whole Blood Method Comparison: De-identified whole blood samples from different clinical locations at CHR Citadelle Hospital were analyzed on the GEM Premier 5000, GEM Premier 4000, ABL 90 and RapidPoint 405 analyzers. Regression results (slope, intercept, mean bias and regression coefficients) are summarized in Table 1. For the analytes where a regression evaluation was not possible due to the limited sample range acquired during the study, the 95% confident interval of the bias results was calculated (COHb and MetHb). Results for some parameters are not included if they were not available in the system menu (hematocrit for ABL 90 and hematocrit and lactate for RapidPoint 405) or if analytes were disabled by the system quality process (calcium and CO-Oximetry on RapidPoint 405).

Conclusions

The GEM Premier 5000 system demonstrated good performance versus other blood gas analyzers selected in this evaluation. Methodology differences between analyzers is attributed to the subtle differences observed between analyzers for some analytes, but should not impact clinical treatment.

A Randazzo and J De Marchin, CHR de la Citadelle, Liège, Belgium and J Cervera, Instrumentation Laboratory (IL), Bedford, MA. Presented at the 69th American Association for Clinical Chemistry (AACC) Annual Scientific Meeting and Clinical, Lab Expo, July 30th – August 3rd, 2017, San Diego, CA, USA.

Table 1. GEM Premier 5000 results from method comparison regression vs reference analyzers

Analyte	GEM Premier 4000					ABL 90					RapidPoint 405				
	N	Slope	Interc.	R	Mean Bias	N	Slope	Interc.	R	Mean Bias	N	Slope	Interc.	R	Mean Bias
pH	177	0.979	0.159	0.98	0.006	194	1.06	-0.445	0.98	0	115	1.039	-0.273	0.97	0.016
pCO_2 (mmHg)	177	1	2	0.98	1.2	194	1.053	0	0.98	2.5	115	0.909	5.545	0.95	1.5
pO_2 (mmHg)	177	0.991	5.319	1	3	194	0.998	4.233	1	4.8	114	0.932	2.737	0.99	12.3
Sodium (mmol/L)	176	1.014	-1.506	0.98	0.3	194	0.911	9.938	0.98	-2.4	114	0.964	4.678	0.94	-0.6
Potassium (mmol/L)	176	1	0.1	1	0.12	194	1.125	-0.362	0.99	0.12	114	1.111	-0.367	1	0.03
Calcium (mmol/L)	176	1.059	-0.058	0.98	0.002	194	1	0.01	0.99	0.013	Results not provided				
Chloride (mmol/L)	176	1	0	0.99	0	194	0.909	11	0.97	1.8	114	1	2	0.98	2.2
Glucose (mg/dL)	176	1.036	1.643	1	4.8	194	1.06	-3.28	0.99	4.5	114	1.021	0.297	1	-0.5
Lactate (mmol/L)	176	1	0	1	-0.04	194	1	-0.1	0.99	-0.16	Results not provided				
Hematocrit (%)	176	1.014	0.389	0.98	1	Results not provided					Results not provided				
tHb, g/dL	174	1.035	-0.096	1	0.37	193	1.013	0.022	0.99	0.21	Results not provided				
O_2Hb (%)	174	1.001	0.617	1	0.09	193	0.951	5.896	1	2.42					
COHb (%)*	174		1.03		0.29	193		1.23		0.68					
MetHb (%)*	174		0.68		-0.16	193		0.71		-0.23					
HHb (%)	174	1.003	-0.907	1	-0.23	193	0.964	-1.8	1	-2.89					
sO_2 (%)	174	1.003	0.626	1	0.19	193	0.962	5.559	1	2.93					

*95% confident interval of the bias

An Exploration of Bronchiectasis and Airway Clearance Therapy (ACT)

NTM Info & Research survey results reveal patient and physician behaviors related to ACT

Submitted by NTM Info & Research

Airway clearance therapy (ACT) for bronchiectasis patients is considered a cornerstone of therapy; however, there are challenges that make adoption difficult. These include knowledge of ACT options for physicians and patients, as well as patients' behavioral characteristics. This paper explores bronchiectasis, its prevalence and relationship to COPD, along with the results of a survey, uncovering patient and physician practices. Its purpose is to gain an understanding of the underlying factors affecting patients with bronchiectasis and to determine the present nature of and future recommendations for care plans.

Understanding Bronchiectasis

Bronchiectasis is an irreversible lung condition characterized by permanently dilated, enlarged bronchial airways with thick walls and scarring that cause mucus-clearing impairment. The disease can manifest early or late in life, sometimes in the wake of a significant respiratory infection, or inhalation of a foreign object or food particles.[1] It can also be present in patients with other chronic conditions, including autoimmune disorders, cystic fibrosis and inflammatory diseases. Most often, patients have other respiratory conditions, such as asthma and chronic obstruction pulmonary disorder (COPD). Patients with bronchiectasis experience symptoms ranging from a daily cough, fatigue and weight loss to coughing up thick mucus and blood.[2] The illness is progressive and, over time, generally impairs abilities and worsens quality of life.

Determining Prevalence

One of the most common respiratory diseases, bronchiectasis affects an estimated 340,000 to 522,000 US adults with 70,000 new patients diagnosed annually.[3] While diagnostic solutions exist for determining the presence of bronchiectasis—including blood tests, CT scan or chest X-ray, and/or a sputum test[4]—medical experts believe it often remains underdiagnosed.[5,6] One reason for this is that bronchiectasis is often mistaken for other respiratory ailments, including asthma, bronchitis, recurring pneumonia and COPD.[6,7] Awareness of the clinical presentation of bronchiectasis and its causes are a vital part of timely diagnosis and treatment.[7]

Managing Bronchiectasis

Treatment of bronchiectasis focuses on managing symptoms, improving respiratory function, avoiding exacerbations and elevating quality of life.[8] Oral antibiotics are most often administered to help manage this incurable illness, but intravenous antibiotics are sometimes prescribed for infections that are particularly difficult to treat.[9] Other treatments may include prescriptions for expectorants and corticosteroids, oxygen therapy and airway clearance therapy (ACT)[9]; the latter includes chest physical therapy and high frequency chest wall oscillation (HFCWO).

Exploring the Bronchiectasis-COPD Connection

Bronchiectasis and COPD are two very different conditions, although they are sometimes confused. Bronchiectasis does not cause COPD; however, patients with COPD can develop bronchiectasis. Studies indicate that the prevalence of bronchiectasis in COPD patients is as high as 42%.[10] Further, while researchers saw bronchiectasis present at all stages of COPD, its presence grew in frequency in more severe cases of COPD.

Gaining Insight into Patient Diagnosis and Treatment Practices: NTM Info & Research (NTMir) Survey

To obtain a more detailed understanding of airway clearance therapy as a part of a care plan, NTMir surveyed 691 patients through the Individual Management of Patient Airway Clearance Therapy (IMPACT) assessment. The IMPACT assessment was formatted into an online survey using a HIPAA- and GDPR-compliant tool. The survey rollout, using multiple online media channels, garnered responses from two online patient communities for nontuberculous mycobacteria (NTM) and bronchiectasis over an 11-week period.

Bronchiectasis and COPD Diagnosis

With regard to diagnosis, 64% of patients reported a diagnosis of bronchiectasis, while 30% stated they have COPD. Given that 42% of COPD patients could have undetected bronchiectasis, it is possible that 64% is a low figure, with the actual number of patients with bronchiectasis potentially as high as 80%.

NTM Info & Research (NTMir) is a 501(c)(3) non-profit patient advocacy organization formed on behalf of patients with pulmonary nontuberculous mycobacterial (NTM) disease, a chronic lung infection, and related comorbid conditions including bronchiectasis. NTM Info & Research is focused on patient support, medical education and accelerating research. International Biophysics Corporation is a medical device manufacturer developing innovative and disruptive technologies for over 25 years. The company is focused on offering patients better outcomes through educational programs and improved treatment therapies. International Biophysics manufactures AffloVest®, the first mobile mechanical oscillation therapy.

ACT Treatment

ACT was recommended for 62% of the patients by their physicians. For 31% of the patients, their physicians recommended ACT within the first month of their diagnosis. Of the 62% of patients engaged in some form of ACT, 21% were using HFCWO.

ACT Compliance

Compliance with ACT was limited among respondents. ACT was believed to be an important part of their care routine for 74% of patients, who added that they believe it makes them healthier. Sixty percent of patients reported engaging in ACT daily, but 26% said they do not. Twenty-nine percent answered that they do not do the recommended treatment twice a day, and half admitted they do not actively perform ACT when traveling. Overall, 27% cited being dissatisfied with their current ACT routine.

ACT Barriers

For many, there were barriers to ACT engagement. For 36%, ACT disrupts daily life. Noise, portability for work and/or travel and feeling ill with treatment were given as other reasons for noncompliance. Forty-one percent said ACT is too time-consuming.

Discussion

Based on the survey results, it is evident that bronchiectasis is a prevalent condition among this representative patient population, and, considering data from other clinical studies, may be underrepresented. While many physicians are recommending ACT, 38% still are not engaging their patients in a therapy deemed valuable based on evidence.[11] Studies show that early ACT can help,[11] yet only 31% of physicians are recommending it within the first month of diagnosis.

In an environment of proactive, preventative healthcare, there is an opportunity to engage bronchiectasis patients in a care plan that may help manage symptoms and improve their overall quality of life. Although there are barriers to compliance, all patients engaged in some form of ACT when it was recommended by their physicians. In addition, patients believed ACT was an important component in helping them to feel better.

It is true, however, that patients might be short-changing themselves in the benefits they could receive by not fully complying with their physician's instructions or finding an ACT option that helps them overcome their barriers.

Recommendations

There is opportunity to educate patients and convey to physicians the information needed to support more active engagement in ACT. Some ACT options involve less noise and less cleaning and allow for portability, while offering gentle treatment that won't exacerbate symptoms. Further investigation is needed to understand patient and physician practices and learn how best to inform both populations of the benefits of ACT and the options available. By this, the healthcare community can support both patient and physician needs and drive greater compliance for improved health benefits.

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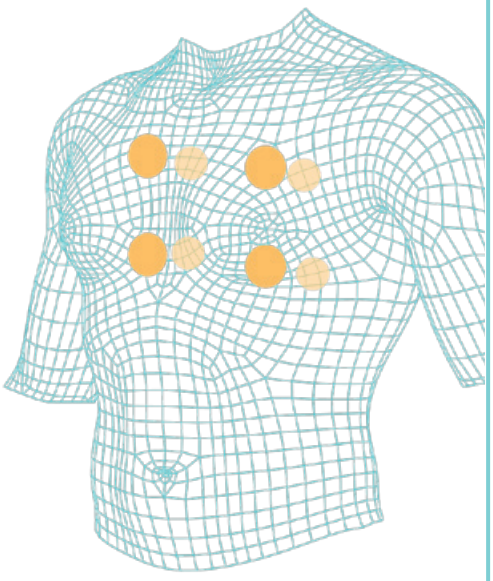

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Above Cuff Vocalisation (ACV)

ACV can enable tracheostomised patients to speak.

Mette From, Kathrine Eggertsen, Rita Halkjær Rasmussen, Karen Schmøkel

Tracheotomised, ventilated patients have difficulty communicating, but thanks to a special method it is possible, for patients to speak to relatives and staff, motivating them for rehabilitation.

Abstract

ACV can enable tracheostomised patients to speak

Being able to talk with people is a fundamental need. When someone is tracheotomised and ventilated, he is deprived of this capacity. For many years, the intensive care unit in Silkeborg, Denmark has had ventilated but conscious patients and the problem of achieving dignified communication. Since 2008, this ICU has served as a national care centre for neurointensive patients from all over Denmark. The object of a stay at this ICU centre is, in addition to early highly specialised neurorehabilitation in close collaboration with the Hammel Neurocenter, also weaning from ventilation. In addition, the centre provides swallowing training. One of the methods is ACV — Above Cuff Vocalisation.

The method trains the laryngeal muscles and additionally enables the patient to speak. The method was described as early as in 1975, but it is our impression that it is not widely used in Denmark.

The procedure has been implemented in the unit and is used for many patients. In this article, the focus is on verbal communication as a core aspect of delivering nursing to medical patients and patients with Guillain-Barré syndrome. Communication by means of ACV has made a great difference for many patients and relatives.

Keywords: Guillan-Barré syndrome, GBS Communication, patient involvement, rehabilitation, respirator treatment, tracheostomy

Mette From – Clinical development nurse, nurse 1979, ICU training 1988, anaesthesiology training 1998, Health Business Manager, clinical training, 2005, Human Health Sciences 2008, ICU, Centre for Scheduled Surgery, Silkeborg Regional Hospital, Regional Hospital Central Jutland. mette.from@midt.rm.dk. Kathrine Eggertsen – Nurse RN, ICU specialist training, ICU, Centre for Scheduled Surgery, Silkeborg Regional Hospital. Regional Hospital Central Jutland. Rita Halkjær Rasmussen – Nurse RN, ICU specialist training, ICU, Centre for Scheduled Surgery, Silkeborg Regional Hospital. Regional Hospital Central Jutland. Karen Schmøkel – Nurse 2007, MSC in Nursing/Clinical Nursing 2012, Head of the research unit at the Centre for Scheduled Surgery, Silkeborg Regional Hospital, Regional Hospital Central Jutland.

The ACV method

Since 2011 the intensive care unit in Silkeborg has been using a special tracheostomy tube with an extra tube for suctioning secretions above the cuff. Via the same tube it is possible to introduce air above the cuff , the ACV method. The procedure serves to stimulate the patient's respiratory tract and contributes to a rehabilitation of the throat muscles, but is also having the side effect of enabling the patient to speak; as air crossing the vocal cords allows sounds to be made. A study from 2013 also shows that ACV significantly reduces the incidence of ventilator-associated pneumonia.[13]

While there are several important reasons for being aware of and using ACV, the purpose of this article is to focus on dignified and considerate communication between the intensive care patient, their relatives and the nursing staff, providing the best possible nursing care for seriously ill patients who are temporarily prevented from speaking.

Every year, the intensive care unit at Silkeborg Regional Hospital, Regional Hospital Central Jutland, receives 25–35 intensive care patients with respiratory insufficiency who therefore require a tracheostomy tube and ventilation. The causes are primarily pneumonia and COPD in exacerbation, or may be part of an impairment of their general health. Although patients receive painkillers as needed, they are often awake for extended periods during which the possibility of communication is given.

As a highly specialised neurointensive care unit, we receive patients once the first acute, critical period after their cerebral trauma or haemorrhage has passed.

Patients can start a highly specialised neurorehabilitation with us while they remain dependent on ventilation and other forms of intensive care. This is a service that is not available in the highly specialised intensive care units. We also receive neurological patients on respirators, patients diagnosed with acute autoimmune polyneuropathy, Guillain-Barré. This illness can affect persons of any age, but we currently have several younger individuals at the unit who have been severely affected by the long-term illness pathway. The patients are often tracheotomised as a result of respiratory muscle palsy and are therefore unable to communicate verbally with the outside world.

For the vast majority of patients, respiratory therapy is associated with some degree of discomfort, stress and anxiety.

Suffering from serious illness and being unable to communicate adequately with relatives, nurses and doctors is very stressful and can reduce the motivation to participate in rehabilitation.[8]

Equal communication requires patient influence over their own care pathway

Being able to talk with people is a fundamental need.[1] Virginia Henderson identified 14 basic needs. Number 10 concerns communication and highlights the ability and opportunities to express emotions, needs, fears or opinions and thereby be able to have meaningful contact with others.

A study shows that people typically spend 61 per cent of their waking hours communicating,[2] an opportunity which critically ill and intubated individuals are often denied. Kari Martinsen writes that patients ought to be treated so that they feel acknowledged and capable of managing their own affairs. Critically ill individuals may feel that they are losing their autonomy and privacy if they do not have a sense of control over their situation.[1] This is why, as far as possible, patients must be involved in, feel in control of and be able to influence their own care pathway. These are indicators that contribute to equality in communication.

With regard to basic nursing, Australian Professor of Nursing Alison Kitson says:

> "Nurses must be able to meet basic human needs including communication based on a psychosocial and relational understanding of the patient's experiences and needs. Care can only be said to be patient-centred if this is the case".[5]

As nurses, we are very mindful of informing patients about every step we would like to take. But if the patient is unable to ask a question, how can we be sure that the information has been understood or that they do not have other questions that need to be answered?

Moreover, the nurse often only provides information about everyday procedures. The patient might also have important and more complex questions relating to their prognosis, fears about the future and concerns for their family.

Fear of dying

An observational study from 2011 followed a patient who was affected by Guillain-Barré syndrome in 2002. The patient talks about the severity of his illness and inability to communicate:

> "I was in bed on a respirator behind a curtain in a two-bed room in the intensive care unit. I couldn't communicate with anyone but heard everything that was going on as if it were a play on the radio. To the extent that seven of my fellow patients on the other side of the curtain died during that period. I was very, very scared. I was sure, I was going to die too".[3]

Another patient, who was severely injured in a traffic accident in 2000, has written about being tracheotomised and incapable of asking and thereby receiving answers to important questions:

> "I still don't understand why the staff never tried to explain to me what had happened, what was wrong with me and why they were treating me the way they were. I think I could have been spared a lot of subsequent psychological distress".[4]

Multi-faceted communication

These two patient quotes illustrate that communication with a critically ill person can have many facets, from providing information on everyday procedures and the outside world to answering questions about life and death. When Kitson says that the nurse must communicate according to the patient's basic needs, the dialogue is important.

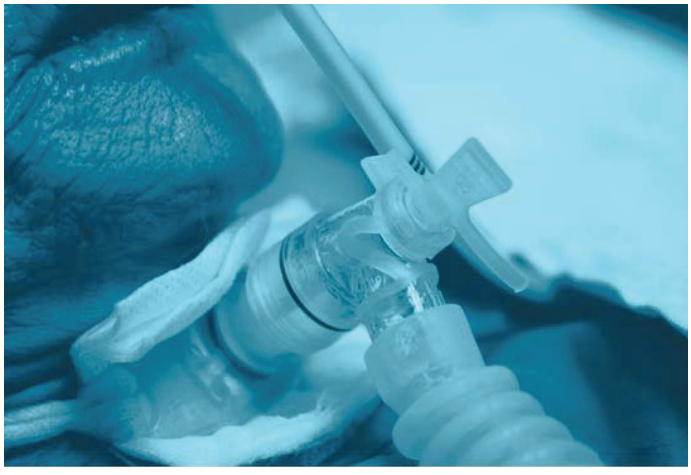
Inadequate answers to questions about the nature of the illness and its prognosis, and not being able to express pain and other discomfort, may contribute to the development of intensive care delirium. This is an extremely unpleasant condition for the patient and very costly for society, and can mean prolonging the stay in both the intensive care unit and main hospital ward.[6]

It is therefore important that the nurse helps the patient communicate and thus explain both basic and more complex needs during the illness pathway. As healthcare professionals, we have a duty to ensure the patient's well-being and to help reduce the risk of complications in the illness pathway and the development of late sequelae. Part of the fundamental nursing process is to make sure that the patient can speak if possible, thereby minimising anxiety and stress.[7]

ACV makes all the difference

Tove's story

Tove was a 65-year-old patient with severe pulmonary disease who was transferred to us from another hospital. She had been a tracheotomised inpatient there for several weeks. Tove was a very independent and active woman who was very close to her daughter and six year-old grandchild, and to her sister. They came to visit every day and it was clear that their visits had a very positive impact on Tove. We began ACV shortly after her admission to our unit. Tove was able to communicate in writing, but once again being able to communicate verbally made a big difference to her, especially in relation to her grandchild. Their time together became more varied, intense and lively. She was more "her old self" when her grandchild visited, during which time they could talk about small everyday events. Tove was also better able to participate in planning her care and the decisions to be made during the day, which she greatly appreciated. She was also very clear in her decision to refuse resuscitation in event of possible cardiac arrest and respirator therapy. It was important for her sister to be sure that this was Tove's choice.



Anna's story

Anna, a 20-year-old woman, was transferred to us with the diagnosis of Guillain–Barré. Anna was referd to Hammel Neurocenter, and the purpose of her stay was early highly specialised neurorehabilitation. As Anna was severely affected by the disease, tracheotomised and ventilated, she was admitted to the Intensive care unit at Silkeborg for weaning from ventilation. When Anna arrived at the unit, her tube was switched to a Tracheostomy tube with subglottic line in order to monitor secretions above the cuff and to enable her pharyngeal muscles to rehabilitate. ACV was started, partly for swallowing training and partly to enable Anna to communicate verbally. Up to this point, she had used lip reading and a spelling board. Her mother had acted as an interpreter as she was very good at lip reading her daughter. However, Anna quickly became frustrated when we were unable to understand her. When she arrived at the unit, she was in the midst of a severe crisis. But once she was able to start communicating normally with the outside world, the condition became easier for her to endure. Her care and training became smoother as she felt she was being heard, and she participated in her rehabilitation with more and more enthusiasm. She was now also able to see the funny side of her situation during training. There were jokes, laughs and stories, which had not been possible before, but are normal for 20-year-olds. But what made the biggest difference to her was that she was now able to use FaceTime with family and friends in Zealand when they were not with her. Being able to talk to them every day was a very positive change for her and for the family and staff around her. There was a completely different atmosphere in the room.

Application of the ACV method:

- Inform the patient about what is going to happen. The patient's cooperation is important, and the procedure is orientated towards the individual patient
- Suction secretion above the cuff through the subglottic tube
- A ACV tube with Y-piece/fingertip is attached to the subglottic tube.
- Insufflate air via the subglottic tube. Start the flow with 1 litre (atmospheric air) and then slowly increase. See how the patient responds. Reduce the flow if the patient feels severe discomfort, or feels nauseous. The higher the flow, the drier the mucosa in the throat become. The air is kept on for approximately five minutes. Use the Y-piece/ fingertip to give the patient air in small quantities. Monitor the patient's breathing, give air on expiration and pause when the patient swallows. In some cases, the patient and/or relatives can be trained to manage the process themselves.

ACV is not difficult. The method requires very little training, but care must be taken to monitor the patient's reaction. The cooperation between patient and nurse is very important. A high flow of dry air can be uncomfortable for the patient and cause the mucosa to dry. The recommended maximum flow rate is 5 l/min, although the nurse's experience and the cooperation with the patient are crucial for assessing flow and length of treatment.[9]

Development of emphysema as a result of a displaced tracheal tube has been mentioned in the literature, but has not been seen in our unit.

Treatment with ACV is also used in the rehabilitation of neurological patients with dysphagia. The aim is to stimulate the throat muscles, thereby training the patient's ability to swallow.[10]

Grateful patients

Based on a number of patient care pathways completed since 2011, our experience is that patients using ACV derive great satisfaction from being able to be participate in their own care pathway. Patients express considerable gratitude at being heard and understood when it comes to daily tasks and having the opportunity to discuss crucial decisions about their treatment and future.[11]

We encounter many different care pathways, and the ACV treatment requires a little getting used to, but the patients express their joy at being able to speak. However, one patient says that the air tastes foul, so perhaps in the future a solution might be found in the form of flavouring. This is an area that is being worked upon. A number of patients are bothered by the dry air, and here too we are working to find a solution whereby the air can be moistened.

Not all patients benefit from ACV, as older and severely impaired patients, in particular, may have difficulty cooperating and summoning up the energy for the procedure. Units that do not use tracheostomy tubes with subglottic tube justify this by citing complaints that the tube is stiff and uncomfortable for the patient. If we asked the patients themselves, they might prefer a slightly stiffer tube requiring some getting used to when the reward is being able to speak.

We encounter very few patients who are so bothered by the stiffness of the tube that they have to switch to a softer tube that does not have the subglottic tube.

Only a few ICUs in Denmark are aware of ACV

ACV is not a new treatment. The method is described in an article from 1975.[12] However, our experience is that very few intensive care units in Denmark, and perhaps also internationally, are aware of and use ACV.

We are very concerned that many seriously ill patients are denied the opportunity for dignified communication during an already very difficult period of their lives. The reason for this is unclear to us. Is it a lack of knowledge, ingrained culture or a lack of focus on communication? We do not know. One research group has observed patient–nurse communication in an intensive care unit and concluded that more than one third of patients did not experience successful pain communication.[13]

We can enable the patient to speak, but very few nurses and doctors do so, thus depriving the patient of their autonomy. This situation is both intolerable and unethical.

Students receive instruction during specialist ICU training

It is important that we investigate causes and relationships to ensure the best care and treatment for the patient. That is why we spend time teaching students undergoing specialist ICU training and training in other units. We have given presentations within our own organization, and in the future we want to teach internationally.

Our expectation is that many intensive care patients around the world will benefit from being able to communicate with relatives

and healthcare professionals. From being able to participate actively in their own care pathway and even being able to say goodbye to their family in a dignified manner if that is what they want.

We have no doubt that ACV makes a huge difference to patients and relatives, although it would be interesting to investigate how important it is to patients and relatives that their communication in connection with critical illness takes place in a dignified manner. It may also be relevant to consider how important it is for staff to be able to communicate reliably with the patient.

Perhaps it would be possible to demonstrate that the incidence of intensive care delirium decreases or that the number of bed days in the intensive care unit is reduced? Perhaps nursing these patients with a focus on communication reduces the number of patients who subsequently suffer PTSD?

The research unit at the Centre for Scheduled Surgery has been involved in communication with ACV and is currently looking into opportunities for research in the area.

From an option to standard practice

We have been using ACV for a number of years, and following a start-up period during which the treatment was an option, ACV is now offered to patients as standard practice. The method requires very little nurse training and takes little getting used to for the patient, but once again being able to speak is clearly of great importance to the patient. Motivation to participate actively in treatment, care and rehabilitation is significantly increased, which is why ACV is a natural part of the treatment we provide.

Debate

- How can you ensure that the tracheostomised patient is involved in their care pathway?
- What challenges do you face in your unit when communicating with the critically ill, tracheostomised patient?
- If you have follow-up conversations with patients, how have they found the communication during the care pathway?

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Intensive Care Unit, Silkeborg Regional Hospital

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Clinical Findings Associated with the Use of Combining Three Different Airway Devices

An Effort to Reduce Ventilator Associated Events 'VAE', Length of Stay on the Ventilator, and Reducing Cost in an ICU

John H Riggs, PhD, RCP, FAARC

Abstract

Background: In previous years we have attempted to reduce the number of ventilator associated pneumonia's, VAP's and now more currently, ventilator associated events, VAE's With the goal of improving patient outcomes. This has been accomplished by improving the methods of mechanical ventilation, using lower tidal volumes, lower pressure limits, and sedation timeouts. While also, addressing the patient themselves. Maintaining body position, like the head of the bed being elevated, oral care, every 2 to 4 hours, pretreating gastrointestinal issues, in order to reduce stress ulcers and possible aspiration, suctioning only when needed and reducing the risk possibility of infections.

While we improved the issues of mechanical ventilation and bettered managed patient care. One area of concern that had not been addressed was the connection of the patient to the ventilator.

Recent articles in Respiratory Care, identified variations in the methods of measuring as well as the volumes in endotracheal tube cuff pressures. We decided to focus on this bridge between mechanical ventilation and the patient's using three different devices.

The first device used is called, SonarMed, AirWave. It uses sound waves as a method of showing ET tube movement, ET tube obstruction and can also show changes in Trachea Size. After initial intubation a chest X-ray was obtained and the ET tube position was measured from the distance of the Carina to the tip of the tube. This information is entered into the SonarMed to zero for tube placement. Changing of the patient's head position or Patient movement was shown to move the ET tube as much as 4.5 cm in some cases, something I had not seen before. These changes in real time help to reduce inappropriate or sub optimal tube placement, as well as, tubes moving into the right main stem or self extubation, above the cords. Another advantage of SonarMed is that it shows airway obstructions. It can be something as simple as the ET tube being tapped too tight or the patient biting the tube. Even something more severe, like the internal diameter being occluded with secretions or blood. In the past, occlusions were seen by changes in ventilator pressures and reduce volumes. With SonarMed these were seen before major increases in ventilator pressures were noted. When sonar med indicated an obstruction, we would suction the patient through a closed suction system. But we noticed the obstruction was still noted on the device. What we discovered was that closed suction catheters do not clean the sidewall of the endotracheal tube. Think of it's like a doughnut. The suction catheter can only clear the center of the ET tube and not the sidewall. The third area that sonar med does address is that of tracheal size, more so, the amount of pressure applied to the tracheal wall. This measurement is a good indicator if the patient is to be extubated and swelling with strider could lead to an unsuccessful extubation. In this case we could be ready to treat the Patient's airway without delay or a delayed extubation.

Methods: Having benefited from the information obtained using the SonarMed. We now can be proactive in treating these previously unknown issues. We place all patients who are intubated on the Cuff Sentry devices. These manage and monitor airway cuff pressures continuously. This reduces the possible human effect, different methods of maintaining cuff pressures. Once this was put into place, we noticed a major reduction in cuff movement on the SonarMed device. Another area that SonarMed provide information was that of airway obstruction. We introduced the EndoClear device in those Patients where SonarMed indicated possible airway obstruction. This device acts like an inflated balloon and squeegees the inside diameter of the tube. The results are remarkable. And of course the SonarMed device is placed on ventilator Patients who are on the vent greater than three days.

Results: 34 Patients were placed on SonarMed for a total of 163 days or 3516 hours. Of these we were able to reduce the total numbers of X-rays by 14%, saving $9,966. this not counting the radiologist reading fees for the 90 day trial. This reduction was due to knowing where the ETT was positioned at all times. Using the CuffSentry, we were assured that pressure inside the cuff was optimal and reduced endotracheal tube movement. We did not see any migration of the endotracheal tube into the right main stem bronchus or up through the vocal cords. We believe that this helps in reducing possibilities of aspiration. We were also able to verify with SonarMed, 30 occlusions on 11 Patients, where we had airway obstructions. Of these one patient was biting the endotracheal and one patient's tube holder was pinching the tube. The remaining occlusions were directly related to secretions and mucous plugs. Having attempted to remove these obstructions with using a standard close suction system without relief. We used EndoClear to remove mucous plugs. After which we had immediate improvement in ventilation and patient comfort.

John H Riggs is with Carolinas Hospital System, Florence, South Carolina.

Conclusions: when using these three devices, we were able to provide optimal airway management, reduce costs, reduce exposure to radiation, possible reduction in ventilator and intensive care stays. While the study did not look at ventilator associated events (VAE), during the 90 day trial we did not have a VAE. But, we did have one the month before and one the month after the month the trial.

Fluid Intake-Related Association Between Urine Output and Mortality in Acute Respiratory Distress Syndrome

Yanfei Shen, Guolong Cai, Shangzhong Chen, Caibao Hu & Jing Yan

Abstract

Background: Acute respiratory distress syndrome (ARDS), a complex response to various insults, has a high mortality rate. As pulmonary edema resulting from increased vascular permeability is a hallmark of ARDS, management of the fluid status, including the urine output (UO) and fluid intake (FI), is essential. However, the relationships between UO, FI, and mortality in ARDS remain unclear. This retrospective study aimed to investigate the interactive associations among UO, FI, and mortality in ARDS.

Methods: This was a secondary analysis of a prospective randomized controlled trial performed at 10 centers within the ARDS Network of the National Heart, Lung, and Blood Institute research network. The total UO and FI volumes within the 24-h period preceding the trial, the UO to FI ratio (UO/FI), demographic data, biochemical measurements, and other variables from 835 patients with ARDS, 539 survivors, and 296 non-survivors, were analyzed. The associations among UO, FI, the UO/FI, and mortality were assessed using a multivariable logistic regression.

Results: In all 835 patients, an increased UO was significantly associated with decreased mortality when used as a continuous variable (odds ratio [OR]: 0.98, 95% confidence interval [CI]: 0.98–0.99, $P = 0.002$) and as a quartile variable (OR of Q2 to Q4: 0.69–0.46, with Q1 as reference). To explore the interaction between UO and FI, the UO/FI was calculated, and a cut-off value of 0.5 was detected for the association with mortality. For patients with a UO/FI ≤0.5, an increased UO/FI was significantly associated with decreased mortality (OR: 0.09, 95% CI: 0.03–0.253, $P < 0.001$); this association was not significant for patients with UO/FI ratios >0.5 (OR: 1.04, 95% CI: 0.96–1.14, $P = 0.281$). A significant interaction was observed between UO and the UO/FI. The association between UO and mortality was significant in the subgroup with a UO/FI ≤0.5 (OR: 0.97, 95% CI: 0.96–0.99, $P = 0.006$), but not in the subgroup with a UO/FI >0.5.

Conclusions: The association between UO and mortality was mediated by the UO/FI status, as only patients with low UO/FI ratios benefitted from a higher UO.

Background: Acute respiratory distress syndrome (ARDS) is a complex response to pulmonary and non-pulmonary insults. This condition, which presents as severe hypoxemia and bilateral pulmonary infiltration, is associated with mortality rates of 30-40%.[1,2] As pulmonary edema resulting from increased vascular permeability is a hallmark of ARDS,[3] optimizing the fluid status is a fundamental concern in critical care practice.

Aggressive fluid resuscitation plays an important role in avoiding additional hemodynamic insults and maintaining adequate organ perfusion. However, considerable evidence indicates that a positive fluid balance (FB) may cause the extravasation of protein-rich fluids into the interstitial space and is strongly associated with poor outcomes in patients with ARDS.[4,5,6] However, most of these studies focused mainly on the absolute FB volume, which may have led to biased conclusions. For instance, hypothetical patient A (fluid intake 2000 ml, fluid output 1000 ml) and patient B (fluid intake 5000 ml, fluid output 4000 ml) might have the same absolute FB volume but very different outcomes. Therefore, a new index that could better reflect the dynamic fluid status has become clinically important.

Two intervenable parameters in fluid management, the fluid intake (FI)[7] and urine output (UO) values,[8] have been investigated. Multiple observational studies involving different cohorts have reported that an increased UO volume was independently associated with decreased mortality.[9,10] A multicenter randomized controlled trial that compared conservative and liberal fluid strategies in patients with ARDS also reported that loop diuretics were more frequently used and the UO volume was higher in the conservative fluid group.[7] In that trial, the conservative fluid strategy was associated with improved lung function and a reduced duration of mechanical ventilation. However, the correlation between UO and the outcomes of patients with ARDS remains unclear.

Furthermore, the UO volume may be easily affected by the FI volume. Therefore, a simple evaluation of the association between UO and mortality that does not adjust for FI may be inappropriate. Here, we created a new index (UO/FI ratio) to reflect the dynamic fluid status and performed this secondary analysis to investigate the interactive associations among UO, FI, and mortality in patients with ARDS.

Department of Intensive Care, Zhejiang Hospital, No. 12, Linyin Road, Hangzhou, Zhejiang 310000, People's Republic of China. YS designed the study, extracted the data, and wrote the draft of the manuscript. GC and CH performed all statistical analyses and revised the manuscript for important intellectual content. JY performed the final revisions of the manuscript. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Methods

Data source

This was a secondary analysis of a prospective RCT that was performed in 10 centers within the ARDS Network of the National Heart, Lung, and Blood Institute research network.[11] The original study was approved by the institutional review board at each study center, and informed consent was obtained from the patients or their legal guardians. All data were uploaded to the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) (https://biolincc.nhlbi.nih.gov) by the ARDS Network. The re-use of these data for a retrospective study was approved by the institutional review board at each center and by BioLINCC, and the need for consent was waived.

Inclusion and exclusion criteria

In the original study, patients under invasive mechanical ventilation support were screened if they met the following Berlin inclusion criteria:[12] an acute decrease in the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen to ≤300, the presence of bilateral pulmonary infiltrates on chest radiography images, and no clinical evidence of left atrial hypertension or a pulmonary capillary wedge pressure of ≤8 mmHg. Patients were excluded if they were aged < 18 years, were pregnant, or had other clinical conditions that could impair breathing, such as high intracranial pressure. Patients without fluid management records were also excluded.

Data extraction

The total UO and FI volumes within the 24-h period preceding the trial were recorded. Demographic data, including age, weight, height, sex, and ethnicity, and information regarding comorbidities such as diabetes, immunosuppression, and leukemia were collected. Biochemical measurements, including the white blood cell and platelet counts; serum creatinine, albumin, sodium, and bilirubin concentrations; and the plasma glucose concentration were also extracted. Other variables, such as the radiographic acute lung injury score, pneumothorax, and ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, were recorded.

Study endpoint

In the original study, patients were divided into three categories based on the following endpoints: (1) discharge with unassisted breathing, (2) death before discharge with unassisted breathing or before achieving unassisted breathing for 48 h, and (3) neither of these conditions. The patients' statuses were checked at intervals of ≤30 days until either condition 1 or 2 was met, with a maximum duration of 180 days. Patients who met condition 2 were reported as non-survivors, whereas those who met condition 1 or 3 were reported as survivors.

UO/FI ratio

The UO/FI ratio was calculated to assess the ability to excrete excessive administered fluid. The association between the UO/FI ratio and mortality was evaluated.

Missing data management

For most of the extracted variables, the proportion of missing values was < 5%, and these values were replaced by their means or medians. For albumin, the proportion of missing values was > 10%; therefore, this variable was excluded from the analysis. For dichotomous variables (diagnosis such as diabetes), missing values were replaced by default value (zero).

Statistical analysis

Continuous variables are expressed as means ± standard deviations or medians (interquartile ranges) as appropriate. Student's t-test and the Wilcoxon rank-sum test were used as appropriate. Categorical data are expressed as proportions and were compared using the chi-squared test or Fisher's exact test.

A multivariable logistic regression was used for covariate adjustment. The logistic models were built using the stepwise backward method. First, variables with *P*-values of < 0.10 in the univariate analyses were included in the multivariable analysis. Twelve covariables were identified in this step: UO, low tidal volume intervention, leukemia, solid tumor, immune suppression, body temperature, mean blood pressure, respiratory rate, hematocrit, platelet count, serum bicarbonate, radiographic acute lung injury score, and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen on day 0. Subsequently, a stepwise backward elimination method was used to remove variables with *P*-values > 0.05 (serum bicarbonate and immune suppression). Multicollinearity was assessed using the variance inflation factor method, and body temperature, hematocrit, and mean blood pressure were removed as significant variance inflation factors (≥5).

The Lowess smoothing technique was used to explore the crude relationship between the UO/FI ratio and mortality, and a cut-off value was detected. A spline linear logistic regression analysis was performed to evaluate the association between the UO/FI ratio and mortality, using the UO/FI ratio cut-off value. The interaction between UO and the UO/FI ratio was evaluated by adding the interactive item in the logistic model, and a subgroup analysis was conducted. The predictive marginal effects of the UO were estimated for different UO/FI ratios. A two-tailed test was performed, and a *P*-value < 0.05 was considered to reflect statistical significance. All statistical analyses were performed using Stata 11.2 (StataCorp, College Station, TX, USA).

Results

The data of 902 patients were available in the dataset downloaded from BioLINCC. Sixty-seven patients were excluded because of a lack of relevant records. Thus, 539 survivors and 296 non-survivors (835 total patients) were included in the final analysis. The overall mortality rate was 35.4%. Compared to non-survivors, survivors had a significantly higher UO volume within the 24-h period preceding the trial (27.9 ± 23.4 vs. 33.2 ± 25.8 mL/24 h, $P = 0.003$) and significantly lower FI volume (71.4 ± 56.8 vs. 63.4 ± 52.5 mL/24 h, $P = 0.039$). The maximum serum creatinine concentration was similar between survivors and non-survivors (1.59 ± 1.54 vs. 1.80 ± 1.47 mmol/L, $P = 0.058$). The detailed baseline characteristics and comparisons are listed in Table 1.

Association between UO and mortality

A multivariable logistic analysis was used to explore the adjusted association between UO and mortality (Table 2). For maximum statistical efficiency, UO was included as a continuous variable in model 1 (Table 2), and the odds ratio (OR) was significant (OR: 0.98, 95% confidence interval [CI]: 0.98–0.99, $P = 0.002$). For interpretation, UO was used as a quartile variable in model 2 (Table 2), and a stepwise decreasing trend was observed from quartile two (OR: 0.69, 95% CI: 0.46–1.03, $P = 0.072$) to quartile four (OR: 0.46, 95% CI: 0.30–0.70, $P < 0.001$) relative to quartile one. The trend of the curve in Fig. 1 is consistent with the abovementioned findings.

Table 1 Comparisons of baseline characteristics between survivors and non-survivors

Variables	Overall (*n* = 835)	Survivors (*n* = 539)	Non-survivors (*n* = 296)	*P*
Age (years)	51.1 ± 16.4	47.8 ± 16.5	59.1 ± 16.4	< 0.001
Male [n (%)]	494 (59.1)	314 (58.2)	180 (60.8)	0.472
Height [n (%)]	171.2 ± 9.7	171.8 ± 9.7	170.2 ± 9.5	0.021
Weight [n (%)]	79.7 ± 21.6	80.5 ± 22.0	78.2 ± 20.9	0.134
Ethnicity (Black, %)	148 (17.7)	90 (16.6)	58 (19.5)	0.294
Ethnicity (white, %)	606 (74.9)	401 (74.3)	205 (69.2)	0.111
Low tidal volume intervention [n (%)]	443 (53.0)	304 (56.4)	139 (46.9)	0.009
Comorbidities				
Leukemia [n (%)]	17 (2.0)	5 (0.9)	12 (4.0)	0.004
Immunosuppression [n (%)]	86 (10.2)	41 (7.6)	45 (15.2)	0.001
Diabetes [n (%)]	118 (14.1)	72 (13.5)	46 (15.5)	0.386
Solid tumour [n (%)]	16 (1.9)	6 (1.1)	10 (3.4)	0.032
Lymphoma [n (%)]	9 (1.1)	3 (0.5)	6 (2.0)	0.075
Cirrhosis [n (%)]	24 (2.8)	12 (2.2)	12 (4.0)	0.136
Elective surgery [n (%)]	73 (8.7)	46 (8.5)	27 (9.1)	0.774
Pneumothoraces [n (%)]	105 (12.5)	68 (12.6)	37 (12.6)	0.961
Chest tube [n (%)]	210 (25.1)	140 (25.9)	70 (23.6)	0.459
Biochemical indexes				
PaO2/FiO2 (mmHg)	150.9 ± 69.8	156.4 ± 71.2	141.0 ± 66.0	0.002
Maximum respiratory rate	30.4 ± 10.8	29.7 ± 11.1	31.7 ± 10.2	0.011
Maximum mean blood pressure (mmHg)	101.9 ± 19.7	103.3 ± 19.9	99.3 ± 19.2	0.005
Minimum mean blood pressure (mmHg)	61.8 ± 13.6	63.4 ± 13.8	59.0 ± 12.8	< 0.001
Maximum white blood cell (10^9/L)	14.9 ± 10.2	15.0 ± 9.9	14.7 ± 10.6	0.672
Minimum white blood cell (10^9/L)	12.1 ± 9.0	12.3 ± 8.9	11.7 ± 9.3	0.366
Minimum platelet count (10^9/L)	161.7 ± 116.7	169.7 ± 121.2	147.3 ± 106.8	0.008
Maximum serum creatinine (mg/L)	1.67 ± 1.52	1.59 ± 1.54	1.80 ± 1.47	0.058
Minimum serum sodium (mmol/L)	136.9 ± 5.5	136.9 ± 5.2	136.9 ± 6.1	0.995
Maximum serum sodium (mmol/L)	139.3 ± 5.3	139.2 ± 4.9	139.3 ± 6.0	0.762
Minimum serum albumin (g/dl)	2.19 ± 0.57 (*n* = 726)	2.26 ± 0.58 (*n* = 469)	2.08 ± 0.54 (*n* = 257)	< 0.001
Minimum serum bicarbonate (mmol/L)	21.4 ± 5.4	21.9 ± 5.4	20.6 ± 5.1	0.001
Fluid records				
Fluid intake (ml/kg/24 h)	66.2 ± 54.2	63.4 ± 52.5	71.4 ± 56.8	0.039
Urine output (ml/kg/24 h)	31.3 ± 25.1	33.2 ± 25.8	27.9 ± 23.4	0.003
UO /FI	0.75 ± 1.82	0.76 ± 0.92	0.72 ± 2.80	0.777

Abbreviation: *UO/FI* Urine output/fluid intake

Association between UO/FI and mortality

The crude relationship between the UO/FI ratio and mortality was explored using the Lowess smoothing technique, as shown in in Fig. 1. A cut-off value of 0.5 was determined and applied in the multivariable linear spline logistic regression (Table 3). Among subjects with UO/FI ratios ≤0.5, an increased UO/FI ratio was significantly associated with decreased mortality (OR: 0.09, 95% CI: 0.03–0.253, $P < 0.001$); however, this association was not significant for UO/FI ratios > 0.5 (OR: 1.04, 95% CI: 0.96–1.14, $P = 0.281$).

Interaction between UO and UO/FI

The interaction between UO and the UO/FI ratio was significant when the UO/FI ratio was used as a dummy variable (≤0.5 or > 0.5, *P*-value for the interaction = 0.044). A subgroup analysis was conducted using this UO/FI ratio cut-off value. The association between UO and mortality was significant in the subgroup with UO/FI ratios ≤0.5 (Table 4, OR: 0.97, 95% CI: 0.96–0.99, $P = 0.006$), but was not significant in the subgroup with UO/FI ratios > 0.5 (OR: 0.99, 95% CI: 0.98–1.01, $P = 0.504$). The predictive marginal effects of different UO values (10, 20, 30, 40, 50, 60, and 70 mL/kg/24 h) on mortality were also estimated at different UO/FI values (≤0.5 or > 0.5) as shown in Fig. 2. The slope of the predictive curve between UO and mortality at a UO/FI ratio ≤ 0.5 was markedly steeper than the slope of the corresponding curve at a UO/FI ratio > 0.5, consistent with the above findings.

Discussion

With this study, we aimed mainly to direct attention to the

Table 2 Two multivariable logistic models using UO as continuous and dummy variables

Model 1			Model 2		
Variables	Adjusted odds ratio (95% CI)	*P*	Variables	Adjusted odds ratio (95% CI)	*P*
UO	0.98 (0.98–0.99)	0.002	UO quartile 1	Ref.	
Low tidal volume intervention	0.67 (0.50–0.90)	0.009	UO quartile 2	0.69 (0.46–1.03)	0.072
Leukemia	3.95 (1.31–11.8)	0.014	UO quartile 3	0.51 (0.34–0.78)	0.002
Solid tumour	3.26 (1.14–9.34)	0.027	UO quartile 4	0.46 (0.30–0.70)	< 0.001
Respiratory rate	1.01 (1.00–1.03)	0.015	Low tidal volume intervention	0.68 (0.51–0.92)	0.013
Platelet count (10^9/L)	0.99 (0.99–0.99)	0.004	Leukemia	3.26 (1.09–9.73)	0.033
PaO_2/FiO_2	0.99 (0.99–0.99)	0.003	Solid tumour	3.57 (1.24–10.25)	0.018
			Respiratory rate	1.01 (1.00–1.03)	0.013
			Platelet count (10^9/L)	0.99 (0.99–0.99)	0.005
			PaO2/FiO2	0.99 (0.99–0.99)	0.004

UO was used as a continuous variable in Model 1 and was divided into four quartiles in Model 2. The VIF value were 2.63 and 2.46 for Model 1 and Model 2, respectively
Abbreviation: *UO* Urine output

dynamic fluid status rather than the absolute fluid management volume. Here, we used the UO/FI ratio to reflect a patient's ability to excrete excess administered fluids. We determined that for patients with a UO/FI ≤0.5, an increase in the UO/FI was significantly associated with decreased mortality. However, this association was non-significant for those with a UO/FI > 0.5. Furthermore, we also found that the UO/FI ratio significantly influenced the association between UO and mortality in ARDS. Moreover, the association between UO and mortality was significant only among patients with a UO/FI ratio ≤ 0.5. Therefore, this study offers novel insights into the complex interactions among UO, FI, and mortality in ARDS.

Appropriate fluid management is critical to the overall management of patients with ARDS, as pulmonary edema resulting from increased capillary permeability is a characteristic feature.[3] Several retrospective studies[5,6] reported that both early and late increased fluid accumulation are significantly associated with poor outcomes in ARDS. Accordingly, recent investigations have focused on strategies to limit FI and increase the fluid output, with the aim of alleviating these poor outcomes.[7,13,14]

In 2006,[7] the ARDS Network compared the efficacy of liberal and conservative fluid strategies and found that conservative fluid administration (more loop diuretics and higher UO volume) was shown to improve lung function and reduce the duration of mechanical ventilation. In another RCT, Martin et al.[15] found that when compared to a placebo, albumin and furosemide combination therapy resulted in a significantly higher UO during the intervention period, which was associated with an improved fluid balance, oxygenation, and hemodynamics in hypoproteinemic patients with acute lung injury. However, as

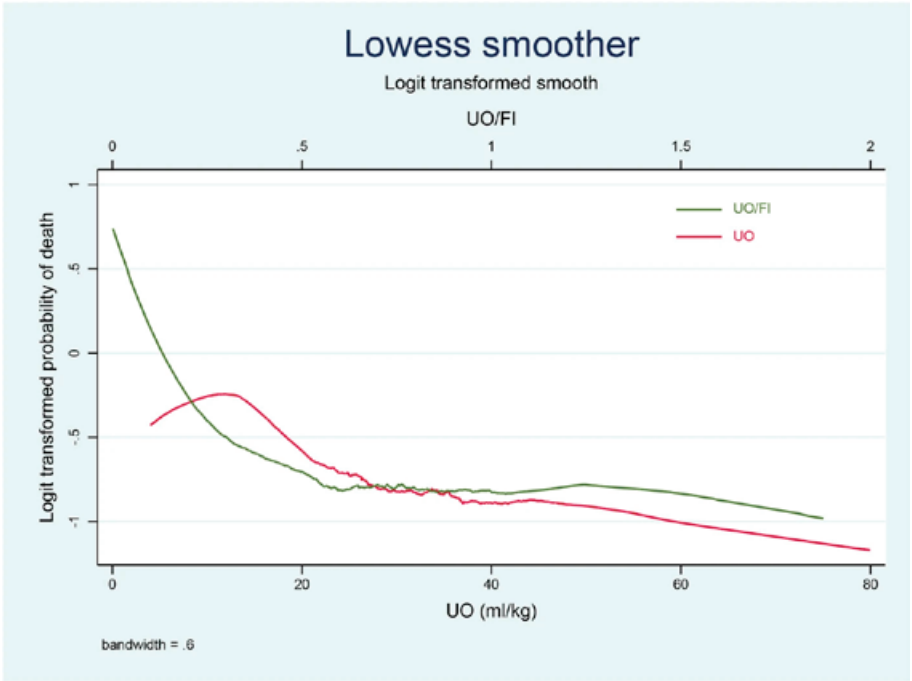

Figure 1 Associations among the urine output (UO), urine output/fluid intake (FI) ratio, and hospital mortality in patients with acute respiratory distress syndrome. A turning point of green curve around 0.5 was observed, top horizontal axis

Table 3 Linear spline associations between UO/FI and mortality

Variables	Crude odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
UO/FI ≤ 0.5	0.08 (0.03–0.22)	< 0.001	0.09 (0.03–0.25)	< 0.001
UO/FI > 0.5	1.04 (0.95–1.13)	0.353	1.04 (0.96–1.14)	0.281
Low tidal volume intervention			0.68 (0.51–0.92)	0.013
Leukemia			3.56 (1.19–10.6)	0.022
Solid tumour			3.38 (1.18–9.67)	0.023
Respiratory rate			1.01 (1.00–1.03)	0.013
Platelet count (10^9/L)			0.99 (0.99–0.99)	0.027
PaO_2/FiO_2			0.99 (0.99–0.99)	0.005

Linear spline function was applied in the logistic models using cut-off value of 0.5 of UO/FI. The VIF value was 3.03 in the multivariable logistic model
Abbreviation: *UO/FI* Urine output/fluid intake

both the diuretic[14,15] and non-diuretic[16,17] effects of furosemide may be responsible for the improved outcomes, the direct association between UO and mortality in ARDS cannot be inferred from these trials.

Multiple observational studies have demonstrated an independent association of increased UO with decreased mortality in unselected critically ill patients[9] or in patients with acute kidney injury.[10] In an observational study of 81 patients with ARDS who were receiving extracorporeal membrane oxygenation support, Hsiao et al.[18] found that the UO within the initial 24 h after the commencement of extracorporeal membrane oxygenation support, the mean arterial pressure, and the platelet count were independent risk factors for hospital mortality. Indeed, a decreased UO may indicate low renal perfusion and consequent fluid overload, which in turn contributes to subsequent organ dysfunction.[8] Nevertheless, it remains unclear whether these findings are translatable to regular ARDS patients, given the remarkable heterogeneity among these cohorts. Furthermore, a simple evaluation of the association between UO and mortality that is not adjusted for FI is insufficient. For instance, the clinical outcomes of two hypothetical patients with a similar UO volume of 1000 ml, depending on the FI.

In the current study, we observed a linear correlation between UO and the probability of hospital mortality. However, after adjusting for FI, we noticed that this association between UO and mortality was significant only in patients with low UO/FI ratios. We further identified a non-linear association between the UO/FI ratio and mortality. To some extent, these findings suggest a point of equilibrium between UO and FI, and also raise some new questions. For instance, would a patient with a low UO/FI ratio benefit from an increase in the fluid intake as guided by the UO/FI? Further, would the benefits of diuretics remain significant in patients with high UO/FI ratios? Of course, the underlying mechanisms, particularly with regard to the cut-off value, cannot be inferred due to the retrospective nature of this study. We speculate that the low UO/FI ratios imply some level of decompensatory organ function, such as cardiac failure, kidney failure, or unstable hemodynamics. However, the ability to excrete a greater UO volume may suggest relatively better organ function and less fluid accumulation, and may thus explain why a greater UO volume was associated with improved mortality. The cut-off value of 0.5 may serve as an indicator of the boundary between decompensatory and compensatory organ function and fluid accumulation. Hence, in patients with the ability to achieve high UO/FI ratios (> 0.5), the association between UO and mortality would not be significant. Further studies are needed to validate our hypothesis and re-evaluate the heterogeneous effects of fluid strategies, such as fluid restriction and diuretic use, in patients with different UO/FI ratios.

Our study had several advantages. First, all data were extracted from a rigorously designed multicenter trial, which guaranteed the accuracy of the data. Second, in contrast to previous studies, both UO and FI were used as continuous variables in our study (the OR was small, as it only represented the change in odds per UO or FI unit increase [1 mL/kg/24 h]), which maximized the statistical power. Third, to the best of our knowledge, this is the first study to report the UO/FI ratio, which may provide a better reflection of the fluid status than the UO alone. Further studies are needed to validate our findings.

Several limitations of our study should also be mentioned. First, we included as many potential confounders as possible, but could not exclude residual confounding bias. For instance, the interactive effects between diuretics and the UO/FI ratio could not be evaluated in this study because the dataset did not

Table 4 Subgroup analysis of patients with high and low UO/FI ratios

Subgroup with UO/FI ≤ 0.5 (Model A, *n* = 421)			Subgroup with UO/FI > 0.5 (Model B, *n* = 414)		
Variables	Adjusted odds ratio (95% CI)	*P*	Variables	Adjusted odds ratio (95% CI)	*P*
UO	0.97 (0.96–0.99)	0.006	UO	0.99 (0.98–1.00)	0.504
Low tidal volume intervention	0.80 (0.53–1.20)	0.295	Low tidal volume intervention	0.57 (0.36–0.88)	0.013
Leukemia	5.83 (1.17–29.1)	0.031	Leukemia	1.92 (0.35–10.39)	0.447
Solid tumour	2.15 (0.42–10.82)	0.351	Solid tumour	4.21 (1.00–17.50)	0.048
Respiratory rate	1.01 (0.99–1.03)	0.165	Respiratory rate	1.02 (1.00–1.04)	0.034
Platelet count (10^9/L)	0.99 (0.99–1.00)	0.161	Platelet count (10^9/L)	0.99 (0.99–0.99)	0.032
PaO_2/FiO_2	0.99 (0.99–0.99)	0.039	PaO2/FiO2	0.99 (0.99–0.99)	0.039

The *p* value for interaction between UO and UO/FI ratio was 0.044. The VIF value were 2.69 and 2.83 for Model A and Model B, respectively
Abbreviations: *UO* Urine output, *UO/FI* Urine output/fluid intake

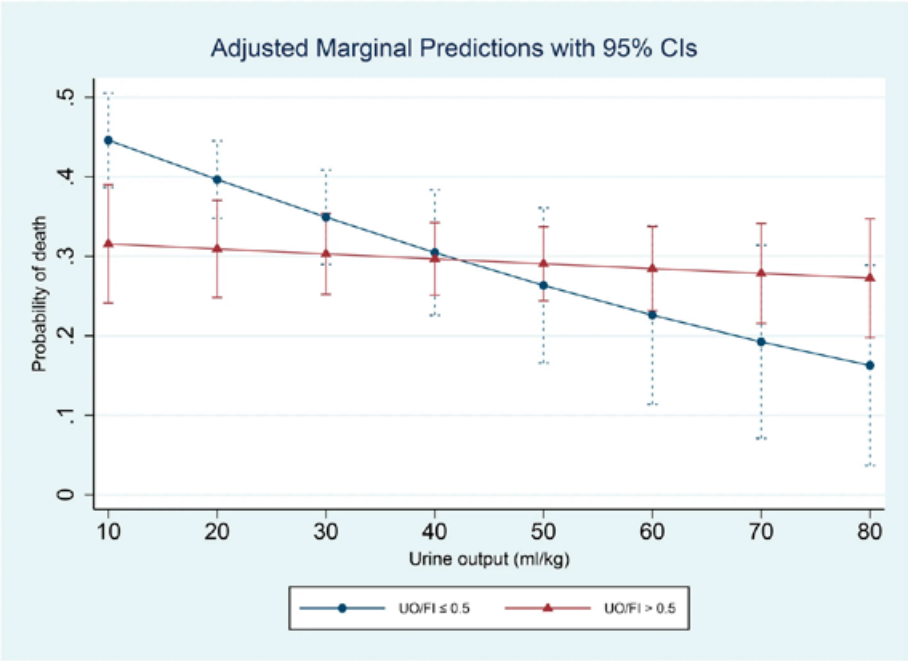

Figure 2 The predictive marginal effect of urine output in patients with different urine output (UO)/fluid intake (FI) ratios

include diuretic records. Second, we only analyzed fluid records obtained within the 24-h period preceding the original trials. Therefore, it remains unclear whether the observed association would remain consistent across different time intervals. Third, the original study included only patients under invasive mechanical ventilation support, which restricts the applicability of our findings. Finally, the retrospective nature of the study limited our ability to determine a causal relationship between the UO volume and mortality. For instance, a higher UO volume may be an indicator of better kidney function, rather than a determinant of mortality. Thus, additional investigation is needed to determine whether strategies designed to increase the UO could improve the clinical outcomes of patients with ARDS.

Conclusion

In conclusion, in patients with ARDS, an increased UO was associated with decreased mortality. However, this association was influenced by the UO/FI ratio, and was only significant in the subgroup with UO/FI ratios of ≤0.5. Further studies are needed to validate and expand our findings.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from YS on reasonable request (with permission of BioLINCC).

Abbreviations

ARDS: Acute respiratory distress syndrome
BioLINCC: Biologic Specimen and Data Repository Information Coordinating Center
CI: Confidence interval
FI: Fluid intake
OR: Odds ratio
RCT: Randomized controlled trial
UO: Urine output

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Ethics approval and consent to participate
This was a secondary analysis of a prospective RCT[11] that was performed in 10 centers within the ARDS Network of the National Heart, Lung, and Blood Institute research network. The original study was approved by the institutional review board at each study center, and informed consent was obtained from the patients or their legal guardians. All data were uploaded in the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) (https://biolincc.nhlbi.nih.gov) by the ARDS Network. The re-use of these data was approved both by the institutional review board at each center and by BioLINCC. Thus, the need for consent was waived for this retrospective study.

Metabolic and Cardiorespiratory Effects of Decreasing Lung Hyperinflation with Budesonide/Formoterol in COPD

Miguel J Divo, Michael R DePietro, John R Horton, Cherie A Maguire & Bartolome R Celli

Abstract

Background: Studies suggest that acute decreases in lung hyperinflation at rest improves cardiac function and increases lung vascular perfusion from decompression of a compromised heart. In those studies, changes in resting oxygen uptake induced by medications, an alternative explanation for compensatory increased cardiac function, were not explored.

Methods: This double-blind, multicenter, double-crossover study enrolled adults with chronic obstructive pulmonary disease, resting hyperinflation, and > 10% improvement in inspiratory capacity after 2 inhalations of budesonide/formoterol 160/4.5 µg. Metabolic, cardiac, and ventilatory function were measured 60 min pre–/post-dose at each visit. Primary endpoint was change in resting oxygen uptake for budesonide/formoterol versus placebo.

Results: Fifty-one patients (median age: 63 years) received treatment. Compared with placebo, budesonide/formoterol significantly increased resting oxygen uptake (mean change from baseline: 1.25 vs 11.37 mL/min; P = 0.007) as well as tidal volume and minute ventilation. This occurred despite improvements in the inspiratory capacity, forced vital capacity, and expiratory volume in 1 s. No significant treatment differences were seen for oxygen saturation, respiratory rate, and resting dyspnea. There was a numerical increase in oxygen pulse (oxygen uptake/heart rate). Correlations between inspiratory capacity and oxygen pulse were weak.

Conclusions: Budesonide/formoterol treatment in resting hyperinflated patients with COPD results in significant deflation. The increase in oxygen uptake and minute ventilation at lower lung volumes, without changes in heart rate and with minimal improvement in oxygen pulse, suggests increased oxygen demand as a contributor to increased cardiac function.

Background: Patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) are likely to have static lung hyperinflation, which confers a poor prognosis.[1] Resting hyperinflation is easily detected by measuring lung volumes during standard pulmonary function testing.[2] Determination of inspiratory capacity (IC) as a reflection of the end-expiratory lung volume at rest and during exercise has been shown to be a reliable, easy-to-measure, and practical variable to determine the degree of static and dynamic hyperinflation.[3,4] Treatment with inhaled bronchodilators with or without corticosteroids decreases lung hyperinflation, and increases IC, which relates well to improvement in exercise endurance and dyspnea in these patients.[5,6,7,8,9]

Hyperinflation has been linked to low cardiac output in patients with COPD,[10] in part by limiting left ventricular stroke volume.[11,12] Reversing hyperinflation through lung volume reduction surgery improves cardiac function at rest and during exercise.[13,14] Measuring the oxygen pulse, obtained by dividing the measured resting oxygen uptake (VO_2) by the heart rate (HR), provides an adequate reflection of cardiac stroke volume when the systemic extraction of oxygen is stable.[12] This method has been used to evaluate the effect of static and dynamic hyperinflation on cardiac function during exercise.[13]

Whereas significant knowledge exists about the interaction between dynamic acute lung hyperinflation and cardiac function during exercise,[7,10,12] only 2 studies have evaluated the effect of pharmacological decrease of hyperinflation on pulmonary tests and cardiac function at rest in patients with COPD.[15,16,17] Using magnetic resonance imaging (MRI) to measure cardiac chamber volume and function at rest, the study by Stone et al. showed that 1 week of once-daily inhaled fluticasone furoate/vilanterol (an inhaled corticosteroid [ICS]/long-acting beta2-agonist [LABA]) decreased resting lung volumes and increased right ventricular end-diastolic volume index, as well as cardiac index, without changes in intrinsic cardiac function.[15] Similar findings were reported in the second study, which used a combination of inhaled dual bronchodilators containing the LABA indacaterol plus the long-acting muscarinic antagonist (LAMA) glycopyrronium, administered over 2 weeks.[16,17] In those studies, the authors attributed the improvement of heart function and increased pulmonary vascularity to an increase in cardiac volume resulting from lung deflation and associated decompression of the heart. However, no measurements were made of other factors that may contribute to an increase in cardiac demands, such as the increase in resting VO_2 that occurs with administration of inhaled beta-agonists, as these agents have been shown to increase the metabolic demand of peripheral muscles.[18,19] Interestingly, those studies did not find a relationship between lung function, including changes in IC and the improvement in cardiac function, suggesting the

Miguel J Divo, Cherie A Maguire & Bartolome R Celli: Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA, 02115, USA; Michael R DePietro & John R Horton: AstraZeneca LP, Wilmington, DE, USA; Michael R DePietro: Current affiliation Teva Pharmaceuticals, Frazer, PA, USA.

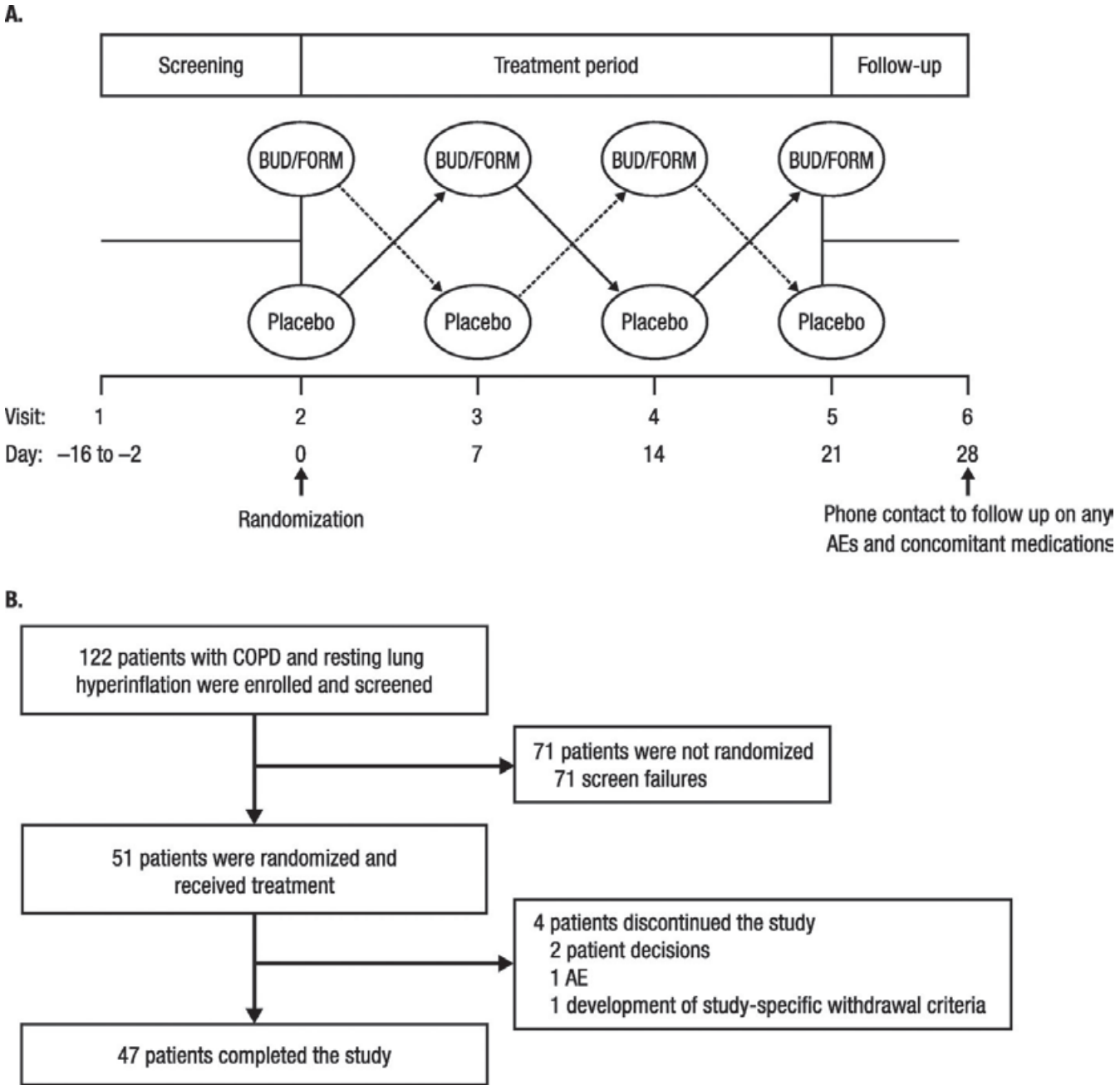

Figure 1 Summary of (a) study design and (b) patient disposition. AEs, adverse events; BUD/FORM, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; pMDI, pressurized metered-dose inhaler

presence of other mechanisms to account for the increase in cardiac function. To our knowledge, no study has evaluated the metabolic function and dynamic ventilatory response in hyperinflated patients with COPD after decreasing resting lung volumes acutely with inhaled pharmacotherapy that includes beta-agonists.

The aim of this study of patients with COPD and resting hyperinflation, therefore, was to test the hypothesis that a single dose of inhaled budesonide/formoterol (administered at 2 different visits), could alter resting metabolic demand (VO_2) while decreasing resting lung volumes. The impact on cardiac and respiratory function in these patients while at rest was also examined. Inhaled placebo randomly administered in the separate visits served as control.

Methods

Study design and patient selection

This randomized, double-blind, multicenter, placebo-controlled, double-crossover study included a screening visit, 4 treatment visits 7 days apart, and 1 follow-up telephone visit (Fig. 1a). Eligible patients were aged 40 to 80 years (inclusive) with a clinical diagnosis of COPD, post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio < 0.7, and post-bronchodilator $FEV_1 \leq 65\%$ of predicted. Lung hyperinflation was defined as an increase in IC of > 10% after 2 inhalations of open-label budesonide/formoterol 160/4.5 µg (total dosage 320/9.0 µg; Symbicort®; AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) from a pressurized metered-dose inhaler (pMDI), administered with a spacer at screening. All patients were in clinically stable condition,

Table 1 Demographic and clinical characteristics

Characteristics	Total ($N = 51$)
Demographic[a]	
Age, mean (SD), y	62.9 (8.32)
Women, n (%)	24 (47)
BMI, mean (SD), kg/m^2	28.02 (6.88)
Race, n (%)	
White	37 (72.5)
African American	13 (25.5)
Other	1 (2.0)
Clinical[b,c]	
IC, L	1.934 (0.526)
Change after administration of BUD/FORM	0.367 (0.169)
FEV_1, L	1.147 (0.366)
Change after administration of BUD/FORM	0.191 (0.114)
FVC, L	2.497 (0.802)
Change after administration of BUD/FORM	0.308 (0.218)
FEV_1/FVC	0.472 (0.097)
Change after administration of BUD/FORM	0.017 (0.036)
TLC, L	6.214 (1.221)
FRC, L	4.314 (1.018)

BMI body mass index, *BUD/FORM* budesonide/formoterol, *FEV_1* forced expiratory volume in 1 s, *FRC* functional residual capacity, *FVC* forced vital capacity, *IC* inspiratory capacity, *SD* standard deviation, *TLC* total lung capacity
[a]At baseline
[b]At screening
[c]All values reported as mean (SD)

per the complete inclusion/exclusion criteria. The study was approved by the local ethics review committee and conducted in accordance with the Declaration of Helsinki; all patients provided written informed consent.

Following current medication washout, patients randomly received 1 dose of 2 inhalations of budesonide/formoterol 160/4.5 µg from a pMDI or matching placebo with a BreatheRite® spacer.

Physiologic measurements

Measurements were taken 60 min pre-dose and 60 min post-dose for each visit. Gas exchange and respiratory variables measured at rest using a metabolic cart with cardiac monitoring were resting VO_2, resting carbon dioxide output (VCO_2), respiratory rate (RR), tidal volume (V_T), inspiratory time (T_i), expiratory time, oxygen saturation, and HR; calculated variables were oxygen pulse (VO_2/HR), inspiratory flow rate (IFR;: V_T/T_i), total respiratory time (60/RR), respiratory time fraction (T_i/total respiratory time), and minute ventilation (V_e; :$RR \times V_T$). Sitting systolic and diastolic blood pressure were also measured during screening and at each visit. To assess pulmonary function, total lung capacity, functional residual capacity, residual volume, and slow vital capacity (SVC) were measured with body plethysmography during screening, and FEV_1, FVC, and IC were measured using spirometry at each visit (post-screening IC was measured using an SVC maneuver). Dyspnea was scored at each treatment visit using the Modified Borg Dyspnea Scale.

Statistical analyses

Statistical analysis was performed using SAS® version 9.4. The efficacy analysis set included all randomized patients who completed ≥1 post-baseline measurement of the primary efficacy endpoint under each of the 2 treatment groups; the safety analysis set included all patients who received ≥1 dose of randomized study medication. Each patient received 2 placebo and 2 active medication treatments (Fig. 1a). Treatment group estimates were provided as least squares means. The primary efficacy endpoint was change from pre-dose to post-dose assessment in resting VO_2 after administration of budesonide/formoterol versus placebo (measured at the 4 post-baseline visits). A restricted maximum likelihood–based mixed model for repeated measures was employed using sequence, treatment, and visit as fixed effects, with patient nested within sequence as a random effect. P values with estimated treatment differences and 95% confidence intervals were calculated for efficacy comparisons. Associations between primary and secondary efficacy endpoints for each treatment group were computed using the Pearson correlation matrix across all treatment visits.

Results

A total of 122 patients were screened, and 51 patients were randomized (Fig. 1b) and included in both the efficacy and safety analyses (first patient was enrolled on August 27, 2015; last patient completed the study on August 12, 2016). The demographic and clinical characteristics of the patients who completed the study are summarized in Table 1. The population was 47% women with a mean (standard deviation) age of 62.9 (8.32) years. Consistent with the inclusion criteria, patients had moderate to severe airflow limitation and hyperinflation.

Gas exchange and cardiac parameters

Resting VO_2 increased significantly after budesonide/formoterol treatment compared with placebo (11.37 vs 1.25 mL/min, respectively; P = 0.007; Table 2). Resting VO_2 values for individual patients before and after treatment with budesonide/formoterol and placebo are shown in Fig. 2a and b, respectively. The observed increase in resting VO_2 was associated with a significant increase in resting VCO_2 with budesonide/formoterol compared with placebo.

(5.99 vs – 4.25 mL/min, respectively; P = 0.011). Although there was no change in HR in either group, there was a non-significant trend toward an increase in oxygen pulse after patients received budesonide/formoterol (Table 2).

Pulmonary function, respiratory parameters, dyspnea

Significant improvements were observed with budesonide/formoterol compared with placebo for IC (0.256 vs – 0.024 L; P < 0.001), FEV_1 (0.187 vs – 0.004 L; P < 0.001), FVC, and FEV_1/FVC (Table 3). V_e also increased significantly after the use of budesonide/formoterol compared with placebo. This difference is explained by an increase in V_T and no change in RR with budesonide/formoterol. In addition, there was a significant increase in the mean IFR (V_T/T_i) after the use of budesonide/formoterol compared with placebo (26.53 vs 3.22 mL/sec; P = 0.021). There were no differences between treatments for respiratory time fraction (T_i/total respiratory time) or RR.

Mean changes in the Modified Borg Dyspnea Scale showed greater numerical improvement with the use of single-dose budesonide/formoterol, with no significant difference compared with placebo (Table 3).

Correlation between changes in IC and other outcomes

Correlations between lung hyperinflation, as measured by

Table 2 Differences in metabolic and cardiac variables before and after administration of BUD/FORM or placebo and comparison of the change between treatment groups

Outcome, unit	LS mean change from pre-dose to post-dose		LS mean (95% CI) treatment difference	*P* value*
	BUD/FORM	Placebo		
VO_2, mL/min	11.37	1.25	10.11 (2.94 to 17.29)	**0.007**
HR, bpm	−2.48	− 2.83	0.35 (−1.02 to 1.72)	0.609
VO_2/HR, mL/beat	0.256	0.168	0.087 (− 0.021 to 0.196)	0.111
VCO_2, mL/min	5.99	−4.25	10.25 (2.47 to 18.02)	**0.011**
SaO_2, %	0.42	0.18	0.24 (−0.26 to 0.74)	0.333

bpm beats per minute, *BUD/FORM* budesonide/formoterol, *CI* confidence interval, *HR* heart rate, *LS* least squares, SaO_2 oxygen saturation, VCO_2 carbon dioxide output, VO_2 oxygen uptake, VO_2/HR oxygen pulse
*Bolded *P* values are statistically significant

change in IC, and changes in other primary and secondary outcomes were weak, with correlation coefficients ranging from an absolute value of 0.016 (IC with IFR [V_T/T_i]) to 0.522 (IC with FVC; Table 4).

Safety

Adverse events (AEs) were reported in a similar proportion of patients after treatment with budesonide/formoterol (26%) and placebo (22%). After budesonide/formoterol treatment, there were no serious AEs, AEs leading to discontinuation, or causally related AEs. After placebo, there was 1 serious AE (pneumonia), 2 AEs leading to discontinuation (COPD exacerbation, chronic bronchitis exacerbation), and 1 causally related AE (headache). There were no deaths during the study.

Discussion

This study of patients with COPD with lung hyperinflation at rest demonstrated that single-dose administration of 2 inhalations of budesonide/formoterol 160/4.5 µg (total dosage 320/9.0 µg) decreased resting lung hyperinflation. Despite this seemingly beneficial effect on respiratory mechanics, there was a significant increase in resting VO_2 and resting VCO_2 with concomitant increases in minute ventilation compared with placebo. The increase in cardiac function after lung deflation in this and other studies with beta-agonist–containing medications may in part be the response to an increase in metabolic demand rather than just better heart function secondary to the improvement in ventilatory mechanics due to lung deflation.

The most novel and clinically relevant findings in this study are the significant increases in resting VO_2 and resting VCO_2 observed after single-dose inhalation of budesonide/formoterol. Because this finding was observed in a double-blind, double-crossover, multicenter design study of patients at rest, it cannot be related to augmented physical activity. The increases in resting VO_2 and resting VCO_2, despite a decrease in resting lung volume as indicated by improvements in airflow limitation and IC, as well as an improvement in all spirometric parameters (FVC, FEV_1, and FEV_1/FVC) were surprising because those changes are associated with decreased work of breathing. The improvement in respiratory mechanics secondary to the deflation should have resulted in either no change or a decrease in oxygen uptake. The findings of an increase in VO_2 at rest are most consistent with an increase in peripheral muscle utilization of oxygen with increased oxygen extraction, as the changes in cardiac function were minimal. Data from previous studies using the beta-agonist salbutamol support this finding.[20] This appears to be a function of all beta-agonists. Indeed, it has been shown that infusion of the beta-agonist epinephrine activates various glycolytic enzymes and elevates carbohydrate oxidation and glycogen utilization in skeletal muscles.[21,22] It could be argued that epinephrine is a non-selective agonist with affinity for

Table 3 Differences in respiratory function parameters before and after administration of BUD/FORM or placebo and comparison of the change between treatment groups

Outcome, unit	LS mean change from pre-dose to post-dose		LS mean (95% CI) treatment difference	*P* value*
	BUD/FORM	Placebo		
IC, L	0.256	− 0.024	0.280 (0.218 to 0.342)	**< 0.001**
FEV_1, L	0.187	− 0.004	0.191 (0.150 to 0.233)	**< 0.001**
FVC, L	0.259	−0.052	0.312 (0.236 to 0.388)	**< 0.001**
FEV_1/FVC	0.017	−0.002	0.019 (0.005 to 0.033)	**0.007**
V_T, mL	71.90	14.28	57.62 (29.70 to 85.55)	**< 0.001**
V_T/T_i, mL/sec	26.53	3.22	23.32 (3.72 to 42.91)	**0.021**
T_i/T_{tot}	0.012	−0.004	0.016 (−0.004 to 0.036)	0.113
RR, breaths/min	−0.19	−0.43	0.24 (− 0.44 to 0.91)	0.484
V_e ($RR \times V_T$), mL/min	838	−23.9	862 (440 to 1284)	**< 0.001**
MBS[a]	−0.45	−0.25	− 0.20 (− 0.45 to 0.05)	0.106

BUD/FORM budesonide/formoterol, *CI* confidence interval, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *IC* inspiratory capacity, *LS* least squares, *MBS* Modified Borg Dyspnea Scale, *RR* respiratory rate, T_i/T_{tot} respiratory time fraction, V_e minute ventilation, V_T tidal volume, V_T/T_i inspiratory flow rate
[a]Dyspnea was scored using the MBS, in which patients were asked to report their perception of breathing difficulty using a scale ranging from 0 (nothing at all) to 10 (extremely strong/maximal)
*Bolded *P* values are statistically significant

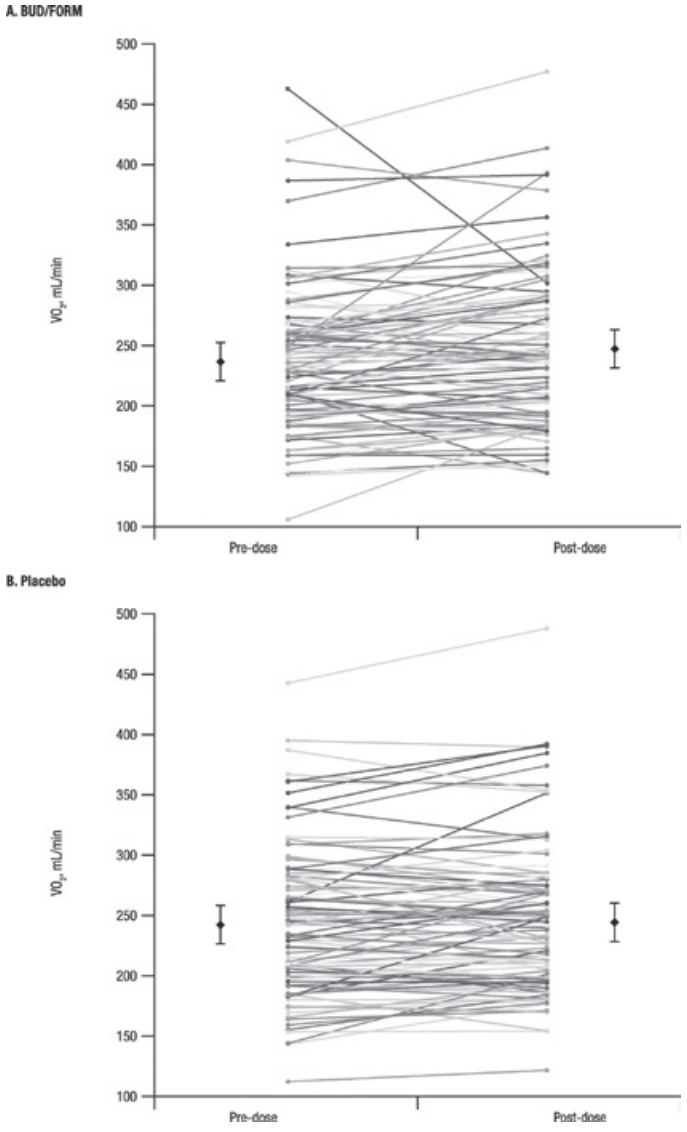

Figure 2 Oxygen uptake pre-dose and post-dose for patients after administration of (a) BUD/FORM and (b) placebo.*,†. BUD/FORM, budesonide/formoterol; CI, confidence interval; LS, least squares; VO2, oxygen uptake. *Each line represents an individual patient and treatment. †In each panel, the pair of data points with error bars are LS mean (95% CI) values at pre-dose and post-dose

both alpha- and beta-adrenoceptors, which may not have the same effect as more selective beta-agonists. However, studies with more selective beta2-agonists including formoterol (as was used in this study) have shown an increase in systemic concentrations of plasma lactate in exercising humans, which suggests a stimulatory action on glycolysis of working skeletal muscles.[18,19,20,23,24,25] The increase in V_T and V_e observed in this study despite improved lung mechanics are consistent with an increased respiratory response to match the peripheral oxygen uptake increase, or from direct central respiratory drive stimulus as has been shown in healthy individuals given intravenous salbutamol.[24]

Interestingly, very few studies have evaluated the acute effect of inhaled beta-agonists on respiratory and cardiac function at rest in patients with COPD, even though inhaled beta2-agonists are among the most widely used agents in the treatment of patients with COPD and asthma.[15,26] We found only 2 studies evaluating the effect of inhaled therapy containing inhaled beta-agonists on respiratory and cardiac function at rest in patients with COPD, but they were completed after days of therapy.[15,16] Both studies attributed the increase in heart volume as well as increased vascularity as a beneficial response of the heart due to a decrease in the load imposed by the baseline hyperinflation of the thorax, once lung volumes decreased. However, resting VO_2 reflecting peripheral oxygen uptake and respiratory function (minute ventilation) were not measured in either of the studies; therefore, it is possible that the increase in cardiac chamber size and output resulted from an adaptive response to the increased metabolic demand caused by the action of the beta-agonists on the muscle compartment. The improved cardiac function reported in those 2 studies may not be solely due to mechanical unloading of the heart with lung deflation; this is supported by the lack of relationship between improved lung function, including better IC, and the cardiac parameters in those reports.[15,16] Consistent with those studies, we observed no relationship between improved lung mechanics and cardiac function. It remains possible that repeated doses of budesonide/formoterol may alter this acute response, as has been shown for 8 weeks of therapy with salbutamol.[23]

This discussion is not meant to imply that decreasing lung volumes is not beneficial when they are the cause of poor cardiac function, as has been shown in over-ventilated patients with airflow limitations in the acute care setting[27,28] and in patients who have undergone surgical or non-surgical lung volume reduction.[13,29,30] Interestingly, in contrast to our findings, the resting VO_2 reported after surgical lung volume reduction is lower and not higher as we have shown in this report.[29] It could be argued whether an increase of 10 ml/min in oxygen uptake is clinically significant. However, patients with COPD spend over 80% of the day at rest, and this seemingly small difference per minute corresponds to 12.4 l of oxygen per day. Importantly, the increase in minute ventilation needed to match the increased oxygen demand observed was 0.862 l per minute. Over the 19 h patients with COPD would typically spend at rest, the daily increase in minute ventilation would be 982 l, a not insignificant amount in patients with a mean FEV_1 of 1.46 l.

Perhaps the finding of an increased metabolic demand as a consequence of the beta-adrenergic effect may explain the weak relationship between the large improvement in lung function observed after maximal bronchodilation and the relatively small changes registered in the perception of dyspnea.[31] Indeed, in an older study with 2 doses of salmeterol, patients on the higher dose scored worse on the St. George's Respiratory Questionnaire than those on the lower dose, even though the bronchodilation effect was significantly larger with the higher dose.[32] Taken together, these results suggest that increased work of breathing and metabolic demand could offset some of the relief a patient experiences from bronchodilation, causing some patients to continue to experience dyspnea despite improved spirometry values.

The current study has the advantages of the large number of observations (over 100 measurements for each treatment) and multicenter implementation (to mitigate center bias); however, there are also several limitations. First, direct cardiac function was not assessed using either central catheter or imaging. Notably, the measurement of metabolic parameters at rest and during steady-state conditions, and simultaneous

Table 4 Correlations between change in IC and selected respiratory and cardiac variables for BUD/FORM and placebo

Outcome, unit	Pearson correlation coefficient (vs IC)[a]
VO_2, mL/min	0.067
HR, bpm	−0.079
VO_2/HR, mL/beat	0.138
VCO_2, mL/min	0.022
SaO_2, %	0.115
FEV_1, L	0.432
FVC, L	0.522
FEV_1/FVC	0.126
V_T, mL	0.191
V_T/T_i, mL/sec	−0.016
T_i/T_{tot}	0.181
RR, breaths/min	−0.063
V_e ($RR \times V_T$), mL/min	0.158
MBS	−0.051

bpm, beats per minute; BUD/FORM, budesonide/formoterol; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; MBS, Modified Borg Dyspnea Scale; RR, respiratory rate; SaO_2, oxygen saturation; T_i/T_{tot}, respiratory time fraction; VCO_2, carbon dioxide output; V_e, minute ventilation; VO_2, oxygen uptake; VO_2/HR, oxygen pulse; V_T, tidal volume; V_T/T_i, inspiratory flow rate

[a]Pearson correlation computed between the given efficacy endpoints (change from pre-dose to post-dose) for BUD/FORM and placebo across all visits

measurement of respiratory variables provide important and novel information that is not readily available and that is less precise when measured during exercise. Second, intrathoracic pressures were not measured during the study, and thus it is possible that changes in such pressures caused some of the observed findings. However, the patients in the study were at rest, which is when intrathoracic swings show the lowest possible variations during tidal breathing[33,34] and, in addition, the higher V_T observed with budesonide/formoterol compared with placebo minimizes this potential confounding factor. Third, the work of breathing was not measured directly, so it is not possible to discern whether the increased work observed is done by respiratory muscles or peripheral muscles. Importantly, the duty cycle was unchanged, which suggests that peripheral rather than respiratory muscles are performing this work; this phenomenon would need to be investigated further. Finally, the choice of medication (combination of ICS/LABA rather than LAMA or others) could be questioned, but it corresponds to the same class combination used in the report by Stone et al.[15] that we attempted to replicate.

Conclusions

In summary, budesonide/formoterol via pMDI is a potent bronchodilator and lung "deflator" in patients with COPD and resting hyperinflation. At rest, there was a significant increase in metabolic and ventilatory demand after medication inhalation, as indicated by increased VO_2, VCO_2, and V_e. These findings complement previous studies that suggested that lung deflation with inhaled bronchodilators improved cardiac function through improved respiratory mechanics. Studies are needed to clarify whether static lung deflation with medications given over longer periods of time increase cardiac function by improving cardio-ventilatory coupling or increasing peripheral oxygen demand. The exact balance between these mechanisms may help optimize medication use.

Availability of data and materials

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Abbreviations

COPD: chronic obstructive pulmonary disease
FEV_1 : forced expiratory volume in 1 s
FVC: forced vital capacity
HR: heart rate
IC: inspiratory capacity
ICS: inhaled corticosteroid
IFR: inspiratory flow rate
LABA: long-acting beta2-agonist
LAMA: long-acting muscarinic antagonist
MRI: magnetic resonance imaging
pMDI: pressurized metered-dose inhaler
RR: respiratory rate
SVC: slow vital capacity
VCO_2: carbon dioxide output
V_e: minute ventilation
VO_2: oxygen uptake
V_T: tidal volume

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MJD and BRC had full access to the data presented in this study and take responsibility for the content of this manuscript, including the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. MJD and BRC contributed to the design of the study and the acquisition and interpretation of the data. MRDP contributed to the design of the study and the analysis and interpretation of the data. JRH contributed to the analysis and interpretation of the data. CAM contributed to the acquisition and interpretation of the data. All authors critically reviewed this manuscript and approved the final version.

Ethics approval and consent to participate
The study was approved by the local ethics review committee and conducted in accordance with the Declaration of Helsinki; all patients provided written informed consent.

Competing interests

BRC reports personal fees and other from AstraZeneca and Menarini; personal fees from GlaxoSmithKline, Boehringer Ingelheim, Novartis, and Sanofi Aventis, outside the submitted work. MRDP was an employee of AstraZeneca at the time of this work and is currently an employee of Teva Pharmaceuticals. JRH was a contractor for AstraZeneca at the time of this work. MJD and CAM declare that they have no competing interests.

News…continued from page 8

Respiratory Treatment Options Receives FDA Clearance

Monaghan Medical Corporation announced the newly approved combination for two of its groundbreaking products—the Aerobika oscillatory positive expiratory pressure (OPEP) device and the VersaPAP positive airway pressure device—to create a low cost, safe and effective "tandem therapy" which allows clinicians to treat a variety of pulmonary conditions requiring lung expansion and airway clearance. Lung expansion therapy is designed to prevent or treat atelectasis—the complete or partial collapse of the lungs—and can also reduce air trapping on exhalation caused by conditions such as asthma or chronic obstructive pulmonary disease (COPD). The overall goal of this tandem therapy is to improve lung volumes by maximizing lung re-expansion (alveolar recruitment) while optimizing airway clearance. The combination of Aerobika OPEP and VersaPAP devices allows for an efficient and effective synergy when used in tandem, optimizing the function of each. Augmentation of maximum flow from the VersaPAP device creates airway expansion on inhalation, allowing for the patient to take in a larger breath. This, in turn, means the patient will have more air to exhale. Oscillations from the Aerobika OPEP device are then maximized on exhalation to improve airway clearance and further lung expansion by the added resistance of both devices. This results in patients receiving positive pressure on inhalation and exhalation, simultaneously optimizing lung expansion and airway clearance. Tandem therapy is yet another added value to a complete system of care for respiratory ailments. The Aerobika OPEP, VersaPAP device, and AeroEclipse II Breath Actuated Nebulizer (BAN) can be used individually or in a variety of combinations to efficiently and effectively treat a patient's pulmonary condition, and easily adjust therapeutic regimens as a patient's condition changes. This "plug and play" model is not only cost effective, but also a true benefit to patients in a hospital setting and as they transfer to a residential setting.

Vyaire Names CEO

Vyaire Medical, Inc. announced that its Board of Directors has appointed Gaurav Agarwal as Chief Executive Officer, effective immediately. Agarwal succeeds Dave Eckley, who is stepping down as Chief Executive Officer, but will remain on the company's Board of Directors. Vyaire Medical is the largest company in the global healthcare ecosystem fully dedicated to respiratory care. With a vision of enabling, improving and extending the lives of patients, the company is committed to innovating and delivering the best respiratory solutions to healthcare customers around the world. Agarwal brings to Vyaire Medical extensive global leadership experience in medical devices and a proven track record in driving innovation, improving patient outcomes, and creating exceptional value for customers. Most recently, as President and Chief Operating Officer of KCI, an Acelity Company, Agarwal transformed the company into an undisputed leader in advanced wound care, by finding ground-breaking healing solutions for current and new customer segments. Prior to that, he served as President, Orthopaedic Reconstruction at Smith & Nephew, where he was responsible for defining a cutting-edge global strategy that expedited product development and redefined the company's portfolio for joint reconstruction. Before that, he held Vice President and General Manager positions at GE Healthcare. "We are thrilled to welcome Gaurav to Vyaire," said Steven Dyson, Chairman of Vyaire Medical's Board of Directors. "He brings a wealth of experience in driving innovation and growing businesses in the medical device industry. In the five years that I've known him, I've seen first-hand the positive impact of his focus on the customer, his attention to employees, and his ability to create value for shareholders. He is the perfect fit for Vyaire at this time." In 2019, the company launched several new products. Most notably, the bellavista 1000e was introduced in the US, a uniquely versatile ventilator system that allows one device to work across a broad range of patients and situations – enhancing workflow, simplifying training, and improving patient outcomes. Two of the latest Pulmonary Function Testing (PFT) technologies were also introduced in the US: Vyntus BODY and Vyntus ONE, both with SentrySuite software. Internationally, SuperNO2VA, the exclusive nasal ventilation mask was brought to market.

Device now Available in the US

Vyaire Medical has announced the US availability of its MX40TM adapter, a reusable telemetry adapter that is compatible with Philips Intellivue MX40 wearable patient monitor. The small, lightweight adapter allows patients to move freely throughout the hospital while they are receiving electrocardiogram (ECG) monitoring. Designed for use with both 5 and 6 leadwire sets, the new adapter can be used in conjunction with the Philips Intellivue MX40 wearable patient monitor. It features a SpO2 port with a securing mechanism that can be used while the patient is walking around with the device. It also has a closure cap that covers the port while it's not in use. The SpO2 port is compatible with the Masimo LNCS pulse oximeter as well as the Philips 9 pin pulse oximeter sensors. The MX40 adapter also utilizes the Vyaire Multi-LinkTM X2 solutions allowing standardization of single patient use leadwires across multiple monitoring platforms, including: Philips, GE, Mindray, Nihon Kohden and Spacelabs. "The MX40 adapter is another example of Vyaire's ability to increase patient mobility and clinician workflow, while providing a decreased risk of infection," said Jeff Zanni, vice president of US Sales. "It also allows our company to partner with both customers and other innovators to implement solutions that are patient—centric." Infection prevention is a key metric in healthcare systems. Using Vyaire's single patient-use leadwire can help eliminate the risk of cross contamination often seen with reusable leadwires.

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