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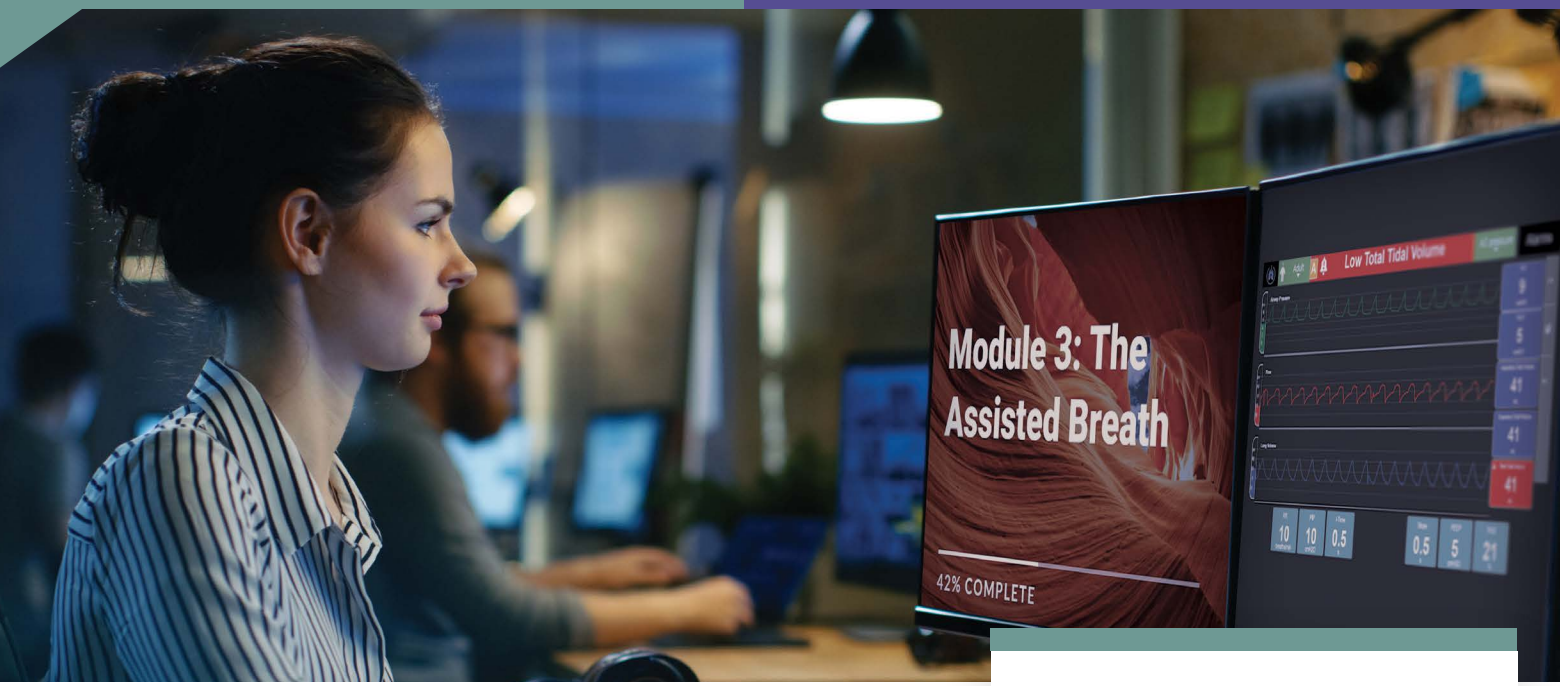

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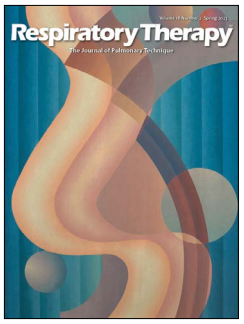

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You Should Be Testing VO2 Max in Your Older Patients

Physicians routinely monitor cholesterol, blood pressure, and glucose levels to get a clearer picture of their patients' overall health. But a group of experts argues that having an accurate read of a person's ability to absorb oxygen during peak exertion—VO2 max—is just as important. Once the focus of cyclists and other elite athletes, VO2 max has in recent years caught the attention of geriatricians, who have linked the measure to maximum functional capacity—an umbrella term for the body's ability to perform aerobic exercise. "Function is prognostic of mortality," said Daniel E. Forman, MD, FAHA, FACC, professor of medicine and chair of the Section of Geriatric Cardiology at the University of Pittsburgh Medical Center. "If you aren't looking at that, you're missing the boat." Although cardiopulmonary exercise testing (CPET) remains the gold standard for assessing VO2 max, Forman said clinicians often overlook CPET because it is old. As a person ages, the amount of physical activity they need to stay fit varies, depending on their genes, their health, and their fitness history. Measuring VO2 max can help doctors better prescribe physical activity, both with regard to specific exercises and for how long, Claudio Gil Araújo, MD, PhD, dean of research and education at the Exercise Medicine Clinic at CLINIMEX in Rio de Janeiro, Brazil, said. The test can also measure progress. "Guidelines talk about how much exercise you should do every week, but it's somewhat misleading because the health outcomes are much more linked to physical fitness than the amount of exercise you do," Araújo said. Treating a patient with hypertension requires an individualized approach. "The same thing is true with exercise," he said.

React Health adds New V-Com PAP Comfort Accessory to its PAP Offering

React Health announced it has entered into a distribution agreement with SleepRes, LLC to provide the recently launched V-Com with new PAP orders in the United States. The V-Com, which is placed between the CPAP mask and the CPAP hose, is engineered to reduce inspiratory pressure and flow to provide comfort with minimal to no reduction in expiratory pressure (EPAP). Introduced in June 2022, V-Com has gained early acceptance with many key thought leaders in the field and is poised to disrupt the way PAP therapy and comfort are approached. "React Health is committed to providing innovative options to improve comfort and patient tolerance to PAP therapy. The V-Com is a novel approach that is focused on solving the adherence issues that the industry has struggled with due to patients not being able to tolerate their PAP" said Clint Geffert, President, Commercial Operations, for React Health. "As a manufacturer, we are in a unique position to complement the efforts that our DME and Physician partners utilize daily to improve patient compliance. Our relationship with V-Com is an example of this. We know when patients are more comfortable, they are more likely to continue therapy." "I have experienced the V-Com myself and believe it is a real difference maker for patients starting CPAP," said Robert Miller, Vice President of Sleep Therapy, Apria Healthcare. "The fact that a manufacturer has chosen to make V-Com available for their patients is tremendous value-add. I congratulate React Health." In the cover story for the December 2022 edition of Sleep Review magazine titled, "A Potentially Huge CPAP Pressure Mistake" early physicians and engineers in the field suggest that current CPAP devices are harder to tolerate than 20 years ago. They attribute this difficulty tolerating therapy to IPAP which the V-Com mproves. "The V-Com' s comfort comes from the IPAP being less than EPAP," said Dr Krishna Sundar, Chief of Medicine at the University of Utah. "This new concept of IPAP less than EPAP appears to have advantages beyond comfort. It is causing all of us in the field to rethink treatment." "Comfort is an ethical matter," said William Noah, MD, CEO of SleepRes, LLC. "If an intervention provides comfort for a difficult therapy,

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and does not adversely affect the therapy, then I believe you have an obligation to offer that intervention. We applaud the leadership of React Health for being so patient-focused and look forward to working with them." "One of the best solutions we've seen is to change the pressure transitions in the devices, and in our partnership with V-Com we look forward to making that happen." said Geffert.

VERO Biotech's Second Generation GENOSYL Delivery System Receives FDA Approval in Anesthesia in the Surgical Suite

VERO Biotech Inc., a commercial-stage healthcare business dedicated to neonatal intensive care and the acute care hospital community, announced FDA approval of its innovative second generation GENOSYL Inhaled Nitric Oxide (iNO) delivery system for use with rebreathing anesthesia in the operating room setting. Second generation GENOSYL Delivery System (DS) is now the first and only device for iNO delivery that is approved for use in both rebreathing and non-rebreathing anesthesia methods, improving patient care, saving money for the hospital, and reducing environmental pollution from waste anesthetic gas. The advantages of rebreathing anesthesia have made this method the standard of care for anesthesia administration in the OR setting. There is a significant advantage in patient care, helping patients retain moisture and body heat. The loss of body heat and moisture can be key complications of anesthesia faced by every patient, especially smaller patients. Rebreathing also allows lower fresh gas flows, which reduces costs for the hospital as well as environmental pollution from anesthetic gas waste. The expected benefits of the second generation GENOSYL DS as approved for rebreathing anesthesia include the following: **Ability to use rebreathing anesthesia**: lower gas flows, i.e., less use of costly anesthetic agents and savings for the hospital; increased patient comfort (by preserving patient body temperature and moisture); **Streamlined process of care**: seamless iNO delivery from the ICU through surgery to post-operative care, resulting in process and workflow improvements for the health care organization that reduce overall cost to the hospital; **Set and forget**: allows anesthesiologists to continue to use rebreathing anesthesia and therefore could prevent potentially dangerous, cumbersome, and time-consuming workarounds; **Reduced environmental impact of anesthesia delivery**: reduction in release of anesthetic to the environment. "Second generation Genosyl DS has proven to be the only iNO delivery system capable of accurately delivering iNO with an anesthesia machine under rebreathing conditions, enabling low flow anesthesia with all its benefits," commented Mark Twite, MD, Director of Pediatric Cardiac Anesthesia, Children's Hospital Colorado and University of Colorado Anschutz Medical Campus, Aurora, Colorado. "Anesthesia providers can now simply set the iNO dose without adjusting fresh gas flow or anesthetic agent. This decreases provider distractions, maintains focus on the patient, and facilitates the transition of care between the ICU and OR for ventilated patients," he added. "We believe this new indication for our second generation device will now provide significant benefits to the anesthesiology and surgical care communities whose patients require inhaled nitric oxide in the operating room setting," said Brent V. Furse, CEO and President, VERO Biotech. "We have addressed an unmet need in facilitating rebreathing anesthesia, a further demonstration of our continuous commitment to neonatal intensive care and the acute care hospital community in providing solutions to the challenges they face," he added. It is important to note the FDA approval of the GENOSYL DS for use with rebreathing anesthesia in the operating room setting is for the second generation device. The recently approved third generation GENOSYL DS has not been tested with rebreathing anesthesia. VERO Biotech is currently in the process of conducting similar validations and expect to have the data available Q1-2023. GENOSYL DS is the first tankless inhaled nitric oxide delivery system approved by the US Food and Drug Administration (FDA). Inhaled Nitric Oxide dilates pulmonary blood vessels and may be used to improve oxygenation in neonates with hypoxic respiratory failure and pulmonary hypertension. Unlike tank-based systems, GENOSYL DS generates and delivers iNO at the bedside using a small disposable cassette. This eliminates the need for hospitals to manage large, cumbersome tanks and helps to simplify clinical workflow.

Flu, RSV on Decline, but COVID Deaths Persist

Respiratory illness levels in the US have declined so much in recent weeks that they are approaching numbers usually seen during non-flu season. Just 3% of flu tests are coming back positive, according to the CDC's weekly Fluview report. Case counts for respiratory syncytial virus (RSV) emergency department visits are now below summertime levels. Both illnesses raged in record-shattering fashion just a couple of months ago. "This flu season started really early because there were so many children with zero experience with flu, common colds, and RSV," David Celentano, ScD, chair of epidemiology at Johns Hopkins Bloomberg School of Public Health, said. Data is now pointing to what may amount to simply an early peak for flu and RSV. About 25 million people in the US have had the flu this year and 17,000 people have died of it. The once record-setting hospitalization rate for the flu has fizzled so much that this season may finish up below average for hospitalizations, the CDC projected. The agency said this year's flu vaccine has been very effective against circulating strains.

Siemens Healthineers and Unilabs launch strategic partnership

Siemens Healthineers, a leading medical technology company, and Unilabs, a leading diagnostic services provider, announced a multi-year agreement valued at over €200 million. Unilabs has invested in Siemens Healthineers' top-notch technology and will acquire more than 400 laboratory analyzers to further improve its laboratory infrastructure to offer an unparalleled service to its customers. "Delivering the best possible patient care is at the heart of everything we do, and we will continue to invest in the latest technology to further boost our services," said Michiel Boehmer, Unilabs' CEO. "Our CARE BIG mantra is driving us in our quest to build the most-digitally driven diagnostics group — enabling better decisions for a healthier tomorrow." Under this agreement, Unilabs will continue modernizing its healthcare infrastructure across its network to improve customer service and quality, and thereby improve patient health. The solutions Siemens Healthineers provides will enhance Unilabs' laboratory operations, throughput, and clinical equivalence across its testing network. In the first years, Siemens Healthineers will install high- and mid-volume immunoassay and clinical chemistry analyzers, including the Atellica Solution and Atellica CI 1900, sample handlers, haemostasis analyzers, and automation solutions. "Siemens Healthineers is uniquely positioned to add value through a portfolio of products that work in harmony to scale technology, especially as testing demand grows," said Sharon Bracken, Head of Diagnostics for Siemens Healthineers. „Our solutions help on many levels. They can improve cost savings and profitability through integrated

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reagents and consumables, deliver sophisticated intelligence software for better data analytics, and reduce unnecessary workflow friction with intuitive system user interfaces. We look forward to how our collaboration with Unilabs, along with its expanded investment in Siemens Healthineers technology, will benefit the company's laboratory operations and patient care for years to come."

Comorbidities and the Prognosis of Chronic Obstructive Pulmonary Disease

Strict control of comorbidities in patients with chronic obstructive pulmonary disease decreases exacerbations, morbimortality, and avoids readmissions. An increasing number of women have the disease, which progresses differently in women than in men and even has different comorbidities. "Comorbidities in patients with chronic obstructive pulmonary disease are more common in older adults, in those with more advanced pulmonary disease, and in those that are hospitalized for an acute exacerbation," said Belén Alonso, MD, PhD, coordinator of the COPD Working Group of the Spanish Society of Internal Medicine. Up to 73 comorbidities associated with chronic obstructive pulmonary disease have been described. Alonso made these remarks during her presentation at the Comorbidities in Chronic Obstructive Pulmonary Disease Panel, which took place during the 43rd Conference of the Spanish Society of Internal Medicine (SEMI), in Gijón, Spain. According to the scientific society's press release, moderator María Gómez Antúnez, MD, stated, "The correct approach and treatment of these comorbidities is fundamental to improve the quality of life of the patient, decrease exacerbations, avoid readmissions, and decrease morbimortality in people with chronic obstructive pulmonary disease." The different works published, two of them by the SEMI COPD Working Group (ECCO and ESMI studies), indicate that the main comorbidities of patients with that pneumopathy are arterial hypertension, dyslipidemia, diabetes, heart failure, atrial fibrillation, ischemic heart disease, chronic kidney disease, peripheral arterial disease, and osteoporosis. Chronic hepatopathy, pulmonary neoplasm, depression, and cerebrovascular disease are less common.

Masimo and Philips Expand Partnership to Improve Telehealth

Masimo and Royal Philips announced an expansion of their partnership to augment patient monitoring capabilities in home telehealth applications with the Masimo W1 advanced health tracking watch. The W1 will integrate with Philips's enterprise patient monitoring ecosystem to advance the forefront of telemonitoring and telehealth. The combined innovation, which draws upon the two global medical technology leaders' extensive expertise in monitoring, connectivity, and automation, will be highlighted later this month at *Arab Health 2023*. Masimo W1 is the first watch to offer accurate, continuous pulse oximetry measurements and other insightful health data. Using Masimo's secure health data cloud, patient information will be relayed to the Philips patient monitoring ecosystem for remote clinician surveillance. Hospital clinicians will be able to seamlessly and remotely monitor key health markers as their patients move throughout their homes and go about their daily lives. Physicians will be able to more confidently discharge patients knowing that their vital signs will still be monitored (via Masimo W1) and their physiological status tracked (via Philips dashboards), helping them catch possible patient deterioration sooner and make more informed interventions. This breakthrough combination of monitoring and connectivity technologies will enable numerous opportunities supporting early discharge initiatives, hospital-at-home programs, and chronic illness management. Bilal Muhsin, Chief Operating Officer of Masimo Healthcare, said, "Expanding our partnership with Philips in this way is a win-win for patients and clinicians everywhere, and is an important part of our multi-year plan to bring the best of hospital monitoring to the home while continuing to improve access to quality hospital care." "At Philips, we believe in an open ecosystem of information that enables physicians in their daily routine, allows for them to access and process vital patient information and deploy a wide range of measurements and patient-worn technologies," added Christoph Pedain, General Manager, Hospital Patient Monitoring at Philips. "Our integration of the latest Masimo technologies is a testament to that strategy and we are delighted to deepen our relationship with Masimo." Masimo W1 for use in medical applications is CE marked and is pending FDA clearance.

Omicron Subvariant XBB.1.5 Accounts for 43% of US COVID Cases: CDC

The fast-spreading Omicron subvariant XBB.1.5 is estimated to account for 43% of the COVID-19 cases in the United States for the week ended Jan. 14, data from the Centers for Disease Control and Prevention showed on Friday. The subvariant accounted for about 30% of cases in the first week of January, higher than the 27.6% the CDC estimated. XBB.1.5, which is related to Omicron, is currently the most transmissible variant. It is an offshoot of XBB, first detected in October, which is itself made from a combination of two other Omicron subvariants. The World Health Organization (WHO) said XBB.1.5 may spur more COVID-19 cases based on genetic characteristics and early growth rate estimates. While it is unclear if XBB.1.5 can

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cause its own wave of global infections, experts say the current booster shots continue to protect against severe symptoms, hospitalization and death. WHO Director General Tedros Adhanom Ghebreyesus tweeted the subvariant has been on the rise globally and has been identified in over 25 countries.

Obesity Impacts Peripheral Airway Reactivity, Asthma

Peripheral airway response to methacholine was similar among obese adults with and without asthma, although forced expiratory volume was lower for those with asthma, based on data from 53 individuals. Obesity remains a risk factor for asthma, and obese individuals with asthma tend to have worse control and more severe disease compared to nonobese asthma patients, wrote Anne E. Dixon, MD, BM, BCh, of the University of Vermont, Burlington, and colleagues.

Previous studies have shown that airway reactivity can occur in obese individuals without airway inflammation, but studies characterizing obese asthma based on lung function are lacking, they said. "Combining spirometry and oscillometry might reveal abnormalities in lung mechanics particularly pertinent to people with obesity and asthma," the researchers noted. In a cross-sectional study published in the journal *Chest*, the researchers reviewed data from 31 obese adults with asthma and 22 obese adults without asthma. The participants were aged 18 years and older, with forced expiratory volume (FEV1) of at least 60% of predicted. All had class III obesity, with an average BMI of 47.2 kg/m2 for those with asthma and 46.7 kg/m2 for nonasthma controls. Demographic characteristics were similar between the groups. Airway reactivity was defined as a 20% decrease in FEV1 and/or a 50% change in resistance or reactance at 5 Hz (R5 and X5), at a concentration of 16 mg/mL or less of methacholine. Patients were assessed using spirometry and oscillometry. Overall, most obese individuals with and without asthma showed significant changes in peripheral airway resistance. For those with asthma, the resistance at 5 Hz, measured by oscillometry, increased by 52% in response to the PC20 methacholine challenge, with an area under the reactance curve (AX) of 361%. For controls without asthma, the resistance at 5 Hz increased by 45%, with an AX of 268% in response to 16 mg/mL of methacholine.

This finding suggests that obesity predisposes individuals to peripheral airway reactivity regardless of asthma status, the researchers wrote in their discussion.

First and Only Asthma Rescue Medication Approved in the US

AIRSUPRA (albuterol/budesonide), formerly known as PT027, has been approved in the US for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in people with asthma aged 18 years and older. The approval by the Food and Drug Administration (FDA) was based on results from the MANDALA and DENALI Phase III trials. In MANDALA, AIRSUPRA significantly reduced the risk of severe exacerbations compared to albuterol in patients with moderate to severe asthma when used as an as-needed rescue medication in response to symptoms. Importantly, in the secondary endpoint of mean annualized total systemic corticosteroid exposure, AIRSUPRA demonstrated a significant reduction compared to albuterol at the approved dose of 180mcg albuterol/160mcg budesonide. In DENALI, AIRSUPRA significantly improved lung function compared to the individual components albuterol and budesonide in patients with mild to moderate asthma. AIRSUPRA is a first-in-class, pressurized metered-dose inhaler (pMDI), fixed-dose combination rescue medication containing albuterol, a short-acting beta2-agonist (SABA), and budesonide, an anti-inflammatory inhaled corticosteroid (ICS) in the US. It is being developed by AstraZeneca and Avillion. Bradley E. Chipps, Past President of the American College of Allergy, Asthma & Immunology and Medical Director of Capital Allergy & Respiratory Disease Center in Sacramento, US, said: "People with asthma are at risk of severe exacerbations regardless of their disease severity or level of control. Current albuterol rescue inhalers alleviate acute symptoms, but do not treat the underlying inflammation in asthma. The approval of AIRSUPRA means that for the first time, adults with asthma in the US have a rescue treatment to manage both their symptoms and the inflammatory nature of their disease." Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said: "With patients experiencing more than 10 million asthma exacerbations each year in the US and uncontrolled asthma expected to cost the US economy billions of dollars in direct medical costs alone over the next 20 years, today's positive decision is good news for those adults with asthma who make up more than 80% of asthma patients in the US. Physicians will be able to offer their patients AIRSUPRA, an important new rescue treatment that reduces the risk of asthma exacerbations." Asthma is a chronic, inflammatory respiratory disease with variable symptoms that affects as many as 262 million people worldwide. In the US over 21 million adults have asthma, representing more than 80% of the total number of people with asthma. Adults have

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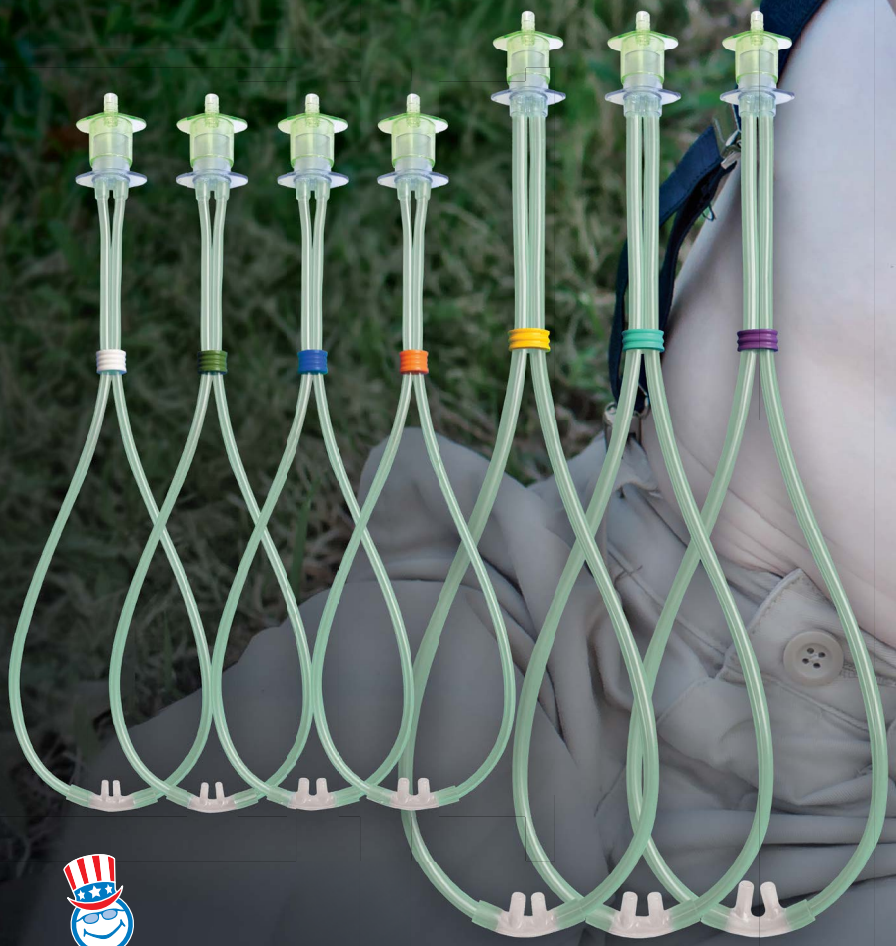

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8.5 million exacerbations each year in the US.[4] Uncontrolled asthma will cost the US economy an estimated $300 billion (in 2018 dollar values) in the next 20 years in direct medical costs alone. The safety and tolerability of AIRSUPRA in both trials were consistent with the known profiles of the components, with the most common adverse events including headache, oral candidiasis, cough and dysphonia.Results from the MANDALA trial were published in the *New England Journal of Medicine* in May 2022.

Financing Founds for Respiratory Care

Honeywell and Telesair, Inc., an innovator of next generation respiratory care, jointly announced that Telesair, Inc. has closed a total of $22 million Series A round financing led by Pasaca Capital with participation from existing and new investors such as ZhenCheng Capital, Shangbay Capital, Device of Tomorrow Capital, Berkeley Catalyst Fund and Ultrastar Ventures LLC. The round of funding will support the commercialization of Telesair's Bonhawa Respiratory Humidifier, a unique, differentiated respiratory solution for use in the ICU and the development of a second-generation, revolutionary product designed to get patients out of the hospital sooner and safely at home longer. "We are excited to be moving into the next step of our evolution as a company," said Telesair CEO, Bryan Liu. "This funding helps us further advance our mission and fully launch our first generation Bonhawa platform technology as we continue to develop second generation innovations to address a multi-billion-dollar market that is underserved today. In an age of dramatically increasing respiratory disease challenges, simple-to-use medical respirators are paramount to treatment and empower patients to experience a better quality of life. We're delighted that our funding partners share our vision and have confidence in our ability to deliver real solutions to a major global need." "Telesair, Inc.'s innovative products, strong team and execution capability fit perfectly to our investment philosophy," said Charles Huang, Founder and Chairman of Pasaca Capital. "We are proud to support Telesair and be a part of its growth. We look forward to supporting Telesair through forthcoming development and commercialization milestones, and we are excited to see the company's progress in the months and years ahead." Honeywell Ventures is the venture arm of Honeywell that invests in early-stage, high-growth companies that have emerging and disruptive technologies which will change how we live, work and use energy. "Honeywell is aligned with Telesair's mission to improve lives through innovation in digital healthcare" said Patrick Hogan, Managing Director of Honeywell Ventures. "We are impressed with their mission and technology roadmap, and we are excited to collaborate with them in critical areas such as advanced sensing and remote patient monitoring, enabled by artificial intelligence and machine learning."

New Study Finds That Masimo Patient SafetyNet Helped Clinicians Reduce CPR Events and Rates

Masimo announced the findings of a before-and-after study published in *PLoS ONE* in which Dr Ahmed Balshi and colleagues at King Saud Medical City in Riyadh, Saudi Arabia, evaluated the impact of implementing remote patient monitoring with Masimo Patient SafetyNet on the efficacy of hospital rapid response teams (RRTs). Comparing outcomes before and after implementation of Patient SafetyNet, they found that the "after" group experienced more RRT activations but had significantly lower incidence and rate of cardiopulmonary resuscitation (CPR), significantly shorter hospital length of stay (LOS), and lower hospital mortality. Noting that RRT activation depends on the "timely detection of [patient] deterioration," the researchers sought to determine whether a remote patient surveillance system that automated calculation and relaying of early warning scores could lead to earlier recognition of changes in patient status and the improved efficacy of RRTs. They hypothesized that implementing such a system could decrease the rate of severe adverse events, as a result of potentially quicker RRT activation. To that end, they designed a "before" and "after" study at a large government hospital (1,200 inpatient beds) in central Saudi Arabia where the ICU provides outreach, in the form of an RRT, to the general ward. In the "before" period (retrospective data) nurses manually recorded patient vital signs, calculated warning scores, and activated RRTs; in the "after" period" (prospective data), vital signs data collected at the bedside, alongside automatically calculated warning scores, were wirelessly relayed to nursing stations for centralized remote patient surveillance and RRT activation. Both before and after, activation of an RRT was triggered when a patient's vital signs deteriorated to the point they scored ≥ 5 on the MEWS (Modified Early Warning Score) scale. "Before" group data was analyzed from 2,346 adult patients from January to August 2020, and "after" group data from 2,151 patients from September 2020 to April 2021. For the "after" group, Masimo Patient SafetyNet was used to automate transfer of bedside monitoring data to central nursing stations, with alarm and notification data also relayed to clinicians' smartphones using Masimo Replica. The researchers found that in the "before" group, there were 78 episodes of CPR over 20,510 total inpatient days, for an incidence of 3.3% and rate of 3.8 per 1000 inpatient days (95% confidence interval: 3 – 4.7 episodes). In the "after" group, there were 42 episodes over 17,945 inpatient days, for an incidence of 1.95% and rate of 2.3 per 1000 inpatient days (95% CI: 1.7 – 3.2). CPR incidence in the "after" group was significantly lower ($p = 0.01$). In addition, the CPR success rate was significantly higher in the "after" group (before: 38.5% vs. after: 59.5%; $p = 0.04$). The average hospital LOS was higher in the "before" group (before: 8.7 days ± 3.4 days vs. after: 8.3 days ± 3 days; 95% CI of the difference: 0.2 – 0.6 days; $p < 0.001$). The number of RRT activations was lower in the "before" group (before: 20 ± 7 vs. after: 23.7 ± 9.4; 95% CI of the difference: 3.2 – 4.2; $p < 0.001$). Overall hospital mortality was lower in the "after" group (before: 5.45% vs. after: 4%; 95% CI: 0.6 – 2.2; $p < 0.001$). Using multivariable logistic regression, they calculated that being in the "after" group decreased a patient's odds of needing CPR by 33% (odds ratio: 0.67; 95% CI: 0.46 – 0.99; $p = 0.04$). The investigators concluded, "Automated activation of the RRT by Masimo Patient SafetyNet applied to medical ward patients significantly reduced CPR events and rates, reduced hospital length of stay, and increased the number of RRT activations. There was no difference in the ICU admission rates. Further evaluation of the system in surgical wards and mixed settings [should be] conducted."

Company Rakes in Awards

Werfen announced that it has received five 2022 IMV ServiceTrak Awards including Best System Performance and Best Service in the Coagulation (Hemostasis) category, as well as Best Customer Satisfaction, Best System Performance and Best Service in the Blood Gas category. These honors mark the fourth-consecutive year Werfen has been recognized in Coagulation since this category was established in 2018, and the second time Werfen has swept Blood Gas, since the category was established in 2020. IMV ServiceTrak 2022 Clinical Laboratory Awards are presented to manufacturers whose customers are highly

Continued on page 60…

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1. Alcoforado L, Ari A, Barcelar J, Brandão S, Fink J, de Andrade A. Impact of Gas Flow and Humidity on Trans-Nasal Aerosol Deposition via Nasal Cannula in Adults: A Randomized Cross-Over Study. Pharmaceutics 2019; 11: 320.

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A Closer Look at Hermanksy-Pudlak Syndrome

Respiratory conditions are sometimes caused by hereditary disorders that have a negative impact on pulmonary function. One such disorder is Hermansky-Pudlak Syndrome. In this feature, Respiratory Therapy takes a closer look at the disease itself, its impact on lung health, and those who support people living with it.

A rare hereditary disorder

Respiratory conditions are sometimes caused by underlying diseases, or hereditary disorders, that have a negative impact on pulmonary function. One such disorder is Hermansky-Pudlak Syndrome.

Earlier this year, at the American Thoracic Society 2022 International Conference in San Francisco, we met with Donna Appell from the Hermansky-Pudlak Syndrome Network and learned about the important work they do in supporting people affected by this rare hereditary disorder. We had the opportunity to understand more about the challenges faced by people living with HPS and to find out how Vitalograph can support those people, particularly in Puerto Rico where HPS affects one of every 1,800 individuals. One in every 21 individuals of northwest Puerto Rican descent is believed to be a carrier of the HPS type 1 gene, due to a genetic founder effect. HPS occurs in other populations as well. (The National Organization for Rare Disorders (NORD), 2022).

Hermansky-Pudlak syndrome (HPS) affects multiple body systems and includes bleeding and visual problems, and abnormally light coloring of the skin, hair, and eyes (oculocutaneous albinism). Other symptoms may include immune problems, lung scarring (pulmonary fibrosis), and colitis. (Dermatol, 2009).

Pulmonary fibrosis is highly prevalent in three out of 11 genetic types of HPS, including type 1. This form of pulmonary fibrosis has a progressive course, is difficult to treat, and usually leads to a poor prognosis with a shortened life expectancy. People with HPS types 1, 2, or 4 who develop pulmonary fibrosis may eventually need a lung transplant.

Respiratory diagnostics and care form an essential part of the management of HPS, and access to professional healthcare services is critical to the detection, monitoring, and management of HPS-related pulmonary fibrosis. (Tadafumi Yokoyama, Mar 2021)

About the HPS Network and the HPS Clinic in Puerto Rico

Founded in 1992, the HPS Network has a mission to provide education and vital support programs to individuals and families with HPS while striving for improved care and innovative research on the journey to cure.

We invited Donna Appell and Carmen Camacho from the HPS Network to tell us more about their work.

What plans does the HPS Network have for plans for next year?

"In March 2023 we will host our 28th Conference in person in New York, during which there will also be a science meeting for HPS researchers. During this conference, researchers are invited to utilize the gathering to collect specimens for science. Up until now, our record is five different research protocols with five different informed consents in Spanish and English, and accessible for our visually impaired community. That occasion, there was a time restriction because the specimens needed to get to labs quickly. We enrolled 38 HPS individuals, drew 96 tubes of blood, and collected 4 stool specimens in 1 hour and 55 minutes! That initiative is called *We're Drawn Together*.

We also organise an annual conference in Puerto Rico for families and physicians, that is CME accredited Med/Ed. Several times a month we offer a virtual support meeting for adults and parents in both Spanish and English facilitated by a licensed social worker. We provide a Registered Nurse to help with the diagnostic journey and have a 'new family' program. We fund and contribute to research in any small way possible."

Tell us about the HPS Clinic in Puerto Rico?

"We have many members in Puerto Rico and there is no lung transplant center on the island. We were instrumental in engaging Dr Jesse Roman, who was incredible, and who established a cost-free multidisciplinary clinic, available to individuals and families with HPS.

It is run in partnership between our physician medical experts on the island of Puerto Rico (Dr Enid Rivera, Dr Rosa Roman and Dr Wilfredo De Jesús Rojas) and the HPS Network. The clinic provides care from volunteer clinical physicians in pulmonology, gastroenterology, haematology, psychology, and dentistry. At the clinic, medical histories are taken, and DNA testing is conducted. 6-minute walk test, Pulmonary Function Testing, Covid Testing, Pulmonary Rehab training, and health coaching are provided. Medical students are also involved and are very helpful.

The clinic is facilitated by volunteer physicians in Mayaguez, Puerto Rico. Medical space is provided free of charge and

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

travel is provided for patients when needed. It takes place approximately every three to four months."

How does spirometry and access to diagnostic spirometers make a difference to this clinic?

"Having spirometry can help the physicians assess a patient's lung status and design an exercise program based on results. Comparisons can be made from clinic to clinic over time, enabling lung transplant evaluations to be recommended earlier."

What other treatments take place at the HPS Clinic

"Oxygen and medications like pirfenidone can be prescribed appropriately. This will also serve to amass data to inform disease burden to get increased services. "

Feedback from users of the Clinic

For those who are affected by HPS in Puerto Rico, the Clinic provides important resources and access to professional and specialized healthcare resources.

Users of the Clinic in Puerto Rico say:

"The clinic was very good; this is the first time I attend an HPS clinic. This experience was wonderful, thank you to all the doctors who helped make it possible."

"I am extremely grateful for everything. It was excellent. A thousand blessings to all the people who made this possible and to the doctors. It is the first time I have been able to attend, and the truth was a joy. THANK YOU!"

"Thank you to everyone who made this clinic possible. It is the first time I attend with my child, and I loved it. Excellent treatment and excellent resources."

Proactive in managing respiratory health

Living with HPS can have a daily impact on respiratory health,

Appell and Carmen Camacho

and for people living with the disorder, managing their daily respiratory health is an important part of managing their disorder.

"For me having HPS is like having your guard up all the time! You've got to be careful, from simple things like allergies to infections like RSV which could be life-threatening. It's like walking on eggshells when it comes to your lung care." Says Carmen Camacho, who has HPS.

When it comes to managing her respiratory health she says: *"it's all about being proactive, exercising, pulmonary rehab, wearing a mask, not smoking, and staying away from those to smoke! I want to keep my lung health as much as possible!"*

Supporting the HPS Network and those living with Hermansky-Pudlak Syndrome

In order to support those living with the disease and further

research into this syndrome, Vitalograph has donated six of its Alpha spirometers to the clinic in Puerto Rico. These arrived in January 2023 and are being used immediately to aid diagnosis and monitor respiratory conditions associated with HPS. Vitalograph will also use its position as a global leader in respiratory diagnostics to raise awareness about HPS among the wider respiratory healthcare community.

Donna says: "It is our dream to increase the accessibility of a good standard of care to all individuals with HPS. We want all our members to get the best possible care. We do not have a treatment specific for HPS but the idea of not having access to "expert care" is intolerable. These Vitalograph spirometers will transform our ability to monitor our community and increase their quality of life. Donating this equipment to our clinic will assist doctors in delivering the care they want to give our families. These spirometers will be directly responsible for better outcomes. "

Dr. Wilfredo De Jesús Rojas, Pediatric Pulmonologist in Puerto Rico says: "Long-term tracking of the pulmonary function test in patients with Hermansky-Pudlak Syndrome (HPS) is vital to making medical decisions and providing counselling and education to our patients about the status of their overall lung health. The acquisition of new tools, like spirometers, to measure the functional pulmonary capacity of our patients with HPS in the clinic, will help to guide medical providers on the island to implement early referrals to specialized centers in the US. Also, the new spirometers will educate our community with HPS about the importance of pulmonary fibrosis surveillance and a better understanding of the natural history of HPS impact on the respiratory system of our patients."

If you or a member of your family have HPS and would like to avail of the support provided by the HPS Network, visit https://www.hpsnetwork.org/ for more information.

The HPS Network is a charitable organisation. You can help them continue their efforts to improve the lives of those affected by Hermansky-Pudlak Syndrome by making a donation.

Thanks to the HPS Network for their help in compiling this insight into Hermansky-Pudlak Syndrome.

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Bench Study: Performance of Three Home Ventilators For Leak Compensation

Jonathan Waugh, PhD, RRT, RPFT, FAARC

Home noninvasive ventilators have advanced beyond the original spontaneous/timed (ST) mode of pressure breaths involving set inspiratory and expiratory pressures. Most manufacturers offer a version of volume-targeted, pressure breaths (i.e. iVAPS, AVAPS, PSV-TgV). These new and sophisticated volume-targeted modes may differ in basic performance. Performance of these modes can be carried out by independent bench studies. These bench studies are set up to use specific ventilation scenarios to allow testing and comparison to be made between different makes and models of ventilators. The aim of the scenarios is to simulate conditions that are like clinical practice.

The aim of this study was to evaluate the volume delivery characteristics and leak compensation of three models of home ventilators (Vivo 45LS, Breas Medical, Mölnlycke Sweden; Trilogy Evo, Philips, Murrysville, USA; and Astral 150, ResMed, Bella Vista, Australia) with regards to:

- Tidal volume (TV) variation
- Variation in delivered TV between 3 devices of the same ventilator model
- The time to reach the set target volume

Average tidal volumes were measured in a volume targeted mode (PSV-TgV, Breas Medical, Mölnlycke Sweden; AVAPS, Philips, Murrysville, USA; and iVAPS, ResMed, Bella Vista, Australia).

Methods

The leak compensation function of three models of home ventilators (Vivo 45LS, Trilogy Evo and Astral 150) were tested at four circuit leak levels (0, 10, 20, and 30 L/min). Three patient respiratory system conditions (normal, restrictive, and obstructive) were imposed at each level of circuit leak and three ventilators were tested from each make and model. Separate runs of triggered and untriggered breaths were done for each level of testing.

Measurement

The study was performed in the Respiratory Therapy Laboratory of Liberty University (Lynchburg, Virginia, USA). The mode of ventilation tested was a volume-targeted pressure support breath using a single-limb patient circuit and passive exhalation. An OEM inline intentional leak port was used for each model of the ventilator. The testing protocol was based upon that used by Carlucci et al (2013) that simulated three different patient conditions (normal, obstruction, restriction) using an ASL 5000 lung simulator (Ingmar Medical Ltd., Pittsburgh, PA, USA). Tidal volume (V_T), airway pressure, and flow rate were measured using a CITREX H3 gas flow analyzer (IMT Analytics, Switzerland) and companion Flow Lab software, version 5.2.0, (Figure 1). The flow analyzer was factory-calibrated prior to testing. Prior to each test session, a 15-minute warm-up period occurred followed by zeroing of the gas flow analyzer and ventilator pre-use check and circuit calibration. The gas flow analyzer zeroing step was repeated in the middle of a testing run.

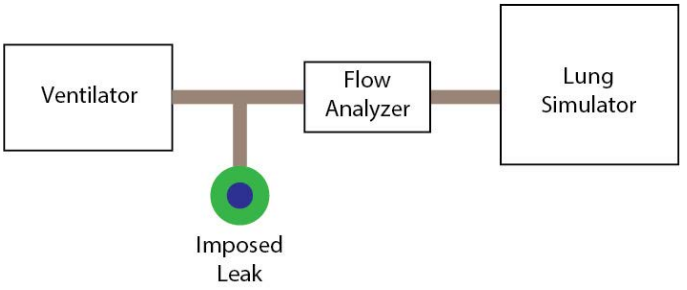

Figure 1. This Figure shows the testing apparatus configuration.

Three different conditions were simulated:

1. Normal respiratory mechanics (resistance 5 cm H_2O/L/s and compliance 50 mL/cm H_2O)
2. Restrictive pattern (resistance 5 cm H_2O/L/s and compliance 30 mL/cm H_2O)
3. Obstructive pattern (resistance 15 cm H_2O/L/s and compliance 50 mL/cm H_2O).

Table 1 shows the lung simulator respiratory muscle pressure (Pmus) settings. This setting was set to prevent auto-triggering or asynchrony. Settings were compatible with all the ventilator models.

Table 1. Lung simulator settings.

Patient	R	C	BR	Pmus
Normal	5	50	10	5
Restrictive	5	30	15	2
Obstructive	15	50	20	8

RespiSim® software, version 4 (Ingmar Medical Ltd.) was used to control the ASL 5000 lung simulator. Neural inspiratory time was

Jonathan Waugh, PhD, RRT, RPFT, FAARC, Professor and Program Director, Respiratory Therapy Program Liberty University, Lynchburg, Virginia, USA.

0.3 seconds and passive expiratory time was 0.7 seconds for all three patient conditions.

Ventilators were set in volume-targeted pressure support mode with the following parameters: expiratory positive airway pressure (EPAP) of 5 cmH_2O, minimal inspiratory pressure positive airway pressure (IPAP) (IPAP/ peak inspiratory pressure (PIP) minimum) of 8 cmH_2O, maximal IPAP (IPAP/PIP max) of 40 cm H_2O, backup inspiratory time 1.0 seconds, rise to inspiratory pressure at the maximum setting, and V_T target of 500 mL. Inspiratory and expiratory trigger levels were set to avoid auto-triggering.

Four levels of leaks (0, 10, 20, 30 L/min) were created with an adjustable flow control valve and calibrated by measuring the leak flows with the IMT CITREX flow analyzer at a constant pressure of 10 cmH_2O.

Three minutes of data were recorded for each test. The last ten breaths of each three-minute recording period were used for comparative analysis. A total of 2,160 raw data items were verified for accuracy by entering the data twice and using a file comparison utility (MS Spreadsheet Compare tool) to confirm parity. Statistical analyses were performed using SYSTAT™ version 13.

Results

Three waveforms (pressure, flow, and volume) were captured during each three-minute recording period, an example is shown in Figure 2.

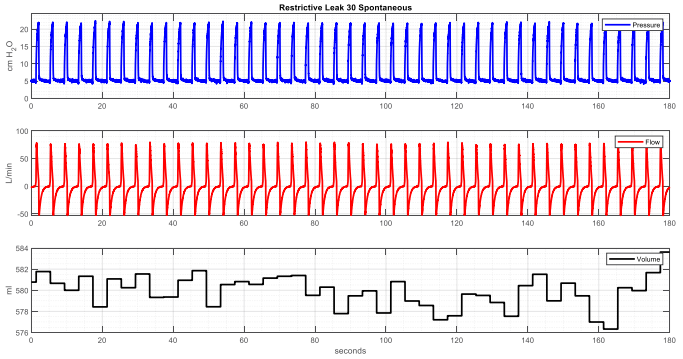

Figure 2. This Figure shows an example of the bench test with a restrictive profile and a leak of 30L/min with a spontaneous trigger. Pressure (blue), flow (red), volume (black).

Tidal volume variation

The Vivo 45LS volume delivery in a target volume mode was the most accurate as the ventilator had the least tidal volume variation. Figure 3 A-F shows the Vivo 45LS was most closely grouped around the volume target of 500 mL when compared to the other ventilator models for all the bench test conditions. The other ventilators performed within an acceptable tolerance.

Device tidal volume variation

Tidal volumes for the 3 ventilators with regards to the specific conditions normal, obstructive, restrictive of the same make are shown in Figure 4. The variability in the results for the 3 Trilogy Evo devices was the greatest.

Tidal volumes were further compared by ANOVA by the level of the leak with each model of ventilator (conditions combined). Table 2 shows a difference when the four models were compared at each leak level. Post hoc analysis showed all four groups differing from each other.

Table 2. Comparison of ventilator models at each leak setting (combined patient conditions).

	Leak 0	Leak 10	Leak 20	Leak 30
Astral 150	457.7	458.2	468.8	474.5
Trilogy Evo	520.1	507.0	510.6	503.7
Vivo 45LS	513.0	515.0	513.9	516.4
P-Value	p<0.000	p<0.000	p<0.000	p<0.000

Time to reach the set target volume

The time required to reach the target tidal volume when transitioning from a normal compliance to a decreased compliance ranged from 35-134 seconds. The Trilogy Evo was the slowest to reach the set target volume taking almost twice as long as the Vivo 45LS. The Astral had the quickest time to reach the set target volume, See Table 3.

Table 3. Time to reach set ±5% of target volume.

Device	Mean (seconds)	Standard Deviation
Astral 150	35	6.9
Trilogy Evo	134	11.7
Vivo 45LS	70	10.9

Measured tidal volume compared to the set tidal volume

The measured tidal volume for each ventilator model under different conditions was compared to the set tidal volume (500 mL) using a one-sample t-test. The comparisons were grouped as follows: normal lung condition with all levels of leak combined, restrictive lung condition with all levels of leak combined, obstructive lung condition with all levels of leak combined, all lung conditions combined with zero imposed leak (triggered and untriggered breaths), all lung conditions combined with a leak of 10 L/min, all lung conditions combined with a leak of 20 L/min, and all lung conditions combined with a leak of 30 L/min. All group means were different from the set tidal volume value of 500 mL except for one (Evo all lung conditions combined with a leak of 30 L/min), as seen in Table 4. The table also lists the coefficient of variation (CV), a measure of the dispersion of data from the mean value (a gauge of the extent of variability of data). When the CVs of each group compared for each ventilator model were summed, the Vivo 45LS had the lowest value (Astral 150=0.269, Evo=0.339, Vivo 45LS=0.177).

The volume data for the three devices of tested for each model of ventilator are shown in Figure 4. The measured volumes for the Astral 150 during "normal" conditions were similar and grouped around the set tidal volume value but the measurement trends for the restrictive and obstructive conditions were all below the target volume. The measure volumes for the Evo were scattered both above and below the set tidal volume value but with greater fluctuation in data points and error bars. The measured volumes for the Vivo 45LS were grouped more closely and consistently around the set tidal volume target.

Figure 5 shows a side-by-side comparison of the measured volumes of the three models of ventilators with all leak levels and breath trigger states combined. There is no one model that excels at having the least variability and the greatest accuracy (with respect to the set volume) but the Vivo 45LS appears to

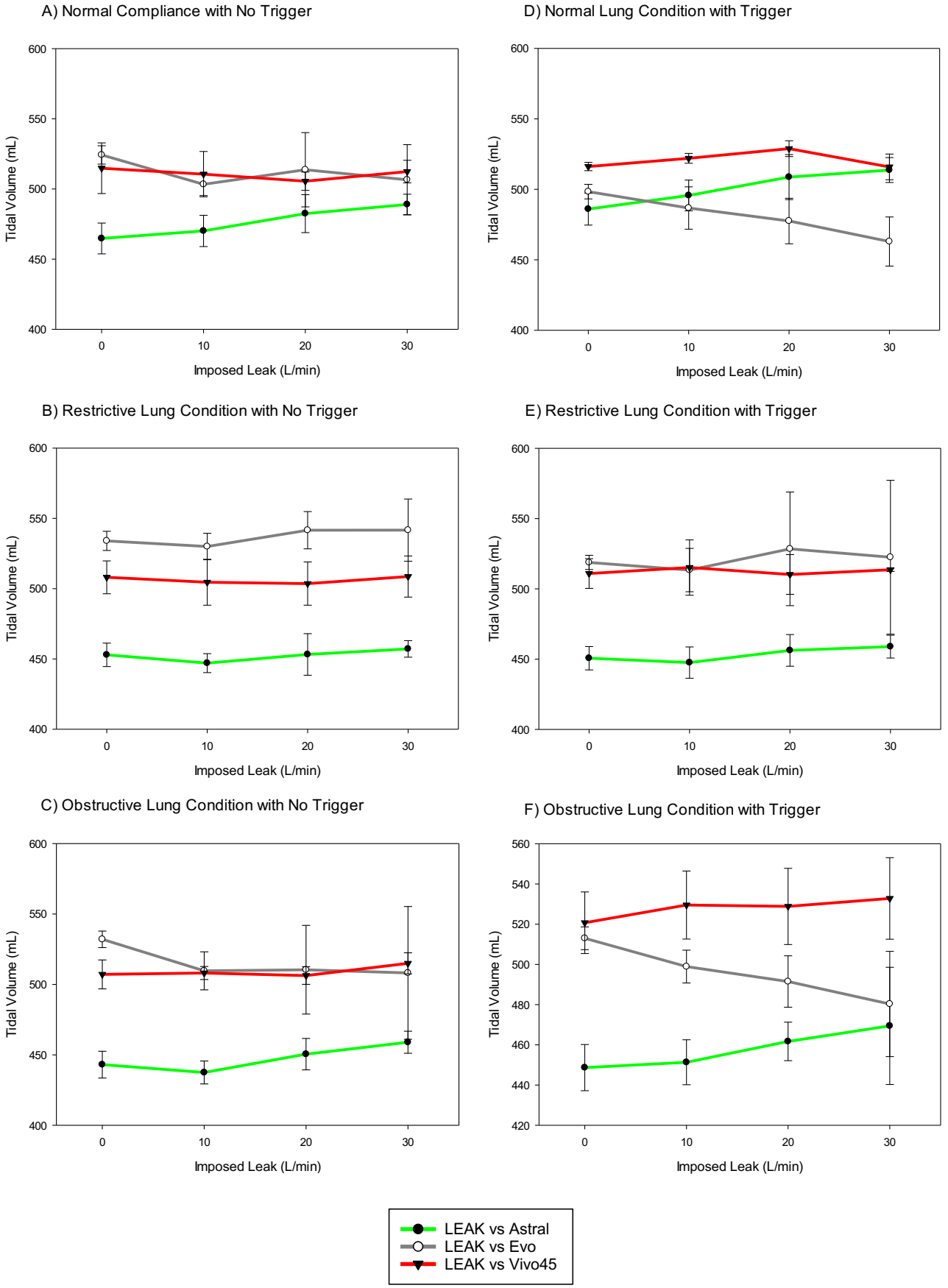

Figure 3. This Figure shows the group mean and SD for each test for the normal, restrictive and obstructive conditions with and without triggering. The measurements were taken at 0, 10, 20 and 30 L/min unintentional leak. The Astral 150 is shown in green, Trilogy Evo in gray, and Vivo 45LS in red.

Table 4. Comparing measured tidal volume to set tidal volume (500 mL).

Group	N	Mean	Standard Deviation	95.00% Confidence Interval		T	Coefficient of Variation	p-Value
				Lower Limit	Upper Limit			
Astral 150								
Normal All Leaks	240	488.8	18.4	486.4	491.1	-9.4	0.038	<0.000
Restrictive All Leaks	240	452.9	9.0	451.8	454.1	-81.3	0.020	<0.000
Obstructive All Leaks	240	452.6	13.8	450.9	454.4	-53.1	0.031	<0.000
Leak 0 – All Conditions	180	457.7	16.7	455.2	460.1	-33.9	0.037	<0.000
Leak 10 – All Cond	180	458.2	21.3	455.0	461.3	-26.3	0.047	<0.000
Leak 20 – All Cond	180	468.8	23.5	465.3	472.2	-17.8	0.050	<0.000
Leak 30 - All Cond	180	474.5	21.9	471.3	477.7	-15.6	0.046	<0.000
Evo								
Normal All Leaks	240	496.7	23.5	493.7	499.7	-2.2	0.047	0.030
Restrictive All Leaks	240	528.8	30.0	525.0	532.7	14.9	0.057	<0.000
Obstructive All Leaks	240	505.5	18.6	503.1	507.9	4.6	0.037	<0.000
Leak 0 – All Conditions	180	520.1	13.1	518.2	522.0	20.6	0.025	<0.000
Leak 10 – All Cond	180	507.0	16.6	504.6	509.5	5.7	0.033	<0.000
Leak 20 – All Cond	180	510.6	32.4	505.8	515.3	4.4	0.063	<0.000
Leak 30 – All Cond	180	503.7	38.7	498.0	509.4	1.286	0.077	0.200
Vivo 45								
Normal All Leaks	240	515.8	14.6	514.0	517.7	16.8	0.028	<0.000
Restrictive All Leaks	240	509.4	9.6	508.2	510.6	15.1	0.019	<0.000
Obstructive All Leaks	240	518.6	13.8	516.8	520.3	20.9	0.027	<0.000
Leak 0 – All Conditions	180	513.0	11.3	511.3	514.7	15.5	0.022	<0.000
Leak 10 – All Cond	180	515.0	14.6	512.9	517.2	13.8	0.028	<0.000
Leak 20 – All Cond	180	513.9	14.8	511.8	516.1	12.6	0.029	<0.000
Leak 30 – All Cond	180	516.4	12.4	514.6	518.2	17.7	0.024	<0.000

have an overall best performance due to a consistently small error bar size and a predictable small bias for the mean volume (always a little above the set volume). The Evo and Astral 150 means have greater fluctuation from one lung condition to the next, and the Evo has larger error bars.

Conclusion

The three models tested were statistically different from the set target volume but clinically acceptable. The most predictable volume output trend with the least variation was observed with the Vivo 45LS. A consistent deviation is more desirable than an inconsistent pattern when the patient condition changes. It is not surprising that the measured tidal volume variability (as measured by the coefficient of variation (CV)) was lower for all ventilator models when no imposed leak was present. When all levels of imposed leaks were considered, the Vivo 45LS had the lowest cumulative CV, indicating it was most stable and consistent in its output in the face of changing levels of leaks. This is a significant consideration. For example, a mean tidal volume of 500 mL that has a range of ±10 mL is potentially safer than a mean tidal volume of 500 mL that has a range of ±50 mL. The Astral 150 had the shortest time to reach the target volume criterion with the Vivo 45 having the second shortest time to reach the target volume. The Trilogy Evo required the longest time to reach the target tidal volume criterion of ±5% of the set volume. Too fast a time to reach the target volume may disturb sleep and too slow a time may impair ventilation. Although the size of the ventilator was not part of the study, the Vivo 45LS is the smallest ventilator of the four models tested. Despite the small size of the ventilator, it can deliver an accurate target volume. When comparing functions under the different lung conditions and varying levels of an imposed leak, the Vivo 45LS had a more dependable and desirable pattern of performance.

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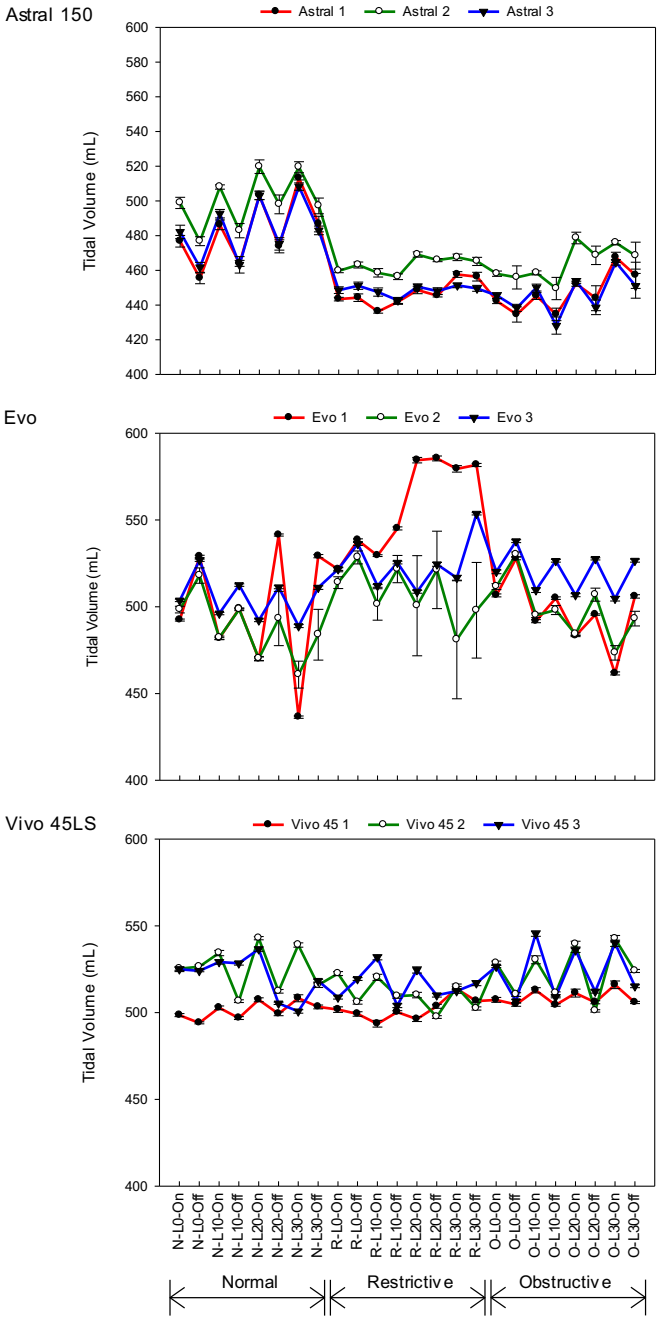

Figure 4. This Figure shows the performance of 3 ventilators of the same model. The Y axis indicates the volume in mL for each test condition. The X-axis has the test conditions for normal (N), restrictive (R), and obstructive compliance (O) for a leak (L) of 0, 10, 20, and 30L/min with the trigger on (on) and off (off).

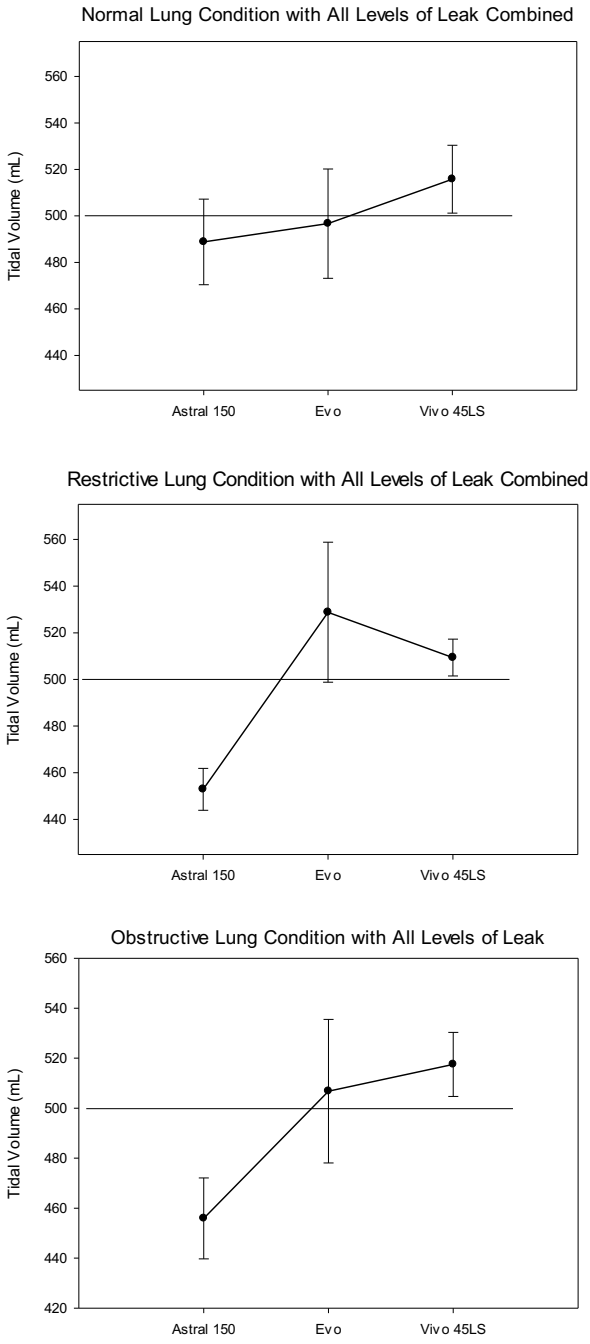

Figure 5. This Figure shows the performance of each model of ventilator for the three lung conditions (normal, restrictive, and obstructive compliance/ resistance) with all levels of leak combined (0, 10, 20, and 30L/min with the trigger on and off). The Y axis indicates the volume in mL for each test condition.

Sequential Rebreathing for the Treatment of Long COVID Cognitive Dysfunction

Alex Stenzler

Introduction

During the worldwide COVID-19 pandemic, a significant population of patients reported different functional complaints one month or later after recovery from the acute infection. This entity has a number of names including "long-COVID" or "post COVID condition."

Long-COVID is on the rise and no effective treatment exists yet to improve cognitive function.[1] Recent research has shown that people with even mild COVID had a greater decline in executive function, notably in their ability to perform complex tasks.[2] These symptoms were associated with changes observed on MRI exams. In this UK Biobank study, 401 COVID patients showed a greater loss of gray matter volume and more brain tissue damage, an average of 4.5 months after infection compared with people who never were infected. A key aspect of this study was its focus on people with mild COVID-19. Only 4% of patients were hospitalized during their bout of acute COVID-19, so the findings come from a population that parallels the experience of most people worldwide who have been infected.

What drives post-COVID cognitive changes is still a mystery. One hypothesis is that there is persistent immune activation resulting in reduction in cerebral blood flow.[3] Hence, one potential therapy is to restore cerebral blood flow regulation in the brain and/or improve the synchronization of brain functional connectivity networks.

Fortune, et al. demonstrated in their 1992 publication the relationship between end-tidal PCO_2 and oxygen delivery to the brain (See Fig 1 below). An increase from 40 to 50 mmHg in $PetCO_2$ resulted in an increase of approximately 30% in oxygen delivery.[4] There is also evidence that increased CO_2 may decrease inflammation, and decreased CO_2 may increase inflammation.[5,6]

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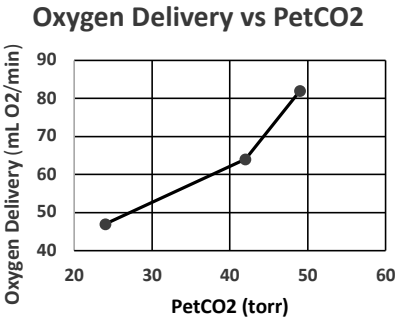

Figure 1. Oxygen Delivery vs PetCO2

Therefore, increased cerebral blood flow, increased oxygen delivery to the brain, and potential reduction in inflammation from an increased arterial CO_2, may be beneficial in this patient population.

Venous blood returns to the lungs from the muscles and organs with a higher carbon dioxide content than arterial blood, which diffuses into the alveoli. When a person exhales, the first gas that is exhaled comes from the trachea and major bronchi (dead space), which do not participate in gas exchange and therefore have a gas composition similar to the inhaled gas. The gas at the end of the exhalation is considered to have come from the alveoli and reflects the equilibrium CO_2 concentration between the capillaries and the alveoli.

In 2005, Somogyi, et al., proposed a sequential rebreathing method of increasing arterial carbon dioxide ($PaCO_2$) to a predetermined level using a breathing circuit which allowed for controlled rebreathing.[7] A commercial device, called the Hi-Ox_{SR}, was developed to enable this method. The advantage of the Hi-Ox_{SR} compared to supplying exogenous CO_2 mixtures to breathe, is that rebreathing circuits require no source of exogenous gas; the PCO_2 of the reserve gas is self-adjusting and follows the target $PetCO_2$ levels. Details of the Hi-Ox_{SR} are provided in Appendix A. The Hi-Ox was tested by the Defence Research and Development Canada at oxygen flow rates of 0.5 to 4.0 liters per minute.[8] At all flow rates, the FiO2 increased, and the mask was determined to be useful for mass casualty situations where oxygen conservation would be beneficial.

Normal end-tidal PCO_2 is in the range of 5-6% (equivalent to approximately 35-45 mmHg). Inhaled CO_2 as a therapeutic treatment has been delivered in concentrations up to 10% CO_2,

with the majority of work at 5% CO_2 and without significant adverse effects.[9,10]

This sequential rebreathing approach has been used in research and clinical applications to evaluate cerebrovascular reactivity during MRI's and retinal arterial blood flow.[11,12,13,14] The retinal blood flow research studies included seventy-three (73) subjects and there were no adverse events reported.

Recent publications by El-Betany and Galganska, suggested that inhaled CO_2 could be used as a treatment for patients with SARS-CoV2 infections.[15,16] El-Betany concluded that, "Depending on the therapeutic regime, CO_2 could also ameliorate other COVID-19 symptoms as it has also been reported to have antioxidant, anti-inflammation, anti-cytokine effects, and to stimulate the human immune system."

Sabel, et al., reported that electrical brain stimulation increased cerebral blood flow and improved oxygen delivery in two subjects with post-COVID cognitive dysfunction.[1] After 10 and 13 days respectively, the subjects had significant improvement in cognitive function. They concluded that, "Because recovery of function was associated with restoration of vascular autoregulation, we propose that (i) hypometabolic, "silent" neurons are the likely biological cause of long-COVID associated visual and cognitive deficits, and (ii) reoxygenation of these "silent" neurons provides the basis for neural reactivation and neurological recovery."

The Hi-Ox (12th Man Technologies, Inc.) is an FDA cleared device and has been sold in the US for approximately 20 years and more than 50,000 patients have been treated using this device to deliver oxygen. The rebreathing component is a Class 1 accessory. The addition of the rebreathing reservoir, when added to the Hi-Ox creates the Hi-Ox_{SR}. Therefore, prescription for use in the US, even for a treatment not previously described, does not require prior FDA or IRB approval.

Methods

Five patients expressing symptoms of post-COVID cognitive dysfunction ("brain fog") were given the Self-Administered Gerocognitive Exam (SAGE) cognitive function test.[17] This is a validated and accepted screening test for cognitive dysfunction. Three physicians, licensed to practice medicine in the US, prescribed treatment with the Hi-Ox_{SR} using low flow oxygen (1.5 to 2.5 LPM) for these patients.

The patients had the Hi-Ox_{SR}, oxygen concentrator and pulse oximeter at home for self-treatment. Twice daily treatments of 30 minutes each was done for 14 days. Oxygen was delivered from the oxygen concentrator at 1.5 LPM to the Hi-OX_{SR}. If the patient expressed an inability to tolerate that low a flow, they were instructed to increase the oxygen flow in 0.5 LPM increments up to 2.5 LPM.

Figure 2. Patient wearing Hi-Ox_{SR}

Patients continuously monitored themselves with a pulse oximeter during treatment. The pulse oximeter served as a safety measure for a tubing disconnection from the concentrator as well as provided assurances to the patients that they were receiving adequate oxygen in the face of a sense of shortness of breath resulting from the rebreathing.

Following completion of the 14-day treatment series, patients were given the SAGE test again to evaluate their post treatment cognitive function. Patients were also asked for their self-perception of changes in brain fog.

Results

The table below reflects the initial SAGE scores and the post treatment scores following 14 days of treatment with the Hi-Ox_{SR} for 30 minutes twice a day.

Most patients reported mild to moderate discomfort rebreathing CO_2, however no subject stopped treatment due to this discomfort. One patient reported a slight increase in blood pressure at a flow of 1.5 LPM, which disappeared at 2.5 LPM. There were no other adverse events in any patient. All patients reported increased oxygen saturation (98-100%) during the treatment as measured with the finger pulse oximeter. All patients provided written consent for their data to be published.

Discussion

Cognitive dysfunction following recovery from COVID-19 is a common occurrence. Although no direct or indirect measurement of changes in cerebral blood flow and oxygen delivery were performed, the results from the cognitive testing

	Age	Gender	Pre-Treatment SAGE	Pos-Treatment SAGE	Comments
Patient 1	65	F	15	22	Pre MRI revealed mild cerebral ischemia. Clear subjective improvement.
Patient 2	69	F	17	21	Clear subjective improvement.
Patient 3	71	M	11	15	Hx of Alzheimer's. Some subjective improvement.
Patient 4	65	F	11	18	Clear subjective improvement.
Patient 5	57	M	22	22	Loss of taste returned on Day 5. Clear subjective improvement in ability to recall names, etc.

Note: SAGE Scores less than 17 are abnormal. Maximum score is 22.

changes following the treatments, suggest a physiologic improvement in neurological function. Follow up conversations with the five patients indicate subjectively sustained improvement in cognitive function, now at 5 to 7 months post treatment.

The limitations of this report include the very small number of patients treated, as well as without this being part of a formal study, there was no control arm for comparison of results. This also limited clarity on the subjective improvement comments not being able to rule out a "placebo effect." The use of the simple cognitive function screening tool (SAGE) may not have been sufficient to finely identify changes in cerebral function, nor assure that there was no "learning effect" on the posttest.

The data from these five patients is encouraging. A larger formal study of the Hi-Ox_{SR} has been started in Canada with the use of more stringent cognitive function testing. It is anticipated that more data will be available during 2023.

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Appendix A. Hi-Ox_{SR} Oxygen Delivery System

The Hi-Ox_{SR} High FiO_2 Mask with use of its Sequential Rebreathing Reservoir is designed to create a partial rebreathing oxygen mask that has more control of the sequence of rebreathing exhaled gas and limits the dilution of inspired oxygen with room air.

The Hi-Ox_{SR} has an expiratory valve into a valve body that is attached to the mask and with the addition of a separate expiratory gas rebreathing reservoir there is no contamination of the inspired oxygen. The mask has no holes to dilute the inspiratory gas. When the patient begins inspiration, all of their inspired gas is ~100% oxygen from the inspiratory reservoir. Only when there is no more oxygen available to them from the inspired reservoir, does the expiratory reservoir sequentially contribute to the inspired gas. This late contribution gas contains the high oxygen and a high concentration of carbon dioxide that was exhaled from the previous breath. This gas will return the previously exhaled CO_2 to the lung and limit the reduction in alveolar CO_2.

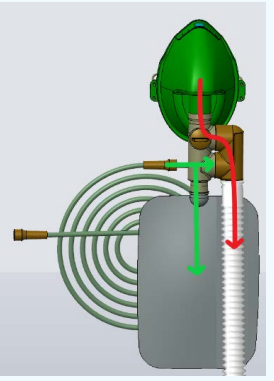

Figure 1. The patient exhales their breath into the 1-liter expiratory reservoir tube through the expiratory valve in the valve body. This exhaled gas contains the concentration of the inspired oxygen, less the oxygen uptake per breath or approximately 3-5 percent less oxygen than was inspired. This reservoir typically contains a high oxygen concentration as well as a 3 to 5% concentration of carbon dioxide. During this period the oxygen flowing into the valve is directed to the inspiratory reservoir bag and applies pressure to keep the sequential dilution valve closed.

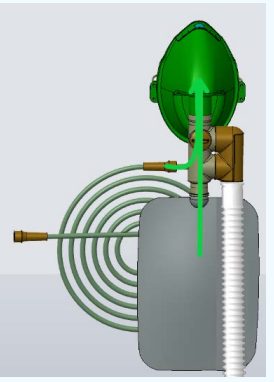

Figure 2. When the patient inhales, they breathe in the ~100% oxygen from the oxygen reservoir bag as well as the low flow oxygen flowing into the valve.

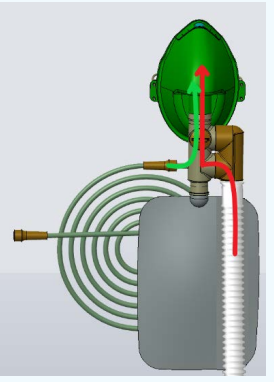

Figure 3. Once the patient has depleted the oxygen in the reservoir bag, the sequential dilution valve will open, and the patient will inhale the oxygen and carbon dioxide from their previous exhalation. The oxygen flow setting assures a minimum flow of fresh gas to exceed the oxygen uptake requirements of the patient. The intentional reduction in the oxygen flow setting is used to cause targeted increases in $PaCO_2$.

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The GENOSYL® DS Nitric Oxide Delivery System Facilitates Safe Care and Transition of Respiratory Support Between the Operating Room and Intensive Care Unit

Dr Mark D Twite, MA, MB BChir, FRCP and Aaron Roebuck, MS, RRT

Inhaled nitric oxide (iNO) is FDA approved for the treatment of hypoxic respiratory failure in neonatal patients who have evidence of pulmonary hypertension. Studies have demonstrated that iNO in this patient population improves oxygenation and reduces the need for extracorporeal membrane oxygenation.[1,2] Neonatal patients receiving iNO are often critically ill and require iNO delivery in the operating room, cardiac catheterization laboratory, intensive care unit (ICU), and during transport.

A seamless continuum of care among ICU ventilation, iNO delivery, and anesthesia machines is optimal for patients and caregivers

Many of these patients receiving iNO may require general anesthesia for surgical procedures. For example, newborn patients with persistent pulmonary hypertension (PPHN) with a congenital diaphragmatic hernia often need surgery in the first few days of life; usually, such patients have been started on iNO soon after birth. Neonatal patients with complex medical needs and on long-term iNO therapy for PPHN often have failure to thrive and commonly require surgery for gastrostomy feeding-tube placement to facilitate enteral feeding. In patients with pulmonary hypertension, precise control of respiratory conditions, including inhaled oxygen levels (FiO_2) and end tidal carbon dioxide levels ($ETCO_2$), are essential, as both parameters directly affect pulmonary vascular resistance.[3,4] In the operative settings, it is helpful if the patient can be transitioned from the ICU ventilator to the anesthesia machine ventilator so that inhaled volatile anesthetic agent can be delivered to maintain general anesthesia. It is therefore advantageous for an iNO delivery system to be compatible with any type of ventilator, including ICU ventilators, transport ventilators, and anesthesia machine ventilators, to facilitate the safe transition of patients between ventilators.

A shift to low fresh gas flow (FGF) and rebreathing in anesthesia delivery provides advantages to the patient

Fundamental differences exist between mechanical ventilators in the ICU and ventilators in anesthesia machines (Table 1).[5,6] In ICU ventilators, FGF is continuous with flows often >6 L/min during the respiratory cycle. The ventilator circuit is an open design with no rebreathing of gases and active humidification of inspired gases. In anesthesia machines, FGFs are often low (<2 L/min) during the respiratory cycle, and the breathing circuit is a "semi-closed circle system," meaning that carbon dioxide is absorbed from exhaled gas, which allows rebreathing of gases to occur. The anesthesia circle system was designed to conserve volatile anesthetic agent by allowing exhaled anesthetic gas to return to the patient in the inspired gases.[5-7]

A shift has been made toward using very low FGF anesthesia (<1 L/min) to build upon the advantages of this circle system design. A practical definition of low-flow anesthesia is the reduction of FGF below patient minute ventilation (MV) to the lowest level consistent with equipment capabilities and provider comfort while ensuring safe and effective care for the patient.[7] The benefits of low-flow anesthesia are well established and include reductions in volatile anesthetic agent waste, potent greenhouse gas emission, and costs.[7-9] Low FGFs and gas recirculation also provide the added benefit of conserving humidity and temperature, which helps maintain a more physiologic environment in the respiratory tract during mechanical ventilation through the anesthesia machine.[10-12] Respiratory function and mucociliary clearance are better preserved with a low-flow anesthetic technique compared with high FGFs. Maintaining temperature, humidity, and respiratory function are particularly important at the extremes of patient age and during long anesthetic use cases.[13,14]

Rebreathing and low FGF in anesthesia circuits require a different approach in iNO delivery

The selective pulmonary vasodilatory (and possibly organ-protective) properties of iNO have led to its use in a variety of surgical and nonsurgical settings.[15-19] When iNO is introduced to the anesthesia machine circuit with current tank-based systems, low FGF anesthesia is not possible for accurate iNO delivery. Inspired NO is dependent on several variables, including patient MV, and several studies have concluded that when using tank-based delivery systems with anesthesia machines, iNO delivery to the patient is only accurate when FGF is greater than or equal to MV.[20,21] These tank-based delivery systems therefore negate the many benefits of low-flow anesthesia practice. Further, for an anesthesia provider unaware of the tank-based iNO delivery system limitations with respect to FGF and MV, there can be incorrect delivery of set iNO concentration and a buildup of toxic nitrogen dioxide (NO_2).[22] When using a tank-based iNO delivery system and transitioning a mechanically ventilated patient from an ICU ventilator to an anesthesia machine ventilator,

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Table 1. Properties of the anesthesia machine ventilator and ICU ventilator

Anesthesia machine ventilator Circle system (variable degrees of rebreathing)	**ICU ventilator** Open system
Designed for low FGF Conservation of inhalational agent Scavenging of waste gas required Carbon dioxide absorber required Manual or mechanical ventilation FiO_2 determined by flow meters or set control	High FGF of air/oxygen only Exhaust gases to the room via filter No need for scavenging system Delivers only mechanical ventilation Operator directly sets the FiO_2
Delivers O_2 and other anesthetic gases (and NO)	Delivers only O_2 and air (and NO)
HME filters	Heated, humidified circuits

HME, heat and moisture exchangers; FGF, fresh gas flow; FiO_2, fraction of inspired oxygen; NO, nitric oxide; O_2, oxygen.

the anesthesia provider will need to divert their attention from direct patient care to adjust FGF and ventilation parameters to maintain ventilation and anesthetic agent goals. In addition, adjusting FGF to greater than MV to meet these limitations can change other parameters such as fraction of inspired oxygen and end tidal anesthetic agent concentrations, which could result in adverse events, such as hemodynamic instability, for a critically ill patient.[23] The increased anesthetic agent usage when FGF needs to at least equal MV can be considerable. Although no studies have yet quantified this increased financial cost in this situation, it is likely substantial.

The increased clinical use of iNO has prompted efforts to improve iNO delivery systems to make them versatile, safe, cost-effective, and appropriate for the patient care setting.[24] The ideal delivery system should be easily portable, reliable, cost-effective, and able to deliver the set iNO dose regardless of the mode of delivery. Currently, tank-based systems are the predominant commercially available iNO delivery system. Pressurized tanks containing various high-dose concentrations of NO are buffered with an inert gas such as nitrogen to avoid the generation of NO_2 within the tank. This pressurized tank is connected to a flow-regulated injector that delivers NO into the inspiratory limb of a ventilator circuit.[25] However, there are disadvantages to tank-based delivery systems:

1. *Tanks containing high-dose NO balanced with nitrogen require purging of NO_2 into the environment prior to use.*[25] System setup takes time and trained personnel.
2. *Tanks providing NO are large and cumbersome.* Large tanks are difficult to handle and necessitate special delivery system carts to be transported around the hospital. In addition, large tanks are not suitable for the land or air ambulance transportation of critically ill patients mechanically ventilated and requiring iNO.
3. *Tank-based delivery systems are unable to accurately deliver set iNO dose through the anesthesia machine circuit when FGF is less than MV.*[25] If the anesthesia provider is unaware of this delivery system limitation, this may lead to errors in iNO delivery, frequent alarms on the tank-based delivery system, and confusion between the anesthesia provider and respiratory therapist on how to resolve the problem.

Transporting the patient to and from the operating room on iNO and then delivering the iNO through the anesthesia machine instead of the ICU ventilator so that anesthetic gases can be delivered to the patient during surgery presents challenges for both the respiratory therapist and anesthesiologist. A single iNO delivery system that can accurately deliver set iNO dose in both the perioperative environment and ICU would facilitate the safe continuity of care for patients transferring between these 2 areas.

An iNO delivery system with a "Smart Feedback System™" provides seamless, accurate iNO dosing regardless of the FGF

The GENOSYL DS† (VERO Biotech Inc.) is the only iNO delivery system that can accurately deliver the set iNO dose through an ICU and anesthesia machine ventilator independent of FGF. This is due to the "Smart Feedback System™" that continuously adjusts and precisely maintains dosing based on the measured iNO dose the patient is receiving. The GENOSYL DS is an FDA-approved, compact, cassette-based NO delivery system that generates NO from dinitrogen tetroxide (N_2O_4) in 2 chemical steps within the cassette.[26] When used with the anesthesia machine, the GENOSYL DS can deliver the accurate set dose of iNO regardless of patient size, mode of ventilation, FGF, and anesthetic agent used.[27] This enables the anesthesia provider to "set it and forget it" regarding the set dose of iNO. The anesthesia provider no longer needs to make any adjustments to the anesthesia machine when using iNO delivered by the GENOSYL DS, reducing distraction and allowing continuous focus on the patient.

The GENOSYL DS is the only iNO delivery system capable of accurately and efficiently delivering set iNO dose regardless of FGF on current and future generations of anesthesia machines.

Summary

The GENOSYL DS simplifies patient care for the respiratory therapist, including ventilator circuit setup, patient transfer, and handoff between the ICU and surgical settings. Moreover, the ease of use of the GENOSYL DS helps reduce the workload for the respiratory therapist while facilitating safe and efficient patient care.

†Testing was conducted on the second generation of GENOSYL DS. Currently, only the second generation of GENOSYL DS is approved for use with rebreathing anesthesia.

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The First and Only Tankless Nitric Oxide Delivery System Now Proven to Accurately Deliver iNO in Rebreathing Anesthesia

GENOSYL®

DELIVERY SYSTEM

for the administration of
GENOSYL® (NITRIC OXIDE) GAS FOR INHALATION

- Provides accurate dose control with low-flow anesthesia
- One device for all care areas from ICU to MRI to OR and during transport
- Sleek, compact design for easy handling and transport
- Tankless, cassette-based system

Indication & Important Safety Information: 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.
- Abrupt discontinuation of GENOSYL (nitric oxide) gas, for inhalation may lead to worsening oxygenation and increasing pulmonary artery pressure.
- Methemoglobin, NO_2, and PaO_2 should be monitored during nitric oxide administration.
- In patients with pre-existing left ventricular dysfunction, GENOSYL may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- The most common adverse reaction is hypotension.
- Nitric oxide donor compounds may have an additive effect with GENOSYL on the risk of developing methemoglobinemia.
- GENOSYL must be administered using a calibrated GENOSYL Delivery System. Only validated ventilator systems or nasal cannulas should be used in conjunction with GENOSYL.
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Airway Injury from Nitrogen Dioxide: Monitor nitrogen dioxide (NO2) levels. Nitrogen dioxide may cause airway inflammation and damage to lung tissue.

Heart Failure: In patients with pre-existing left ventricular dysfunction, Noxivent may increase pulmonary capillary wedge pressure leading to pulmonary edema.

Adverse Reactions

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Drug Interactions

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Administration

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Please see the full Prescribing Information for additional important Noxivent® safety and risk information.

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Nitric Oxide from Room Air – The Development of the LungFit PH Technology

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Dr Fred Montgomery, Inventor of LungFit and who has spent over 30 years developing and patenting nitric oxide delivery system technology that resulted in the commercialization of nitric oxide therapy.

Can you provide us with the history of your work in nitric oxide and designing technology to deliver nitric oxide to patients?

For the past three decades, I have devoted my career to developing nitric oxide delivery systems and making inhaled nitric oxide (iNO) more accessible for clinicians and patients. My involvement in nitric oxide began in 1993 at Ohmeda, the medical systems division of British Oxygen Company, an industrial gases company. We were one of the few businesses that had pharmaceutical and device development programs, as well as high quality, medical grade gas. We started iNO device development with a very basic delivery device that was being used in clinical trials. My development partner and co-inventor, Duncan Bathe, was on site in the UK when they put the first patient on iNO. The baby responded well and went home a few days later — it really was an exciting time for our team. After the clinical trial device, we started work on a commercial delivery system (INOvent) that could be taken to the bedside of a patient needing iNO treatment and be connected to any ICU ventilator. In January 2000, the FDA cleared the INOvent delivery system, making it the very first commercial system to be approved by the FDA.

Commercialization, along with the R&D program, shifted to INO Therapeutics, then Ikaria, followed by Mallinckrodt. We continued to develop delivery technology, focusing on ease of use, automation, and patient safety. In 2006 we received FDA clearance for the next-generation device, the INOmax DS. Additional next-gen system advancements quickly followed with the INOmax DSIR. These advancements and FDA clearances included adding a transport system for air and ground, increasing the geographic area and reach of iNO to treat and transport critically ill patients.

Our device development team also created the INOblender for bagging patients and the INOpulse for use in ambulatory patients with PPH. Duncan and I are on these patents as well and are proud of the work our team accomplished to innovate iNO delivery and make it easier for clinicians to access and treat with iNO.

However, the main challenge that we could not address at the time was how the iNO was supplied. The 45 lb pressurized iNO cylinders required for administration are big and bulky to transport. A sophisticated network and infrastructure are also required to manufacture and distribute the gas supply and then return the empty iNO cylinders. If you think about it, iNO cylinders might be the most inefficient drug packaging out there, with only 2 grams of actual iNO in a 45 lb package with 99.92% of the content being nitrogen. There was some promising research that provided evidence that we might be able to address this challenge, so Duncan and I decided to pursue development of an iNO system that took cylinders out of the equation.

What gave you the idea to create nitric oxide from air using electricity?

It's been known that lightning produces vast quantities of nitric oxide, and that it can also be produced in the lab by arc discharges. There was almost 20 years of published scientific research that demonstrated nitric oxide could be produced from electricity and room air. Various patents were filed, but the research did not progress to a level where you could produce the iNO in a controlled and continuous manner.

In 2011 Duncan and I left Ikaria to see if we could replicate what others had published and take it a step further to develop an alternative to iNO cylinders using electricity. The challenge was that if we wanted more iNO we had to use large spark discharges, and the bigger the spark, the more intense the current and the shorter time the electrodes lasted. The arcs only lasted a few micro-seconds and they could not generate the amounts of continuous nitric oxide we needed. While we were focusing on trying to control the quick, big spark, Duncan had an "aha" moment and asked a couple of crucial questions:

- What if we could inject current into the plasma and extend the time of the spark to produce more iNO?
- How do we control the current to a low level and maintain the spark for longer at a lower energy level?

Dr Fred Montgomery has spent over 30 years developing and patenting nitric oxide delivery system technology that resulted in the commercialization of nitric oxide therapy. He led the development of the INOvent delivery system for Datex-Ohmeda, which in 2000 was the first FDA 510(k) cleared nitric oxide delivery system that introduced inhaled nitric oxide therapy to the commercial market. He then established the Medical Device Group at INO Therapeutics, which developed the INOmax DS and INOmax DSIR products, the leading nitric oxide delivery systems in the United States to this day. Dr. Montgomery left Ikaria (formerly INO Therapeutics) in 2011 and cofounded NitricGen Inc. Since 2017 he has worked at Beyond Air, commercializing its LungFit PH family of products and further innovating delivery of iNO. He received his Doctor of Philosophy degree from the University of Salford, England and his Master of Business Administration from the University of Bradford, England.

Dr Fred Montgomery with the FDA-approved LungFit PH, the first and only 3-in-1 integrated system that generates and delivers inhaled nitric oxide from room air.

We brainstormed a few approaches and finally reached the stage where we could control the current at 70 mA in the plasma and extend the duration of the plasma from 10 µs to 20 ms, a range of 2,000:1. This change provided the flexibility to generate very small to very large quantities of NO from room air, a range of 0 ppm to 1500 ppm. We then developed a filter to remove the resulting impurities, O_3 and NO_2. In October 2011 we filed a patent.

In 2017 Duncan and I joined Beyond Air to commercialize this new technology, creating the LungFit family of products. At Beyond Air we have made significant investments in the technology with a robust product development team and research pipeline. Our current research focuses on a range of applications and therapeutic areas using high-concentration iNO (80 to 250 ppm) for antimicrobial treatment: Viral community-acquired pneumonia (VCAP), including COVID-19, bronchiolitis, and nontuberculous mycobacteria (NTM) lung infection, with additional research planned for the use of iNO to treat severe exacerbations due to lung infections in COPD patients.

What is the Ionizer™?

The Ionizer technology is the core of our LungFit platform and family of products. It is what generates the iNO from room air over a wide range of concentrations and at low electrical power. The LungFit product family includes the FDA (PMA) approved LungFit PH, which generates low concentration iNO (0-80 ppm) for use in the NICU to treat persistent pulmonary hypertension in newborns; as well as our LungFit PRO and LungFit GO, which generate high concentration iNO and are being studied for antimicrobial treatments in the hospital and home settings.

How does it work?

The Ionizer is a small chamber with two electrodes within each LungFit system that draws in room air and uses the power equivalent to a 60-watt light bulb to ionize the nitrogen and oxygen molecules. The molecules recombine as nitric oxide, and low levels of NO_2 are created as a by-product. The NO_2 Smart Filter then removes the NO_2 from the internal circuit. It's the Ionizer that gives us the flexibility to generate unlimited, on-demand iNO from room air.

We've come a long way since we first started testing this concept in 2011. With this simple, user-friendly technology, we can open access to iNO treatment at the global level in countries and on continents that don't have the infrastructure to support the use of cylinder-based iNO delivery systems. This is really exciting for me—removing barriers to care and empowering clinicians with this life-saving therapy.

Can you describe the LungFit Technology and how it fits into NICU operations?

We received US Food and Drug Administration approval for the LungFit PH on June 28, 2022. The LungFit PH generates iNO, a selective pulmonary vasodilator, and delivers it into the inspiratory limb of the patient breathing circuit of an ICU ventilator in a way that provides a constant concentration of nitric oxide, as set by the user. In the US, iNO is indicated to improve oxygenation in neonates with evidence of pulmonary hypertension. Outside of the US, including Europe, iNO has this same indication, and is also indicated for patients of all ages who are undergoing or have undergone heart surgery and develop pulmonary hypertension. We are currently working with the US FDA to expand our label to include this indication.

The LungFit PH is the first and only 3-in-1 integrated system for iNO generation, delivery, and monitoring. The system is fast, precise, and simple—power on and in seconds you can generate unlimited, on-demand iNO from room air, regardless of dose or flow. Because we generate iNO from air we are finally able to give clinicians in the NICU access to iNO at the bedside without pressurized 45-lb cylinders used by incumbent technology.

Given our involvement in the R&D that went into developing the first iNO system approved in the US and then subsequent systems, we had years of clinical, real-world feedback from users that helped inform the development of other key elements of the LungFit PH. It was also imperative to simplify the pre-use check and provide clinicians with immediate, on-demand access to iNO to treat their critically ill patients.

We kept the elements from our previous developments that worked well, such as the simple user interface, gas monitoring, and connections to the ventilator breathing circuit. At the same time, we eliminated the things that caused problems for users that came with using bulky 45 lb high-pressure cylinders. Examples are: no need to transfer heavy cylinders around in the NICU, no regulator connections to high pressure cylinders, no leak checking the connections, and no purging the gas lines of NO_2 before it is used on the patient. This all streamlines the workflow and reduces the setup time required to start iNO therapy.

How is the LungFit PH different than alternative nitric oxide delivery systems used in the NICU?

The incumbent iNO delivery systems in the NICU uses 45-pound

cylinders that deliver 800 ppm iNO and are pressurized to 2200 psi. The traditional cylinder-based iNO delivery system have worked well since their conception in 1999, but have various burdensome hurdles, specifically the iNO cylinders. These cylinders take up a large amount of storage space, must be returned to the manufacturer once used, require physical monitoring and cylinder emptying, pressure-testing, manual purging, and there is the potential for iNO leaks and wasted iNO before patient use.

The LungFit PH system generates iNO from room air, and consistently delivers and monitors iNO all in one compact system in under one minute. This system does not require reservoirs of iNO and automatically purges the delivery line with room air, eliminating the risk of unintended NO_2 bolus delivery to the patient. Additionally, the LungFit PH system includes a 2.5 oz NO_2 Smart Filter that removes NO_2 from the internal circuit, only takes a few seconds to replace, and can be stored at the point of care. The filters last 12 hours regardless of iNO dose or flow, creating predictability for the clinicians.

Nitric oxide has been researched and proposed as a therapeutic option to treat various cardiopulmonary conditions. What therapeutic areas are you currently focusing on as part of the research and development pipeline at Beyond Air?

Thanks to the Ionizer technology at the center of the LungFit family of products, Beyond Air is designing systems for a variety of clinical settings with the potential to treat across a broad spectrum of therapeutic areas. FDA approval currently includes PPHN, but we are not stopping there. We are researching treatments for viral and bacterial infections and NTM lung infections. Pending FDA review, we plan to conduct a pilot study to evaluate high concentration iNO to treat severe COPD exacerbations due to lung infections in hospitalized patients.

Beyond Air has conducted multiple pilot studies with the LungFit PRO system at 150 ppm of iNO to treat viral community-acquired pneumonia (VCAP), including COVID-19, resulting in promising safety and efficacy data. We are currently in discussion with the FDA on a US trial design for VCAP, including COVID-19.

This past fall, *The Annals of the American Thoracic Society* published a detailed review of our third pilot study of iNO in bronchiolitis patients. The study concluded that efficacy outcomes suggest intermittent administration of 150 ppm of iNO may be favorable, compared to the lower concentration, in shortening the time to improvement in clinically significant endpoints for hospitalized infants with moderate to severe bronchiolitis. The publication offers an overview of the study design and previously announced results, as well as the rationale for conducting a pivotal study.

We also released favorable safety, tolerability, and efficacy results from the at-home pilot study in patients with NTM lung infections treated with high concentration iNO using the portable LungFit GO System.

Beyond Air is the first bio-pharma company to prioritize investment in the research and development necessary to harness the power of nitric oxide. From hospital to home, our goal is to deliver global access to iNO and empower clinicians with more treatment options across a range of therapeutic areas.

Impact of a Tracheostomy on Pressure and Function: Adult and Pediatric Considerations

Kristin A King, PhD, CCC-SLP

The number of adult and pediatric patients with tracheostomies are growing each year secondary to advancements in medical care and interventions to sustain life more so than seen historically. In a study conducted in 2008, it was estimated that by the year 2020, there would be over 600,000 adult patients requiring prolonged mechanical ventilation.[1] But little did that author know that, in 2020, a pandemic would change the face of medical care. It was estimated that in 2020, 965,000 people would require mechanical ventilation due to COVID-19, not including other disease and injury processes.[2] Just considering COVID-19 patients, the potential incidence of tracheostomies is thought to be much higher than the prediction given in 2008.

Aerodigestive changes following tracheostomy

With tracheostomies, changes in the aerodigestive system become evident through impacts on voice, swallowing, cough, and other functions. The prevalence for these aerodigestive challenges, which may lead to feeding and swallowing difficulties, is high.

The placement of a tracheostomy tube and prolonged mechanical ventilation with an inflated cuff causes a disconnect between the upper and lower airway. The lack of airflow through the upper airway can often lead to multiple negative changes affecting speech and swallowing: reduced subglottic pressure;[3] decreased sensation to the pharynx and glottis;[3] reduced laryngopharyngeal reflex;[4] decreased ability to manage secretions, requiring more frequent suctioning;[5] decreased sense of taste and smell;[6] inability to vocalize; increased aspiration risk; and muscle disuse and atrophy.[7] A disconnect between respiration and swallowing also may negatively impact the ability to coordinate breathing and swallowing. For pediatrics, long term tracheostomy placement also has been associated with delayed acquisition of language, delayed social development, and risk of impaired parent-child bonding.[8,9]

A primary means for closing the system to restore more normal physiology and pressures for patients with tracheostomies is the use of a bias-closed position, no-leak valve. When a patient has a tracheostomy, airflow is directed in and out through the tracheostomy tube and bypasses the upper airway. The Passy-Muir® Valve works by closing at the end of inspiration, which redirects 100% of airflow upwards through the vocal cords and upper airway. Research has shown that this redirection of airflow assists with improving secretion management, increasing sensory awareness, improving swallowing, and restoring natural physiologic PEEP (positive end- expiratory pressure), among other benefits.[10]

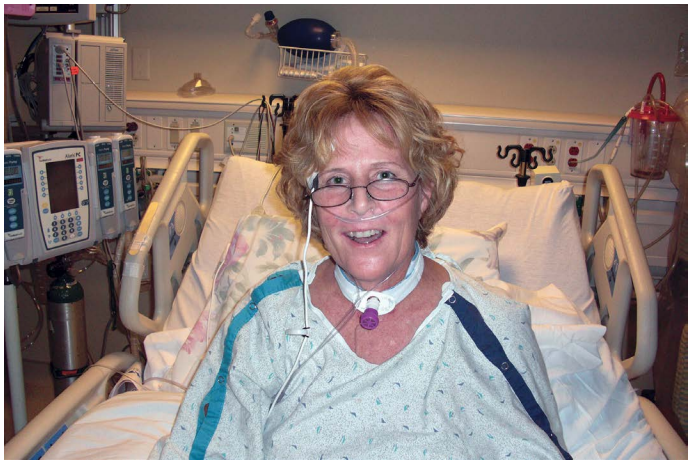
Normalizing function

Assessment and usage of a Valve also is important for the normalization of functions for all patients and for development in children. The primary consideration during assessment is that the patient has a patent airway, meaning the patient can exhale around the tracheostomy tube. Having a qualified team, familiar with airway management, is a key component of successful Valve use. The participation of infants, toddlers, and young children in the assessment process may be more difficult than with adults because of their limited ability to follow commands and volitionally vocalize; therefore, additional methods, such as transtracheal pressure (TTP) measurements, may be used to assess airway patency.[11] TTP is a method for measuring the pressure in the airway with the tracheostomy tube in place. It can be used with finger occlusion or a speaking valve to determine airway patency. TTP has been found to be a predictor associated with successful use of the Passy-Muir Valve (PMV).[12]

While speech and language development is an important consideration in pediatrics, research from the adult population suggests significant benefits for improved secretion management, cough function, and swallowing, all of which are influenced by pressure.[1] Research has shown that subglottic pressure is reduced with a tracheostomy, negatively impacting feeding and swallowing, cough, and secretion management.[13] Pullens and Streppel (2021) discussed the importance of restoring normal airway physiology to assist with feeding and swallowing, which would include restored pressure, by using a speaking valve in the pediatric population. The adult population has several studies which indicate the need to restore subglottic pressure to assist with improved laryngeal function, swallowing, cough, and secretion management.[1,14]

The negative impact on pressures and the diminished stimulation of sensory receptors may affect feeding and swallowing in the pediatric population, to include oral-motor sensation.

With 25 years of experience in medical, academic, and industry settings, Dr King brings a unique perspective of medical speech pathology. Her research, publications, and teachings focus on traumatic brain injury, swallowing disorders, and critical care (tracheostomy and mechanical ventilation) for both pediatric and adult patient populations. She has been an invited speaker both domestically and internationally and has published in peer-reviewed journals. Currently, Dr King is the Vice President of Clinical Education and Research for Passy-Muir, Inc.



Using a nasal cannula with a speaking Valve may assist with oxygenation, if an extra boost is needed.

Henningfeld, Lang, and Goday (2019) reported that g-tube feeding and delayed feeding skills were associated with tracheostomy. They also hypothesized that children with tracheostomies would have more feeding issues than their age-matched peers without tracheostomies.[15] During review, they found that a history of ventilator-dependence, cuffed tracheostomy tube, and speaking valve use during inpatient care were inconsistently associated with later feeding and nutrition evaluations. However, the authors suggested that their findings also indicated that earlier speaking valve use has the potential to decrease later issues with feeding.

Early assessment for speaking valve use either in-line with mechanical ventilation or with a spontaneous breather leads to early intervention – in this case, establishing treatment plans, accommodations, and interventions earlier during their care. Early intervention and use of the PMV has been shown to have benefits with restoring the physiology of the upper airway to its more "normal" state by returning airflow through the upper airway during exhalation.[7] This restoration of airflow to the upper airway allows evaluation of airway patency, vocal cord function, secretion management, swallowing, and communication skills.[7] Research has shown that the use of a Passy-Muir Valve can provide benefit during swallowing by increasing laryngeal excursion, returning cough and throat clear, and providing overall improved protection of the airway.[7]

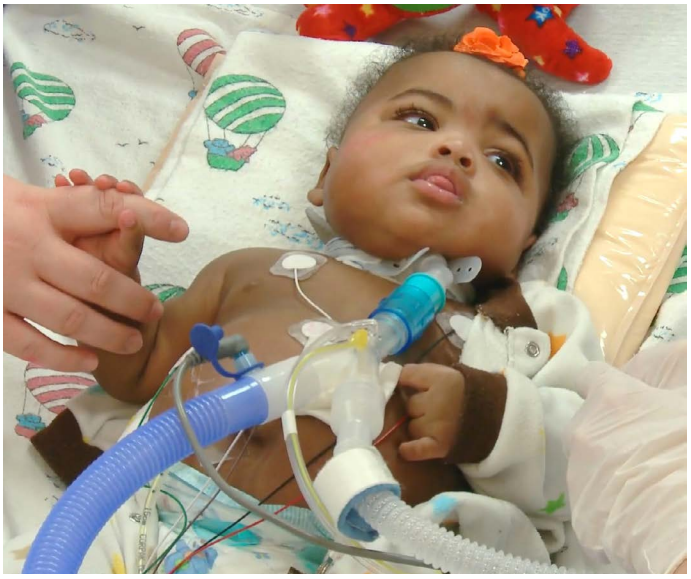
Furthermore, patients on mechanical ventilation often experience psychosocial distress related to their inability to communicate with family and caregivers and to participate in their own care. Early implementation of the PMV increases the opportunity for patients to speak, swallow, and participate in direct therapy and to do so sooner. This early intervention has the potential to reduce anxiety, wean times, and lengths of stay. The restoration of communication and restoring oral nutrition have both been shown to have positive psychological benefits and to decrease anxiety, stress, fear, and other negative effects.[16]

Whitmore et al. (2020) also reported that the use of speaking valves for patients with and without mechanical ventilation was highly supported among the reviewed literature to promote speech and communication, which had an additional impact on patient satisfaction, and has been shown also to contribute to alveolar recruitment, weaning, and quality of life.[17] One barrier identified to using measurement tools with patients for assessing pain, cognitive status, and other areas while in the ICU is the ability of the patient to participate verbally.[18] Zaga et al. (2020) identified that the use of a one-way valve in-line with mechanical ventilation would assist with increasing the relevance of some measures.[18]

Intrathoracic and intra-abdominal pressures

Additional primary areas of pressure to consider when addressing the needs of patients with tracheostomies are the effects on the respiratory system and intrathoracic and intra-abdominal pressures, which also are diminished by having an open system.[19] With the redirection of airflow, the patient is no longer using the upper respiratory airway-airflow does not go through the upper airway and glottis (vocal cords). Use of the upper airway and glottis typically allows for control of exhalation and assists with controlling expiratory lung volumes.[20] This loss of pressure may impact gross motor function for mobility and postural stability.

Use of the Valve during physical therapy helps restore the pressure support in the trunk, allowing for natural increases in intrathoracic pressure (ITP) and intra-abdominal pressures (IAP) in response to increased postural demands. With an open tracheostomy tube and therefore, an open system, thoracic pressures cannot be increased or sustained as airflow passes through the tracheostomy tube and bypasses the upper airway. This difficulty would be observed when a patient needs to crawl, sit, push, or stand up. The typical means of gross motor movement for mobility is to engage the glottis (vocal cords) to restrict the expiratory lung volume to stabilize the chest and upper body.[7,8] Placing a Passy Muir Valve on the tracheostomy tube closes the system and restores a patient's ability to use the upper airway to control expiratory flow and improve ITP and IAP.



Infants may use a Valve in-line to assist with crying, cooing, swallowing, and more.

Consider that with infants and young children, a tracheostomy also could limit or diminish gross motor development. During infancy and early development, children are progressing through the stages of head control, trunk control, sitting, reaching, standing, and walking. Without good ITP and ITA, these functions could be significantly impacted and even delayed. A vicious cycle may begin as fine motor skills related to feeding, self-feeding, and other levels of function are directly linked to

gross motor development. These delays and limitations can be mitigated by using a Passy Muir Valve to return the young child to a more normalized use of the upper airway with control of volumes and improved trunk control and postural stability. For adults, restoring pressure improves and restores functions that aid in recovery and quality of life.

Conclusion

The provision of multiple services for these patients with tracheostomies assists with overall care and recovery. Having these patients receive intervention to restore communication and swallowing, improves overall mental health which in turn impacts motivation and recovery.[9] Taking into consideration the impacts disease processes and intubation or tracheostomies have on communication and swallowing, early assessments may be a key component to restoring patients' abilities to communicate, eat, and return to more normal function, no matter the age.

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Epidemiological Analysis of Nitric Oxide Nasal Spray (VirX™) Use in Students Exposed to COVID-19 Infected Individuals

Chris Miller, PhD, BA, RT and Keith Moore, PharmD, FCCP, BCPS

Introduction

On March 11, 2020, Coronavirus disease 19 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO).[1] By December of 2021, the WHO reported that over 278 million people and just under 5.4 million deaths had been reported globally.[2] This pandemic caused quarantines and closure of many businesses and schools.

In December 2021, the Srinakharinwirot University in Bangkok, Thailand, resumed its health professions' academic operation and required its students to be onsite for classes. Students were housed in university accommodations with 4-5 students sharing private apartments, and depending on the layout of the apartment, most sleeping with 2-5 people sharing a bedroom.

January 2022, saw another wave of COVID-19 in Thailand with a prevalence of Omicron variants reaching more than 99%. The university experienced a cluster outbreak among the university students and staff. In response, the on-campus University Hospital, in collaboration with the university and following the Thai Centre for Disease Control recommendations, organized a "testing and tracing" plan, modified for the university setting to control the outbreak.

The plan called for opening two new quarantine buildings with one for confirmed COVID-19 positive students and another for "high-risk contacts" who were exposed to COVID-19 positive individuals. A high-risk contact (HRC) person was defined as a student who self-reported being in direct contact with a confirmed positive COVID-19 person for more than 5 minutes without wearing a mask, usually when both were either eating or sleeping together in the same room.

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Keith Moore, PharmD, FCCP, BCPS is the Chief Medical Officer of Sanotize. He is a clinician, inventor, and author with experience in global drug and device research. He has been a startup member of multiple pharmaceutical, R&D and medical device companies. He has more than 40 years of investigator-initiated and Pharma Sponsored global Phase 1-4 clinical trials development, execution and regulatory submissions experience.

As part of the testing and tracing plan, the university offered the high-risk contacts the option to use a nitric oxide nasal spray (VirX™, Sanotize Research and Development Corp., Canada) supplied by its distributor at no cost to them for added protection against infection. The use of VirX™ was completely voluntary and not mandated by the plan.

VirX™ has been demonstrated to be safe and was approved in Thailand in 2021 by the Ministry of Public Health as a mechanical and chemical barrier against viruses within the nasal cavities. VirX™ is a liquid nasal spray and works to protect the nasal passages with two mechanisms. A mechanical barrier is created by the use of hydroxypropyl methylcellulose (HPMC) in the VirX™ formulation. HPMC is a film forming hydrophilic matrix material that impedes the attachment of viruses to nasal host cells.

The chemical protection comes from both the acidic pH of the citric acid in the solution due to its physical forces on virus' outer envelope and membrane, and the release of nitric oxide gas from the liquid as the liquids from the two chambers mix when sprayed.

Nitric Oxide (NO) is well-known to be an efficient broad-spectrum anti-infective agent. It has been reported to have antimicrobial activity against bacteria, yeast, fungi, and viruses both in vitro and in vivo animal studies.[3-13] NO has been shown to have a direct effect on virions. NO, after nitrosylating cysteine moieties, causes conformational changes on surface glycoproteins and binds to proteases within the virus preventing viral replication.

VirX™ is supplied as a manual pump action nasal spray container with 25mL of solution. Each spray into the nostril dispenses approximately 110-120µL of the nasal solution (Figure 1). The proprietary bottle contains nitric oxide releasing solution (NORS™) that produces the nitric oxide gas, enabling long term stability of the product, so that the gas is created and released only as the spray is dispensed. As an approved product, informed consent was not required for the students to use VirX™.

Sanotize contracted with an independent group of the hospital medical staff to request access to the data for a retrospective epidemiological analysis to evaluate VirX™ safety and efficacy. This was approved by an independent institutional ethics committee.

Figure 1. Pump action of VirX™ in use.

Material and Methods

Inclusion criteria for analysis (based on student forms and self-assessment questionnaire)

- Age 18-24 years.
- Male or female students.
- If female, not pregnant (VirX™ is not approved for use during pregnancy).
- Determined by the hospital to be a high-risk contact based on the student's household and exposure risk.
- Enrolled in the university's quarantine system either at the quarantine building (majority) or home isolation (minority) for 10 days.

Exclusion criteria

- Baseline positive antigen test for SARS-CoV-2 (confirmed with 24 hours by RT-PCR).
- Used concomitant nasal sprays.

Of the 1039 students entering the program, those testing positive by rapid antigen tests had been isolated in the newly established single roomed confirmed COVID-19 student building. Reverse transcription polymerase chain reaction (RT-PCR) was performed to confirm the diagnosis as follow up after a positive rapid antigen test. The students testing negative were housed in a multi-student per room quarantine building or at home if they had their own room. After 7 days of quarantine, all 1039 students were allowed to return to classes, however, they were required to continue wearing protective masks and return to their quarantine rooms after classes for 3 more days.

VirX™ was provided to each faculty head who informed HRC students of the availability of VirX™ and distributed by staff coordinators to students who learned about the therapy and were interested in using it. Students who wanted to use VirX™ were asked to fill out a questionnaire which included demographic information, VirX™ usage, any new symptoms and follow-up information. Compliance was encouraged but not a mandatory requirement for access to VirX™. Questionnaires were approved as part of the hospital plan for recording and tracing.

Results

The investigators performed a retrospective data analysis on 1039 students who reported that they were in contact with a confirmed COVID-19 student between February 8th and April 16th, 2022 (Figure 2). They were housed in either one of the new quarantine buildings or in their own accommodations. Upon data review, 199 students were excluded due to having had low-risk of exposure, while 215 students were excluded due to a positive antigen test for COVID-19 within the first 24 hours.

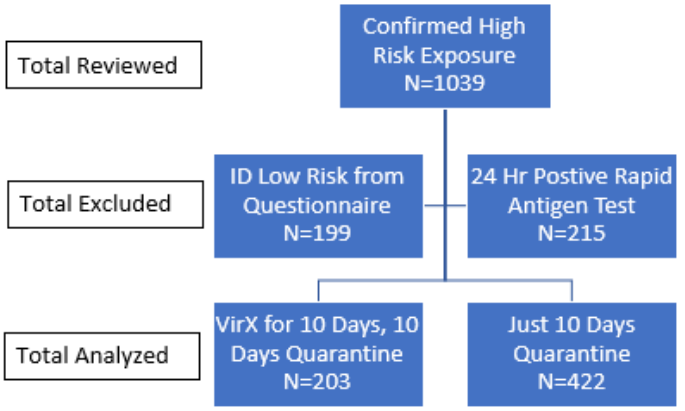

Figure 2. Population in Database

Of the 625 students not in the confirmed COVID-19 student building, 203 students had accepted using VirX™ at the manufacturer's recommended instructions of at least 4 times per day with additional doses ad lib (maximum of six doses daily per the User's Guide), and 422 students did not use VirX™. All students performed a rapid antigen test on the 5th, and 10th day, or if they developed a fever or respiratory symptoms. There was a daily record of symptoms and adverse events as part of the questionnaire.

Table 1. below shows the results of SARS-CoV-2 testing within the 10-day window of the quarantine period.

Table 1. Infection Rate Comparison (SARS-CoV-2 Test Results)

	Positive	Negative	Total
VirX™	13	190	203
Controls	108	314	422
Total	121	504	625

Of the 203 students who used VirX™, 190 tested negative for SARS-CoV-2 on all test days, and 13 tested positive on at least one test day. Of the 422 students who did not use VirX™, 314 students tested negative on all test days and 108 tested positive on at least one test day. These results demonstrated a statistically significant difference at the $p<0.0001$ level in infection rate of 6.40% (13/203) in the VirX™ group versus 25.59% (108/422) in the group that did not use VirX™.

Safety

No severe adverse events were reported. Only 34.5% (70/203) of students receiving VirX™ answered the safety questionnaire. Eight students (11.4%) reported an adverse event. All were mild, most were temporary nasal burning or irritation with VirX™ use. Two students required medical services. Abdominal pain following completion of the quarantine period was diagnosed as a peptic ulcer in a VirX™ treated student and was determined to be unrelated to its use. A second student who did not use VirX™ reported symptoms of an upper respiratory infection with chest tightness (normal SpO_2). The student tested positive for COVID-19 by RT-PCR, without lung pathology by a normal chest X-ray.

Discussion

SARS-CoV-2 is a serious and highly contagious virus that has caused a significant number of deaths and long lasting health sequela. This pandemic has had a major impact on health care

delivery as well as its economic impact worldwide. Therefore, a simple nasal spray that might reduce infection and the spread of this disease could be a major contributor to containing the pandemic. A positive social, leisure, health and economic impact could be realized as a global benefit from this therapy.

This epidemiological report suggests that use of the VirX™ nasal spray can reduce the spread of COVID-19 between individuals who are in close contact. Although the number of participants allowed for identifying a statistically significant differences, limitations of this report include that it was a retrospective analysis, and the students were not randomized. Additionally, as participation was voluntary, returned questionnaires were not mandatory. The study was open-label and not managed by a clinical trial team. The reported 11.4% incidence of adverse events is difficult to interpret. It is possible that only students who experienced the transient nasal discomfort with VirX™ reported it, which would lower the overall percentage of adverse events. However, with a mild adverse events profile and suggestions of statistically significant benefits, future studies should be conducted under a formal clinical trial structure.

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Note: VirX™ is not approved for use in the US. It is sold under the trade name of enovid™ in Israel and Indonesia, VirX™ in Thailand, Singapore, Hong Kong and South Africa, and FabiSpray™ in India.

Acknowledgement

Drs. Miller and Moore thank Assistant Professor J Sirirattawan, MD, (Hon) Associate Professor A Narkwichean, MD, PhD and Dr K Khuancharee, PhD for their collection and providing the data.

Mountain View Hospital Delivers Family-Centered Care, with Healthy Outcomes and Happy Nurses, Through Innovative NICU Design

Anduin Anderle, RN

In the U.S., one in 10 babies are born prematurely, but in many areas of the country, families struggle to access the maternity and neonatal care they need. Each year, approximately 150,000 babies are born to moms living in communities where there can be difficulties obtaining high-quality healthcare before, during and after pregnancy.[1]

At the same time, the nursing shortage continues to impact healthcare delivery throughout the U.S. A 2021 American Association of Critical-Care Nurses (AACN) survey found only 14% of registered nurses were very satisfied in their current positions, and more than two-thirds (67%) intend to leave their current nursing positions within three years.[2]

Mountain View Hospital (MVH), a physician-owned hospital located in Idaho Falls, Idaho, has established a new Level III neonatal intensive care unit (NICU) to better serve families in its community. The innovative NICU design keeps families of premature babies together, while creating a work environment where clinical staff feel valued and supported in caring for their tiny patients.

Meeting the community need for neonatal care

In the state of Idaho, where Mountain View Hospital (MVH) is located, the pre-term birth rate is 8.5% and infant mortality rate is 4.4%, according to the 2021 March of Dimes Report Card.[3] MVH's original NICU, built 20 years ago, could only care for babies born at 35 weeks' gestational age or older.

Babies born earlier than 35 weeks and/or with conditions that exceeded MVH's Level II NICU, needed to be sent to another facility for care, which sometimes meant temporarily separating them from their mothers.

"It was clear that the community needed more places to care for these sick babies and expanding to a Level III NICU let us be able to keep families together," said Brandi Klingler, BSN, RN, MVH NICU Manager.

MVH's goal was to create a Level III NICU that simultaneously met the needs of babies, families and staff. The hospital teamed with Dräger on an integrated contemporary design with innovative neonatal equipment to enable the NICU to achieve its care objectives.

"Mountain View wanted to do more than create a NICU. We wanted to create the best NICU in the area, so we shot for the moon. We worked hard to develop a facility that could help deliver parents peace of mind," said Jake Maughan, RRT-NPS, MVH's NICU Clinical Project Manager.

Focused on family centered care

Design priority number one for MVH was to keep families together.

"We believe keeping parents closely involved with their child's care not only helps their peace of mind, but it has also been shown to reduce stress for babies and improve their short- and long-term health outcomes," said Klingler.

In MVH's new Level III NICU, each of the 14 care rooms is designed to provide a private space and nurturing environment in which neonates can thrive and be with their parents. Parents have 24/7 access to the new NICU.

One of the rooms is large enough to host twins or sicker babies, complete with a queen-size Murphy bed so parents can sleep comfortably.

"We wanted families to have their own space to be with their baby. Our NICU was set up to always allow mom and the dad or whatever support person the neonate needs to be at their bedside," said Brandi Watt, RN, NICU Registered Nurse. "There is also enough room for our team to provide high quality care with the family in the room."

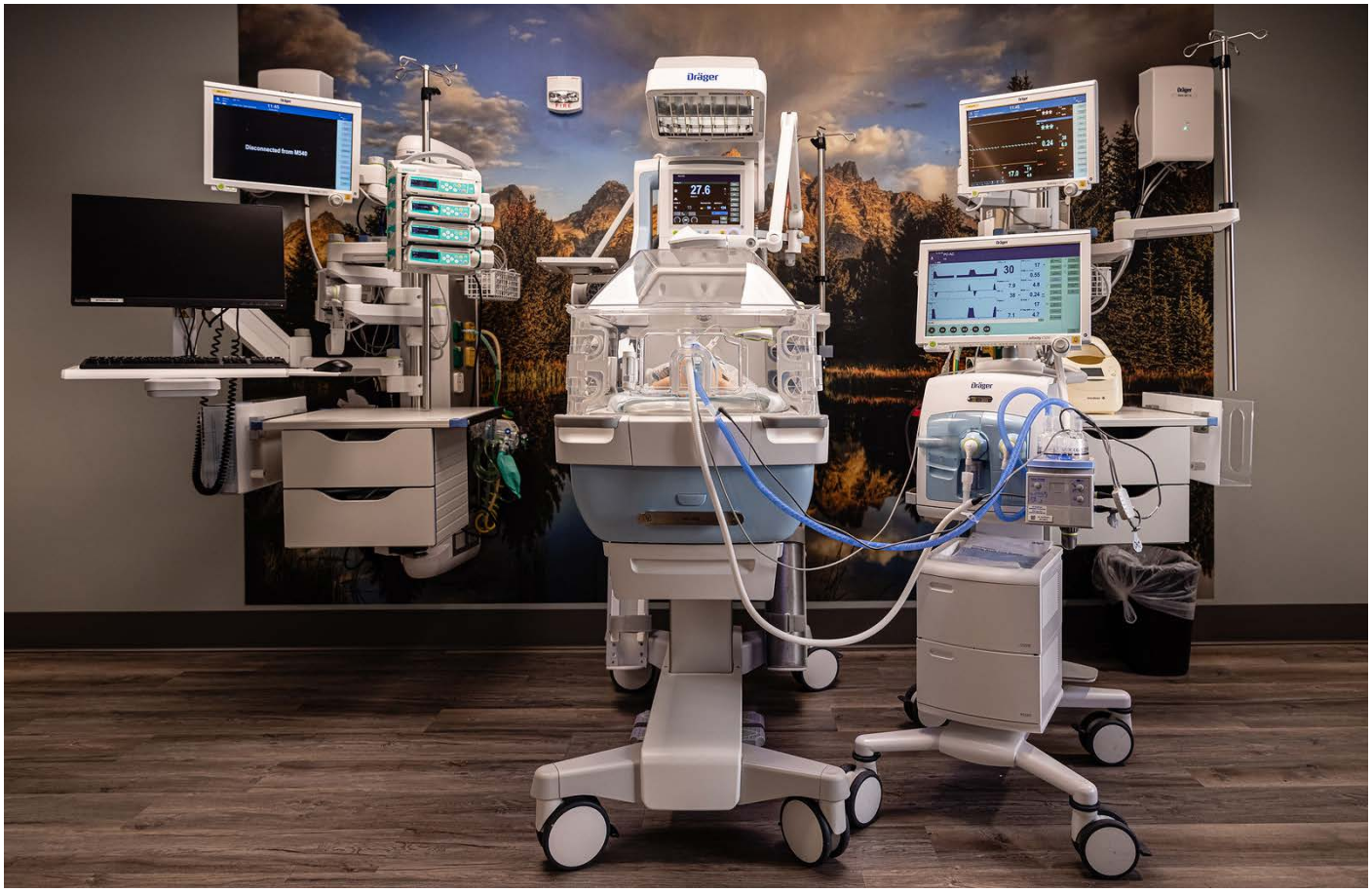
Technology driven for optimal outcomes

Standardizing on advanced neonatal technology was essential for the new NICU.

"Most of our neonates' problems are respiratory-driven," Watt commented. "So, we knew if we could provide amazing respiratory care, we were going to have good outcomes along the way."

The NICU team chose the Babylog VN500 ventilator featuring lung-protective technologies including volume guarantee, which stabilizes mean delivered volumes to prevent lung injury and can reduce the total duration of ventilation.

Anduin Anderle, RN, serves as Marketing Manager for Neonatal Care & Thermoregulation, North American region, for Dräger, an international leader in the fields of medical and safety technology.



They have also implemented the Babyleo TN500 IncuWarmer, which provides a neuro-supportive environment to help reduce toxic stimuli that neonates are usually protected from in utero. This feedback supports developmental care initiatives to reduce harmful stimuli that can negatively impact neonate development, family stress levels, and staff well-being.

"We have everything we need to take care of the sickest infants here," said Klingler.

"I'm really looking forward to being able to do more for these babies," said Kendall Hanson, RN, MVH NICU Registered Nurse. "It was hard when we would get a baby that we couldn't keep because we didn't have the equipment we needed. I'm excited to be able to care for more of these babies and keep them with their families."

Designed for staff satisfaction and seamless care delivery

MVH's NICU, with what Watt refers to as "top-of-the-line in respiratory care" equipment, supports high nursing satisfaction and the ability to both retain and recruit new staff members.

"Recruiting excellent nurses is one thing we have been focusing on – and our state-of-the-art equipment really is a selling point," said Klingler. "I think it shows we are invested in taking good care of these babies, and a lot of nurses really want to be a part of that."

MVH considered not just the diagnostic and therapeutic technology, but also how the overall look and feel of the NICU could help support a happy and healthy work environment.

Because medical caregivers spend long hours in the NICU, it is essential that the environment mimic circadian rhythms and reduce toxic stimuli such as unnecessary alarms. In MVH's new NICU, light and sound levels in all care rooms are continually monitored. MVH chose to fill the walls with restful outdoor scenes from the local area for parents and staff to enjoy. Every space optimizes workflow, adheres to infection prevention practices, and provides privacy.

In addition, the ergonomic GeminaDUO wall-mounted supply system improves NICU workflow by placing critical connections and components within easy reach of caregivers. This head wall system was configured to create a dedicated family space, while lighting options provide high-quality light sources for examination and allow caregivers to safely navigate their workspace when the overhead lights are dimmed.

"Whether it is air, oxygen, suction or plug in cords, [GeminaDUO], the way it is made and how you can just plug things on either side of it, frees that up and makes more space," said Maughan. "It is more user-friendly, and I can see that producing better outcomes."

"Having an edge with equipment is definitely a good thing," Maughan added. "We hope people who want to take care of babies like we do will see that advantage and want to come here because of it."

"We like it all," said Watt. "From the environmental comfort our technology provides for families and infants to the easy-to-use monitoring systems for nurses."

Healthy babies, happy families, satisfied clinicians

The MVH NICU team is now able to care for up to 14 neonates as young as 25 weeks gestational age, keeping families together within a dedicated environment that is pleasant for babies, family and staff members.

Advanced technologies, improved workflow with easy patient access, and ample room for point-of-care equipment help nurses and other clinicians provide high levels of care efficiently and safely.

MVH's Ned Hillyard, Ph.D., Chief Clinical Operations/Compliance Officer, offers this advice to other hospitals on NICU design:

"Quality and patient outcomes should always be at the forefront. The patient must be the centric focus."

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Unplanned Extubations in the Neonatal Intensive Care Unit

Brian Walsh, PhD, RRT, RRT-NPS, RRT-ACCS, RPFT, FAARC

Well, thanks for that warm introduction and then happy Respiratory Care Week to all you guys out there. Appreciate everything that you do for our patients.

One of the things that we're going to talk about today is unplanned extubations, in the NICU. It's something that, I think, many of us have worked really hard to reduce, but it still often occurs, quite often.

When it comes to the introduction, we'll talk about the definition of unplanned extubations and we'll step through an overview of unplanned extubations in the NICU, clinical outcomes, financial implications, evidence-based approaches to try to reduce unplanned extubation and then it will end with technology solutions.

Let's first talk about what the definition is of an unplanned extubation.

You may have heard the term "accidental", which we shouldn't try to stay away from that term in this space, because it really is an intentional dislodgement of the endotracheal tube or unplanned, from that aspect of it.

Sometimes people say: "Hey, well the baby decided to remove the tube themselves", they know better, things like that. Really take the emphasis around this extraordinary event. We need to shy away from that and really use the UE or unplanned extubations because we don't want to take the emphasis off of this event. That obviously may occur when the child pulls at it, or bats at the tube or pulls the ventilator circuit. It could be done by hands-on care when we're actually carrying, weighing those types of things and then also family centered care that we often encourage as we go along.

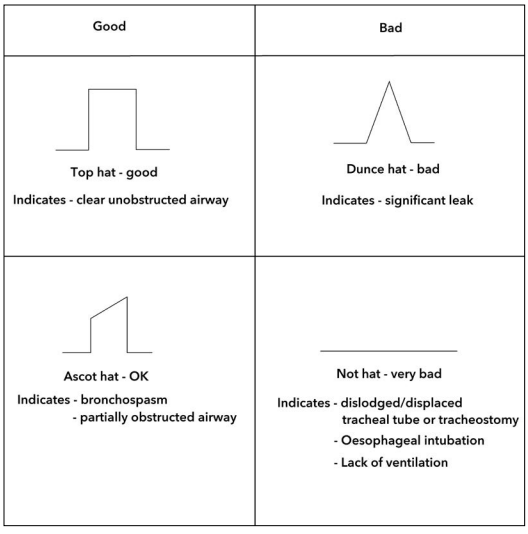
Let's talk about the incidences of unplanned extubation in the NICU. Reports vary between .54 to 16.1.

Obviously if you worked at that 16.1 place, that's pretty big range. It's per 100 endotracheal tube days, so, don't be confused with the associated pneumonia, which is per thousand days. Think about that as we go along. Often the benchmark is to try to get it to 0, but less than one is often preferred. The incidences are that between 14 and 41% of infants experience a UE during their hospitalization.

When it comes to quickly assessing the patient for an unplanned extubation, I often like to use the DOPE algorithm. And I'm not calling someone a DOPE, I'm just saying: "Hey, this is something that we need to think about." We're thinking about Displacement. And so, confirming that, whether it's Obstructed, Pneumothorax or Equipment failure.

So, let's step through this as we go along.

First is Displacement. One of the tools that we often use is look and see, like an inspection. Is there chest rise and fall, is there favor, and then the endotracheal tube will caution you. Chest rises and falls, particularly in the micro-preemies, it is really difficult to understand, especially when they're spontaneously breathing all around, because we tend to encourage that, obviously. Certainly, you can listen to breath sounds. And it may be louder on the right than the left showing you that there's maybe a right mainstem intubation. But really the hallmark is endtidal CO2, whether you use colorimetric CO2 or capnography, where you're actually looking at a waveform. I have some examples over here of waveforms that are actually detecting rather good versus bad.



Brian K Walsh, PhD, RRT, RRT-NPS, RRT-ACCS, RPFT, FAARC is an Associate Professor and the MSRC Bridge Program Director in the Department of Respiratory Care in the School of Health Professions. He received a Bachelor of Science in Health Sciences from Old Dominion University, a Master of Business Administration from Liberty University, and a Doctor of Philosophy degree in Health Sciences (Respiratory Therapy) from Rush University.

The one that we are really focused right now is obviously very bad, there is no rise of End Tidal CO2, which means that the patient is probably extubated.

When it comes to Obstruction, we'll quickly go through these. This is not really the focus of our talk today, but certainly in- line suctioning has become the standard. It allows us to quickly look and grab those secretions if we need to.

Obviously, we want to use our brain and wonder if they had a history of secretions after suctioning, do they improve their saturation, chest rise and fall, or EtCO2.

When it comes to Pneumothorax, this is an area in which I'm really proud of us. I think we've done a magnificent way of reducing the incidences of pneumothorax and to the point where it's actually become pretty rare. I often will suspect the airway before a pneumothorax just because of our improvements in our strategies of ventilating these kids.

When I first started in the early 90s, this was actually fairly common because we used pressure control ventilation and we did not monitor routinely tidal volumes. That's something that we have to think about. But you need to roll it out, that's part of the DOPE algorithm.

Inspecting that chest rise and fall, if you see asymmetrical chest rises and falls, that's obviously a very big sign that there's something going on there, whether it's an obstruction or a pneumothorax.

Certainly, auscultation is important, and then still the gold standard is transillumination, although I think ultrasound and those types of things are really starting to become standard of care at the bedside because ultrasound has become so much smaller, so much easier to use, and we're starting to train lots of people to actually be able to use that. But, until then, transillumination has been helpful in that.

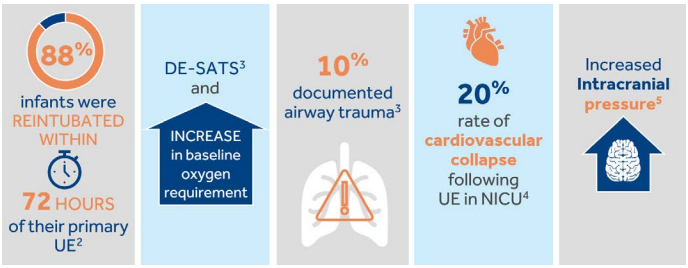
But what you need to do is to make the space dark, and sometimes that's a little bit difficult to do in a very busy ICU. Obviously, when it comes to Equipment Failure and troubleshooting the ventilator if the ventilators is alarming.

We train our nursing colleagues to take over and bag, until we can actually troubleshoot or get to the bed space to troubleshoot it if you're there already.

As a Respiratory Therapist, you can troubleshoot the ventilator and manually ventilate as appropriate, to see if you can actually improve the desaturation or whatever caused the event to begin with, from that aspect.

Let's talk about clinical outcomes. I think that is something that's really important as we go along. We'll think of short term as well as long term impacts to health.

Short term sequelae are that 88% of infants get reintubated within 72 hours. You may think that's high but pay attention to the 72 hours. In a study, they looked at that at a longer period of time, a lot of people do 24 hours, therefore the instances dropped quite a bit because sometimes these babies can do fairly well for the first day or two, but when you go out to three days then obviously that increases and so, so don't downplay it. It's an important event that actually occurs in the short term.



Of course, the desaturations increased baseline oxygen requirement 10% documented airway trauma from having to re-intubate 20%, and this is the ones that, at least in my experience, cost me the most heartburn, and often say one unplanned extubation is too many, because you can actually have patients who actually have cardiovascular collapse and it happens as high as 20% of the time.

And then, last but not least, it is particularly important in our micro- preemies the increased intracranial pressure either from the high CO2 that goes up because they can't ventilate themselves, or from the intubation itself causing high intracranial pressures. These guys have very delicate general metrics and they can actually have a bleed as a result of that as well. We certainly don't want to contribute to that if we can avoid it.

Some long-term ones are associated with bronchospasm, aspiration pneumonia, and particularly these children that we are feeding quite a bit, so they can actually have a pretty whopping pneumonia that occurs in these situations.

And even aspiration of just gastric content in the beginning can cause these bronchospasms and be really devastating to their lung function.

For the short-term as well as the long-term hypotension and arrhythmias can occur typically from hypoxia and then of course cardiopulmonary arrest and even death, which can occur in the wrong patient and certainly they are at increased risk of unplanned extubations or repeat of that as well.

There are a couple others where repeated unplanned extubations are associated with longer term. Tracheostomy, subglottic stenosis, and other injuries that can occur from the multiple repeated events of putting endotracheal tubes in there. And we already talked about the intraventricular hemorrhage.

When it comes to financial implications, this is something that was a little bit eye opening to me when we were diving into the literature about this topic, because a lot of times some people have the opinion that, you know, it's a risky business, right? We're saving kids' lives and things like that. Unplanned extubations are bound to happen and often many of the kids don't get re-intubated. So, these are attitudes that I've heard as time has gone on about unplanned extubations. Some of them, I think, are unfounded a lot of times, but we went through short term and the long-term implications, but now let's talk about the financial implications as well.

Some of the long-term financial implications are that they often, when they have an unplanned extubation and get re-intubated,

they have approximately a week longer duration of mechanical ventilation. This leads to about 10 days length of increased length of stay in the hospital and is associated with about 50,000 dollars of increased hospital cost. These are pretty recent data, only a couple years old.

Obviously, inflation is hitting all of us, right? And so, I have a feeling this may go up from there. When it comes to evidence-based approaches of how to look at reducing unplanned extubations, there's been a lot of work in this area and a lot of these folks should be applauded for their hard work. And of course, like we've done with ventilator associated pneumonia, extubation bundles have been really helpful in reducing unplanned extubations. We'll stop a little bit deeper into that.

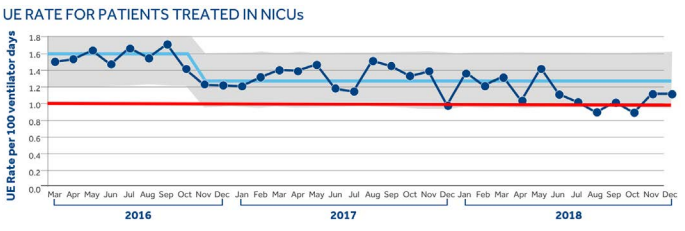
When it comes to unplanned extubation bundles, a lot of times what people are talking about is standardization. That's really important, in other words, the standardization of how we actually secure endotracheal tubes, how we manipulate those endotracheal tubes, even do chest X-rays. You want to make sure that we're all either assessing the landmarks from the gum or the nare, and not using things that move, like the lips or can swell because it can actually be hard to tell if it actually is in the same place or not. We all have to use the same landmark.

Same thing with standardized securing method, whether that's a NeoBar like we'll talk about it in a few minutes, or just taping, types of taping techniques that we're all doing it the same.

Protocols for invasive procedures, particularly when we're covering the head, kangaroo care, where we are giving over to the parents to hold and secure the ventilator circuits, routine positioning of babies when we turn them to help with their head molding and such, and then even switching beds or weighing a lot of times can be a high risk situation that we definitely want to do.

Multidisciplinary is also something that we need to continue to support and make sure that we have education across the dimensions, as well as doing root-cause analysis, or apparent-cause analysis following an unplanned extubation, and again, not contributing to a high-risk service that we provide and that we're always going to have some things. We really need to shoot for zero unplanned extubations if at all possible and always continue to strive until we get there.

When it comes to bundles, in this study, you can see here in their chart over a basically a three-year period of time, they've actually been able to reduce their unplanned extubation rates from roughly 1.55 to 1.2. Again, sadly not below that 1 threshold that we are still striving for.



When we assess the patients, we want to eliminate unplanned extubations and that harm that's associated with it, and we should always strive for that zero that I was mentioning before.

I know it seems impossible, especially for you guys that take care of these guys day in and day out, but I promise you if we don't continue to strive for it, we will miss it every time, right?

Other things that have been on the focus now is looking at the endotracheal tube positioning and decreasing unplanned extubation by using that method.

Obviously, high endotracheal tubes are a problem. When it comes to these really small neonates, half a centimeter can mean the difference between intubation and extubation. So high ETT tubes are associated with that unplanned extubation. We want to optimize it to make sure that it's at that T1 level on chest X-ray.

Additionally, when we're advancing the endotracheal tubes, a lot of times there is a low risk, a lower risk of unplanned extubation during that. So, we should always be cautious when we're doing that, and I'll often stick my finger further back to keep it from kinking or pressing into the back and not actually advancing during that process.

Let's review some technologies that have come along the way. One of the things that we want to think about is that, when we have this current challenge of unplanned extubation, neonates have an increased risk factor for unplanned extubation. Some people contribute that to

sedation, or lack thereof sometimes, that we use in our neonates and their ability to move and pull their head away.

We already mentioned the high prevalence rate that 14 to 41% of infants will experience an unplanned extubation during their NICU hospitalization.

Obviously, if they do have an unplanned extubation, a lot of times they'll increase their cost and worsen their clinical outcomes. And because of those clinical outcomes, we have a longer length of stay.

They're obviously on the ventilator longer and that can actually contribute and makes this cycle continue on and repeat over and over again. So, we need to something to try to interrupt that cycle.

Some current limitations of our current practice are that unplanned extubation rarely can get below that one goal that we're often shooting for to review. People have obviously assessed the location of the endotracheal tubes by chest X-rays, which is technically the gold standard, but we often don't do them frequently or daily because we want to reduce the exposure to radiation. And it is a snapshot in time, it doesn't mean that it can't move from there a lot of times. So, when we're doing the chest X-rays and their routine assessments of the endotracheal tube and standardizing the markings, a lot of times that will help you understand where the tube is. But when it actually does occur, the DOPE mnemonic can address these decompensations. A lot of times.

One of the things that I was thinking of when I was developing this talk is that we used to often encourage restraint therapists in particular if you could not quickly go through this DOPE algorithm and assess to pull the tube because we were actually encouraged by the neonatologist that the likelihood of it actually occurring was pretty hot and therefore it would be easier to bag

valve mask them and avoid the hypoxia related to a delay in diagnosis. So, it was almost preferred in those situations.

We've been able to reduce our unplanned extubations, pretty well, but sometimes the thought still goes through my mind that if I can't quickly do this, I'd rather just pull the tube and bag valve mask and call for help versus watching a baby who's really hypoxic and really struggling to breathe. And then, me trying to go through this algorithm in a quick fashion, because it happens so frequently; people have started to employ that approach. I'm not saying it's right or wrong, it's just one of those things that, in my practice, I've seen us do quite a bit, and I really would like to change that.

So, one of the technological solutions that I'm excited to chat with you guys about is SonarMed. What is this device? It's a pretty cool device in that it uses acoustic waves to interpret the changes in the distance, as well as the diameter of the endotracheal tubes. This can actually be a real time warning system and it can help us determining whether the endotracheal tube is in or out or up or down in these situations.

One of the really innovative ways that it does this is it has a really nice display that allows us to give real time feedback of the positioning of the endotracheal tube, and you can have an audible alarm when it changes from that baseline. It also can give you real time feedback on ET tube obstructions.

So, whether it's suction and secretions of the endotracheal tube, especially the really small ones when they get warm and they become pliable and they get like fish mouth as I call it.

And, depending on the positioning of the endotracheal tube, it can actually kink and so this would help identify those types of obstructions, as well as secretions.

You can use it to determine the quality of your suctioning, whether you got all the secretions out or removed those potential mucus plugs in those situations, as well as the airway circumference.

Another thing that I was thinking of is that some of you guys that have done this as long as I have, you've seen us keep babies intubated for prolonged periods of time and sometimes the numbers wear off of the tubes. So, we end up taking a permanent marker and lining up to where it used to be. Often, that has become a problem, as well, because these endotracheal tubes sometimes will stay in for weeks, if not months, in these infants, because we do a really good job of monitoring that. But sometimes we lose that location aspect in which this particular SonarMed tool would be able to help us with that aspect of it.

I want to share with you a really cool experience that Children's Hospital Illinois shared last year. They had no standardized collection of unplanned extubations. They discovered that they had a high rate of unplanned extubation compared to their other centers. They utilized the NeoBar in the majority of their cases, but they had no routine nasal intubation, and so their major interventions trial was that they used the SonarMed system and they did root cause analysis for all unplanned extubation.

They educated the RT's on proper use of the NeoBar and sizing and taping. They audited that bundle of measurements. They did ET tube annotation by radiology on the chest X-ray to verify the endotracheal tube positioning to be at that T1 space. They did mass education on the unit to proper positioning for chest X-ray. They encourage two-person care for all intubated subjects and then their baseline rate was 2.1 of 100 ventilator days prior to the interventions. They started off two times what we would like to see.

The "So what?" here is that they've chronically had a low lung disease rate compared to other centers. And unplanned extubations were associated with physiologic changes, and hypoxemia and hypercarbia, and increased arterial pressure, and increase in cranial pressure, which often leads to this less than controlled in an endotracheal tube intubation.

So, if you intubate at night in those types of situations, we know that repeat intubation is not great and especially when they're done emergently. They have a risk of airway injury, ventilator induced lung injury, associated pneumonia from potential aspiration pneumonia, and then other non-pulmonary complications such as HIVH.

Unplanned extubations obviously are a core measure by the US News and World Report, and that's an indication of quality, right?

If you're really particular about your endotracheal tubes and you can keep that number lower, then it is assumed that you provide a higher quality of care. So, the team knew that they could perform better.

The SonarMed system is the only intervention that we've been able to actually do recently. We've tried bundles and things like that, and they were able to drop their unplanned extubation from that baseline of 2.1 to 1.4, but they really still cannot go below that 1 that has been the goal of care.

They also noted that unplanned extubation were actually occurring during kangaroo time or skin to skin. We encourage two people to help with those situations, but sometimes there's just not a lot of space. Not all the staff were completely bought in on the two-person care that a lot of people have gone to with the standard of care and they presumed that the ET tube tended to move. Often, we've seen it, I've seen it. It's like I've almost magically re-intubated someone because I've seen the tube come way out and then I just pushed it back in as a natural reaction and somehow it stayed in. I have no idea sometimes how that actually occurred. The ways of measuring that shift when you're positioning, especially a child that's on the oscillator, it can be really difficult.

Then, the preference of the mother or the father or the caregiver to do skin to skin and positioning that they'd like to hold has been difficult to understand how to hold, how to actually tape or secure the ventilator circuit in the endotracheal tube.

Some of the unplanned extubations also occur outside of care. So, normal respirations, typical movements, they even have hiccups, they can swallow. I've even seen them turn the tube out that caused that endotracheal tube that seems to be at the right spot to be higher or lower in the trachea.

We obviously know the head position is important as well. Whether it's up or down can change the position of that endotracheal tube.

And so, they wanted a better way to monitor, particularly in real time, those situations of kangaroo care and such and so. They were actually one of the NICUs that were able to come lower than that 1 down to .51 per 100 ventilator days for the last six months. They certainly should be applauded for being able to do that.

They observed a more focused approach to invasive mechanical ventilator patients. They're doing the bundles, they're doing all the right things, but now they have that added tool of the SonarMed to be able to make us aware of where the tube is at any moment in time with that migration.

Here are all the things that they started to do. The two-person standard of care, the education with chest X-ray and the positioning and labeling of that, they did NeoBar reeducation, they did debriefings after unplanned extubation and they updated that process as they went along and then they implemented the SonarMed system, and they finally got below that 1 with the implementation of all these plus the SonarMed during this process. They continue to support, and they have an overwhelming belief of, that skin to skin or kangaroo care and bonding between that infant and that parent. It's part of their culture, and they do not want to limit that, especially for patients who are really sick, such as high frequency ventilation. That situation can be scary and intimidating for the parent because certainly no parent wants to cause the demise or a complication of their child.

They found it in those situations, the center has offered that reassurance that they needed to make sure that that endotracheal tube was in place allowed them to have a much more enjoyable time bonding with their infant and they tended to be more up to participate when it comes to monitoring the status of that airway.

So, eliminating unplanned extubation and harms associated with those events remains achievable. And now we have a new tool in the toolbox.

There's no such thing as the silver bullet, but now we have something that's really, really helpful.

I'll stop there and take any questions that may have come up.

The recording of this presentation can be found at https://www.medtronic.com/covidien/en-us/clinical-education/catalog/webinar-wednesdays.html on October 25, 2022.

Lung Inflammation in alpha-1-antitrypsin Deficient Individuals with Normal Lung Function

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Abstract

Background Alpha-1-antitrypsin deficient (AATD) individuals are prone to develop early age of onset chronic obstructive pulmonary disease (COPD) more severe than non-genetic COPD. Here, we investigated the characteristics of lower respiratory tract of AATD individuals prior to the onset of clinically significant COPD.

Methods Bronchoalveolar lavage was performed on 22 AATD with normal lung function and 14 healthy individuals. Cell counts and concentrations of proteases, alpha-1-antitrypsin and proinflammatory mediators were determined in the bronchoalveolar lavage fluid from study subjects. In order to determine the airway inflammation, we also analyzed immune cell components of the large airways from bronchial biopsies using immunohistochemistry in both study subjects. Finally, we made comparisons between airway inflammation and lung function rate of decline using four repeated lung function tests over one year in AATD individuals.

Results AATD individuals with normal lung function had 3 folds higher neutrophil counts, 2 folds increase in the proteases levels, and 2-4 folds higher levels of IL-8, IL-6, IL-1β, and leukotriene B4 in their epithelial lining fluid compared to controls. Neutrophil elastase levels showed a positive correlation with the levels of IL-8 and neutrophils in AATD epithelial lining fluid. AATD individuals also showed a negative correlation of baseline FEV_1 with neutrophil count, neutrophil elastase, and cytokine levels in epithelial lining fluid ($p < 0.05$). In addition, we observed twofold increase in the number of lymphocytes, macrophages, neutrophils, and mast cells of AATD epithelial lining fluid as compared to controls.

Conclusion Mild inflammation is present in the lower respiratory tract and airways of AATD individuals despite having normal lung function. A declining trend was also noticed in the lung function of AATD individuals which was correlated with pro-inflammatory phenotype of their lower respiratory tract. This results suggest the presence of proinflammatory phenotype in AATD lungs. Therefore, early anti-inflammatory therapies may be a potential strategy to prevent progression of lung disease in AATD individuals.

Background

Alpha1-antitrypsin (AAT) is the major plasma serine protease inhibitor, playing an important role in limiting tissue injury mediated by proteases during inflammation. Alpha1-antitrypsin deficiency (AATD) is an inherited monogenic disorder associated with reduced circulating levels of AAT, linked to increased susceptibility to chronic obstructive lung disease (COPD).[1,2] COPD, one of the top five leading causes of death in the world, is a destructive lung condition with a slow progression.[3-6] AATD Individuals with COPD have a two-to-eightfold increased rate of decline in FEV_1 (ΔFEV_1) as compared to non-genetic COPD individuals.[7-11]

AAT is an acute phase protein mainly produced by the liver, and circulating concentrations of AAT increase two to four fold during inflammation. The function of AAT is described as neutralization of proteases such as neutrophil elastase (NE) in the lung's lower respiratory tract of the lung.[12] NE is the major serine protease released by activated neutrophils and the main substrate for AAT inhibitory function. Increased numbers of neutrophils, have been reported in the lower respiratory tract of AATD individuals with COPD, contributing to lung destruction.[12,13] Lung low levels of AAT therefore contribute to increased activity of proteases and are thought to be a major cause for the development of AATD lung disease.[14]

Chronic inflammation of the lower respiratory tract due to inhalation of cigarette smoke (CS) is the major cause of COPD.[15,16] Exposure to dust,[17-19] and infections[20] are also associated with an increased rate of lung function decline in COPD patients. CS stimulates lung resident immune cells to release pro-inflammatory mediators that enhance neutrophil's recruitment.[21,22] During inflammation, activated neutrophils arrive in the lung via a cytokine gradient to provide host defense releasing proteases such as NE, proteinase 3 (PR3).[23,24] An increase in airway neutrophil recruitment in COPD correlates with the lung function decline.[25] NE induces the production of pro-inflammatory cytokines and inactivates extracellular immune mediators such as complement components in favor of inflammation.[26] NE also increases vascular permeability that amplify lung inflammation and tissue damage during inflammation[27] As an anti-inflammatory molecule, AAT provides protection against NE cytotoxicity and therefore insufficient

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AAT, in combination with increased lung recruitment of neutrophils, resulting in the development of AATD lung injury.[28]

Increased pro-inflammatory mediators have been showed in the sputum and bronchoalveolar lavage fluid (BALF) from AATD individuals with COPD, indicating presence of airway inflammation.[29-31] Therefore, it is reasonable to believe that the intensity of inflammation correlates with the proteolytic environment and inflammatory mediators' burden in AATD lungs. However, little is known about the temporal appearance of inflammation and neutrophil's recruitment, in the lungs of AATD individuals. Here, we focused on immune cells and proinflammatory mediators in the lower respiratory tract of AATD individuals with normal lung function to explore the temporal inflammatory changes in AATD lungs. The cellular profile of BALF and immunohistochemistry analysis of bronchial biopsy samples showed the preinflammatory phenotype of AATD lungs as compared to control subjects. Furthermore, investigation of the levels of inflammatory mediators in the BALF and their association with lung function rate of decline suggested a declining trend in the lung function of AATD individuals which was correlated with pro-inflammatory phenotype of lower respiratory tract. Given these findings, we speculate that early anti-inflammatory therapies may prevent further progression of lung disease in individuals with AATD.

Methods

Study population

Normal and AATD individuals were recruited at the NIH Clinical Center after providing consent for the NIH IRB protocol # 95-H-0016. All individuals were free of any signs of respiratory tract infection at the time of study. All BALF samples were screened using clinical laboratory methods for common viral and bacterial pathogens. AAT PI-typing was determined by isoelectric focusing of the serum proteins and AAT serum levels were determined by nephelometry (Behring Diagnostics, Marburg, Germany) using in-house standards and controls.[32]

Lung function tests

AATD individuals were evaluated every three months for one year, and pulmonary function tests were performed according to American Thoracic Society (ATS) standards.[33] The post-bronchodilator FEV_1 for each individual was used to calculate the rate of decline for FEV_1 expressed in ml per year (FEV_1).

Bronchoalveolar lavage fluid

All bronchoscopies were performed by at the NIH Clinical Center, Bethesda MD, USA as previously described.[34,35] A flexible video bronchoscope was inserted through the mouth via a mouthpiece with the subject. Instillation of 100 mL of saline was performed in 5 sequential 20 mL aliquots for each of the three lobes (typically right middle medial, right upper anterior and lingula superior or inferior, 300 mL in total). The aliquots from each lobe were collected separately in 50 mL conical tubes and stored on ice until processed.

Determination of antigenic AAT level in ELF (Epithelial Lining Fluid)

AAT concentration in BALF was determined by indirect sandwich ELISA. Briefly, Immulon-2 plates (Dynatech, Chantilly, VA Cat # 112079, 81079) were coated overnight with goat anti-human AAT antibody (ICN, Costa Mesa, CA. Cat # 855111). Plates were washed, and samples and standards were added. Purified AAT from normal plasma was used to generate a standard curve.[32] The plates were washed and incubated at with rabbit anti-human AAT antibody (Dako, Santa Clara, CA. Cat # A0012) followed by incubation with horseradish peroxidase conjugated goat anti-rabbit IgG (BioRad. Hercules, CA. Cat # 1706515). Finally, o-phenylendiamine-dihydrochoride (Fluka Biochemika, Milwaukee, WI. Cat # R1413) substrate was added to develop the ELISA. For each subject, an ELF dilution factor was calculated by taking the ratio of their plasma urea concentration to BALF urea concentration. BALF measurements are multiplied by this factor to standardize ELF measurements.

Determination of functional AAT levels in BALF (anti-NE capacity assay)

All BALF samples were treated with 4 M methylamine (Sigma, St.Louis, MO. Cat # 534102) at room temperature for 1 h. Standards and samples were added to the plates and were incubated at 37 °C for 5 min. Human NE was added and incubated for 5 min (Athens Research and Technology Inc., Athens, GA. Cat # 16–14-051200). Methoxysuccinyl-ala-ala-val-pro-p-nitroanilide (Sigma, St. Louis, MO. Cat # M4765) was added and kinetic optical density at 405–490 nm was determined.

Determination of AAT:NE complex concentrations in BALF

Plates were coated with sheep anti-human NE (ICN, Costa Mesa, CA. Cat # LS-C23012-200) and incubated at 4 °C overnight. Plates were washed and samples and standards were loaded for incubation at 37 °C for 1.5 h. Rabbit anti-AAT antibody was added and incubated at 37 °C for 1.5 h. The plates were then washed and horseradish peroxidase conjugated goat anti-rabbit IgG was added. Reactions were terminated by H_2SO_4, and the optical density at 490 nm was determined. Values were corrected for BALF dilution to give ELF concentrations of AAT:NE complexes.

Determination of antigenic NE concentrations

Samples and standards pre-treated with 1 mM PMSF (Sigma, St. Louis, MO. Cat # P7626) were loaded to the sheep anti-human NE coated plates and were incubated at 37 °C for 1 h. Rabbit anti-NE (Athens Research and Technology, Athens, GA. Cat # 01-14-051200) was added and incubated for 1 h 37 °C. The plates were washed and horseradish peroxidase conjugated goat anti-rabbit IgG was added. Reactions were terminated by adding H_2SO_4, and optical density at 490 nm was determined using a SPECTRAmax (Molecular Devices, Sunnyvale, CA). Values were corrected for BALF dilution to give ELF concentrations of NE.

Determination of inflammatory mediators in BALF

Cytokine levels were measured using R&D Systems ELISA kits (Minneapolis, MN) according to the manufacturer's instructions. Briefly, samples were diluted in assay buffer before being applied to the assay plates for incubation. The plates were then washed and conjugated antibodies applied for the second incubation. Plates were washed and substrate was added. The optical density was measured and sample concentrations were calculated based on the standard curve.

Bronchial biopsies

Bronchial biopsies were taken from the carinas of the right lower lobe (RLL) and right middle lobe (RML) using a small cut biopsy forceps as previously described.[36] A maximum of 5 biopsies per individual were taken. Biopsies were stored in 10% formalin for further evaluation. Immunohistochemical analysis was performed on a subset of the 11 AATD individuals (6 males and 5 females) and 6 control volunteers (4 males and 2 females).

Tissue processing and immunohistochemistry (IHC)

Tissues were fixed in formalin and following standard paraffin embedding procedures, 4 µm sections were collected onto clean glass slides. The tissue sections were deparaffined with xylene and rehydrated. To study the airways histological features, sections were stained with hematoxylin and eosin. IHC was used to determine presence of inflammatory cells. Primary antibodies against leukocyte markers, including anti-human NE (ICN, Costa Mesa, CA. Cat # LS-C23012-200) (neutrophils), anti-human CD68 (ThermoFischer Scientifics, Waltham, MA. Cat # MA5-12407) (macrophages), antihuman CD45R0 (ThermoFischer Scientifics, Waltham, MA. Cat # MA5-11532) (T lymphocytes), anti-human CD3 (ThermoFischer Scientifics, Waltham, MA. Cat # MA5-12577) (T lymphocytes), anti-human CD4 (ThermoFischer Scientifics, Waltham, MA. Cat # MA5-32166) (T-helper cells), anti-human CD8 (ThermoFischer Scientifics, Waltham, MA. Cat # MA5-14584) (cytotoxic T cells), anti-human CD20 (Abcam, Waltham, MA. Cat # ab78237) (B cells), anti-human EG2 (Abcam, Waltham, MA. Cat # EPR20357) (eosinophils), and anti-human AA1 (Abcam, Waltham, MA. Cat # ab2378) were used. The dilution factor for the antibodies were according to the manufacturer's instructions. The sections were incubated with 3% H_2O_2 in 95% alcohol for 10 min to block endogenous peroxidase activity and primary antibody solutions were applied for antigen detection. Positive (tonsil and lymph node sections) and negative (no primary antibody) controls were run in each experiment.

Airway biopsy image analysis

Cell counts were carried out by using a light microscope at a magnification of 40× using the Image-ProPlus Imaging software (Media Cybernetics, Inc. Rockville, MD). Positive cells were counted in representative areas that were subtended by 100 µm of intact basement membrane and that extended 100 µm into the submucosa. Counting was performed at locations where the thickness of submucosa was more then 100 µm and smooth muscle and mucosal glands were absent. A grid system was set up to select areas correctly. Each site in each square in the grid was 100 µm. 10 of those squares, which met the above criteria, were counted. The cumulative count was expressed as the number of the positive cells per mm of BM (cells/mm^2).

Other measurements

The LTB4 measurements and determination of ELF volume were performed as described previously.[24] Samples were treated with ethanol, centrifuged at 375 ×*g* for 10 min, acidified, and applied to C18 cartridges at a rate of 0.5 ml/minute. The C18 columns were sequentially washed using distilled water, 10% ethanol, and petroleum ether before elution of the sample using methyl-formate (Sigma, St.Louis, MO. Cat # 291056). The methyl-formate was dried under nitrogen gas and the sample was suspended in assay buffer. LTB4 was measured using an ELISA kit (Cayman Chemical. Ann Arbor, MI. Cat # 5220111).

Statistical analysis

We extracted data on sample size, mean cytokine concentration, standard deviation (SD), and p-value to calculate the effective size. Statistical analysis was performed using GraphPad Prism 9 software (San Diego, CA). The results are shown as mean ± SEM unless otherwise stated. p-value of < 0.05 was considered statically significant. Data were tested for normal distribution using the Kolmogorov–Smirnov test. For the comparison of cell counts, proteases, and inflammatory mediators between the disease and control groups, student *t* test and Mann-Whitney U test were performed. The Spearman's correlation coefficient was calculated to analyze the correlation between inflammatory mediators, proteases and the lung function test results. The "r value" is being used to indicate the correlation value referring to the Pearson correlation.

Results

Profile of study subjects

The study population consisted of 22 AATD individuals (9 male, 13 female) with a mean serum AAT level of 5.2 ± 0.2 µM. Of the AATD group, 8 were ex-smokers, with average history less than a 5 pack/year and quited smoking at least one year before the study. The remaining 14 were never smokers. No AATD patients were on AAT replacement therapy. We also recruited 14 healthy nonsmoking homozygous PiMM controls (10 male, 4 female), with mean serum AAT levels of 27.7 ± 1.0 µM. Except for the serum AAT level, the demographic and clinical characteristics were similar between the two groups (Table 1).

BALF cellular features

We examined BALF cellular features every three months, over a one-year period. We found no significant differences in the cellular and biochemical features of four sequential four BALF samples from AATD subjects, therefore only the first BALF results are presented. We also observed no significant differences in the features of the three lobes and the data are reported from a single lobe, typically the right middle lobe, for simplicity. There were no differences in the ELF volume, total cells of the recovered ELF fluid, as well as percent of macrophages or lymphocytes in BALF between AATD and normal individuals (Table 2). By contrast we observed a significant increase in the ELF number of neutrophils (Additional file 1: Fig. S1A) in AATD individuals compared to healthy controls. The ELF percentage of neutrophils of AATD individuals was persistently increased and did not significantly vary over the one year of the experiment duration (Additional file 1: Fig. S1B).

ELF inflammatory mediators

ELISA showed tenfold higher AAT concentrations in the ELF of normal individuals compared with AATD, as expected (Fig. 1A). There were higher levels of functionally active AAT within the ELF of normal subjects compared to AATD individuals (anti-neutrophil elastase capacity, ANEC) (Fig. 1B). Median NE concentration and PR3 levels within the ELF of AATD individuals were also higher than controls (Fig. 1C and D). There were no differences in the concentration of NE-AAT complexes in the ELF of AATD and normal volunteers due to low levels of AAT

Table 1 Study Population Characteristics

Study	Deficient	Normal	p value
Age (years)	42 + 2	40 + 4	0.17
FEV_1 (% predicted)	101 + 3	107 + 4	0.058
FVC (% predicted)	103 + 6	104 + 4	0.43
TLC (% predicted)	105 + 4	104 + 4	0.82
DLco[a] (% predicted)	112 + 4	103 + 5	0.22
ΔFEV_1 (ml/year)	− 174 + 59	NA	NA
α_1-AT Level (µM)	5.2 + 0.2	27.7 + 1.0	< 0.0001[b]

Values are expressed as mean and standard error of the mean (SE)

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; DL_{CO}, diffusing capacity; Δ FEV_1, rate of decline FEV_1/year

[a] Single breath (uncorrected)

[b] Significant correlation

Table 2 Bronchoalveolar lavage fluid features in alpha1-antitrypsin deficient individuals with normal pulmonary function and normal individuals

	Deficient	Normal	p-value
Return[a]	50.1 + 3.9	56.8 + 4.2	0.88
Total cells (ml^{-1} ELF)	$1.4 \times 10^7 + 0.25 \times 10^7$	$1.2 \times 10^7 + 0.19 \times 10^7$	0.25
Macrophages (%)	89.6 + 0.9	91.1 + 1.1	0.59
Neutrophils (%)	3.3 + 0.6	1.0 + 0.1	0.006[b]
Lymphocytes (%)	6.6 + 1.0	7.8 + 1.1	0.20
ELF volume (mL)	0.89 + 0.13	0.93 + 0.11	0.74

Values are expressed as mean and standard error of the mean (SE)

ELF epithelial lining fluid

[a] Percentage of BALF recovered

[b] Significant difference

in AATD group and low levels of NE in the normal controls (Additional file 1: Fig. S1C).

Next, we measured the concentrations of IL-8, IL-6, IL-1 beta and LTB4 in the BALF samples and found that AATD individuals had significantly greater levels of the pro-inflammatory mediators than controls (Fig. 2A–D) including a sixfold greater ELF concentration of LTB4 in AATD individuals.

Lower respiratory tract inflammation

Our correlation studies indicated a positive correlation between the percentage of neutrophils and NE concentrations in the ELF of AATD individuals (Fig. 3A). Importantly, the percentage of neutrophils and the levels of NE also showed a positive correlation with IL-8 levels in the lower respiratory tract (Fig. 3B and C), whereas neither IL-1beta nor IL-6 correlated with NE concentration. Similarly, the levels of IL-8 in the lower respiratory tract were also positively correlated with the levels of PR3 (Fig. 3D). Furthermore, IHC analysis of the bronchial

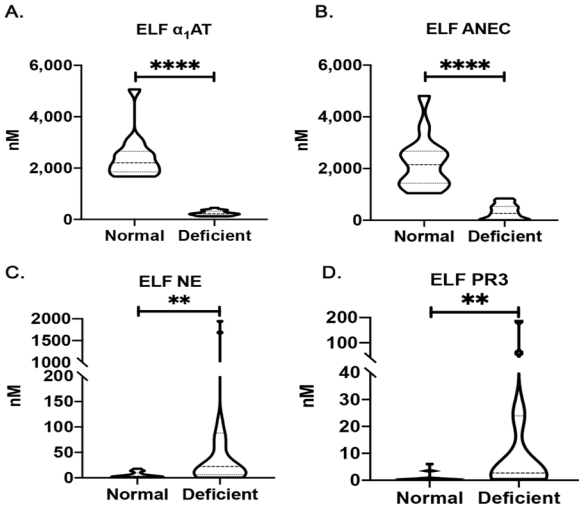

Fig. 1 Protease-antiprotease imbalance in the epithelial lining fluid (ELF) of alpha1- antitrypsin deficient individuals. Bronchoalveolar lavage was performed in control subjects (N = 14), and alpha1- antitrypsin deficient (N = 22) individuals as described in the methods. **A** The concentrations of alpha1- antitrypsin, **B** Alpha1- antitrypsin:anti-neutrophil elastase capacity (ANEC), **C** neutrophil elastase (NE), and **D** protease 3 (PR3) were measured by ELISA and expressed as levels of analyte in the ELF. $^{**}P < 0.005$, $^{****}P < 0.00005$

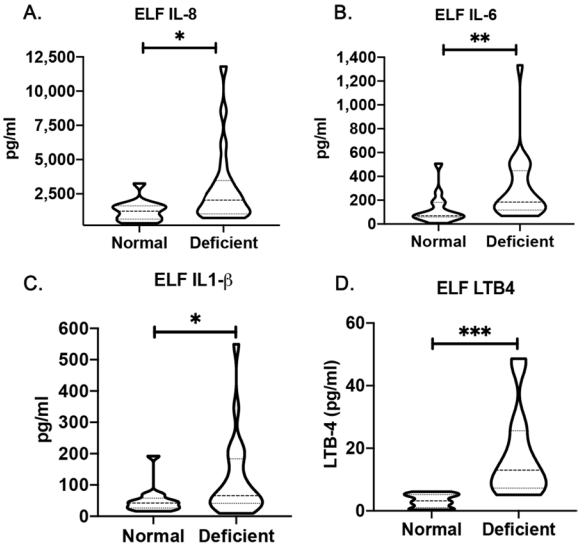

Fig. 2 Increased pro-inflammatory mediators in the epithelial lining fluid (ELF) of alpha1- antitrypsin individuals. The concentration of pro-inflammatory cytokines was measured by ELISA and expressed as pg/ml levels of analyte in the ELF. **A** IL-8; **B** IL-6; **C** IL-1β; and **D** LTB4. $^{*}P < 0.05$, $^{**}P < 0.005$, and $^{***}P < 0.0005$

biopsies showed higher neutrophils and $CD68^+$ macrophages in AATD airways compared to controls. Additionally, there were also an increased numbers of $CD8^+$ and $CD4^+$ T cells, and $AA1^+$ mast cells in the bronchial epithelium of AATD individuals (Fig. 4A and B).

Lung function

To determine the relationship between the inflammatory state of the AATD lower respiratory tract with lung function rate of decline, we examined FEV_1 values over a one-year period. Initial FEV_1 showed a negative correlation with the percentage of neutrophils (Fig. 5A), NE and PR3 levels in the lower respiratory tract of AATD individuals (Fig. 5B and C). Furthermore, our results also indicated that FEV_1 does not correlate with age in AATD individuals (Fig. 5D). Importantly, ΔFEV_1 was significantly correlated with NE levels (Fig. 5E), and the percentage of neutrophils (Fig. 5F) in the AATD lower respiratory tract.

Discussion

Approximately 1:120 COPD patients, have the disease secondary to AATD.[37] While some studies indicate that AATD individuals may live a normal life span with little functional lung impairment,[28] others may develop progressive disease, even in the absence of known risk factors.[38] However, it has been unclear when the AATD-mediated lung inflammatory phenotype starts to develop and how early it is clinically detectable. To answer this question, we evaluated an AATD cohort who presented normal lung function, using a protocol that included lung function tests, bronchoalveolar lavage fluid, bronchial biopsies, and 4 visits over a year. This protocol allowed us to explore relationships between pulmonary inflammation, immune cell infiltration and lung function in our study subjects. Here, we illustrate that AATD individuals have higher neutrophil counts and levels of NE, IL-8, IL-6, IL-1β, and leukotriene B4 in their epithelial lining fluid prior to the onset of symptomatic lung destruction. The levels of proteases shows a positive correlation with the levels of IL-8 and neutrophils in AATD epithelial lining fluid. We also observed that there is a negative correlation between the baseline FEV_1 and neutrophil counts, neutrophil elastase, and cytokine levels in epithelial lining fluid of AATD individuals. Our results also

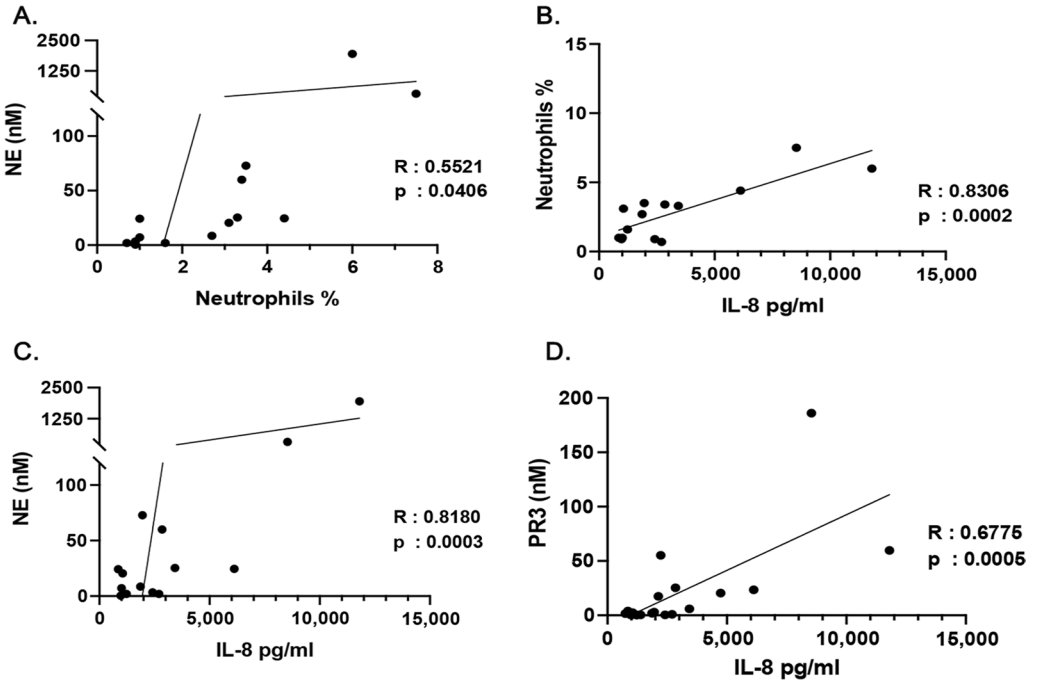

Fig. 3 Correlation of pro-inflammatory mediators in the epithelial lining fluid (ELF) of alpha1- antitrypsin deficient individuals with neutrophils and neutrophil derived proteases. **A** The correlation between the percentage of neutrophils and neutrophil elastase concentrations (NE), and **B** the correlation between neutrophil percentage and the levels of IL-8 in the ELF of alpha1- antitrypsin subjects. **C** The correlation between the levels of neutrophil elastase and IL-8 in the ELF of alpha1- antitrypsin subjects. **D** The correlation between protease 3 (PR3) concentration and the levels of IL-8

show an increase in the number of lymphocytes, macrophages, neutrophils, and mast cells of AATD epithelial lining fluid as compared to control subjects.

Lungs have been shown to serve as a target organ for airborne pathogens and allergens that cause inflammation due to continuous exposure.[39] Previous studies have reported that air pollution, and inhaled particulates stimulate neutrophils infiltration within the airways[40] and increase AAT levels,[41] resolving within days in normal individuals.[42] In contrast, and consistent with our results, there is an increased risk of lung damage associated with neutrophil infiltration in AATD individuals, due to low levels of AAT and unopposed activity of proteases regardless of CS exposure.[43] Furthermore, CS causes lung neutrophilic inflammation which is expected to be larger in AATD smokers than in smokers with normal AAT levels.[44] Neutrophilic inflammation in AATD airways could be exacerbated as a result of AAT polymers deposited in alveolar and bronchial epithelial cells, acting as potent chemoattractants for neutrophils.[36] Previous studies have shown that CS polymerizes AAT, exacerbating inflammation.[45] Therefore, our results may also support the notion that AATD lung resident cells including alveolar macrophages and epithelial cells play a role in early AATD lung inflammation due to toxic gain of function, analogous to hepatocytes. In this regard, we and others have shown that AATD macrophages with AAT accumulation have impaired efferocytosis, and activation of the unfolded protein response, and spontaneously produce pro-inflammatory cytokines.[37-39] Overall, these findings suggest that early lung inflammation due to a lack of AAT might be part of the mechanism for the progression of AATD lung disease.

NE has been shown to increase the production of LTB4 by macrophages which is a potent neutrophil chemoattractant. LTB4 prompts macrophages to secrete proinflammatory cytokines in an autocrine manner.[46] Our data reveal higher concentrations of LTB4, as well as IL-6, IL-8, and IL-1beta in the ELF of AATD individuals with normal lung function compared to healthy controls. A similar observation was also made in sputum from AATD individuals with severe lung function impairment by Woolhouse et al.[40] In agreement with these findings, we observed that higher levels of IL-8 positively correlated with the number of neutrophils, and the levels of NE and PR3 in the ELF of AATD individuals with normal lung function. IL-8, an important chemoattractant,[47] can additionally activate neutrophils to release proteases. Likewise, it has been shown that IL-8 causes physiological changes in neutrophils during inflammation.[47] Therefore, IL-8 derived neutrophilic inflammation is a fundamental mechanism for pathogenesis of many of the lung diseases.[48] Our observation confirms an increase in neutrophils and proteases that correlate with the levels of IL-8 in AATD lungs, despite lack of clinical symptoms. This suggests a further contribution of early airway inflammation to the development of the lung deterioration observed in AATD individuals later in life.

AATD individuals with significant lung disease have excessive inflammatory cells in the lungs,[13] However, it is unclear when this inflammatory process begins.[20] Here, we observed an increased number of inflammatory cells in the bronchi of AATD individuals with normal lung function compared to the controls. This increased number of cells including $CD4^+$ and $CD8^+$ lymphocytes, is consistent with the report from Baraldo, et al. indicating increased lymphocytes in the lungs of AATD individuals with severe emphysema.[49] Our results also indicated increased number of neutrophils, macrophages, and mast cells in the bronchi of AATD individuals with normal lung function. Therefore, we believe infiltration of inflammatory cells to the airway epithelium happens secondary to the inflammatory environment of the AATD airways, and prior to the onset of clinically significant lung function impairment. This early

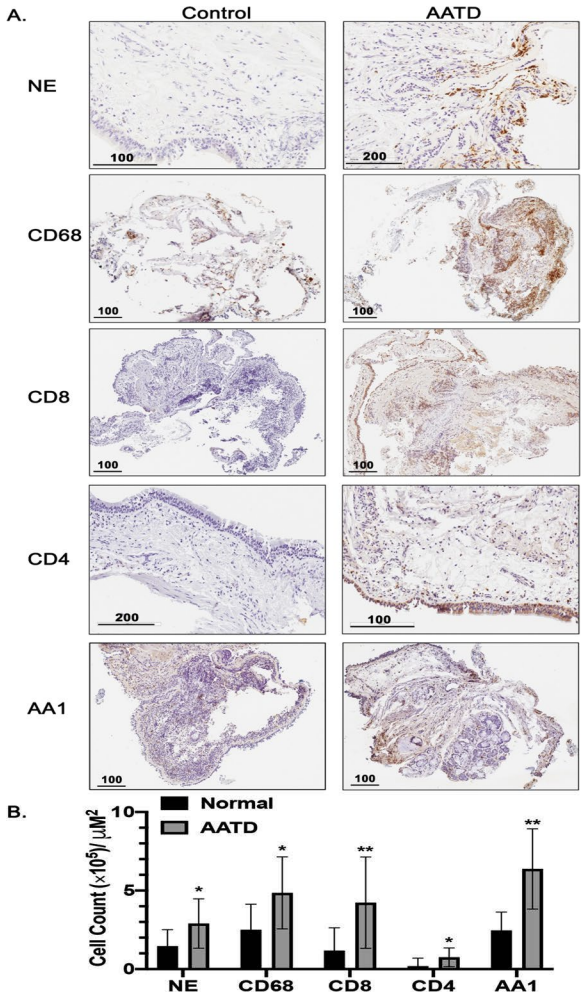

Fig. 4 Large airway inflammatory cells in normal and alpha1- antitrypsin deficient Individuals. **A** Bronchial biopsies from normal and alpha1- antitrypsin deficient individuals were incubated with primary antibodies against CD68, CD45, CD8, neutrophil elastase (NE), and AA1; HRP-conjugated secondary antibody and HRP-DAB developer as described in the methods. **B** The cells were counted and expressed as the number of cells per mm2 of basement membrane in the section. * $P < 0.05$, ** $P < 0.005$

abnormal presence of inflammatory cells perpetuate the inflammatory niche, and may explain the hyper-responsiveness and progressive lung damage in AATD individuals.

Chronic airway inflammation plays a central role in the pathophysiology of COPD and is associated with an accelerated decline in FEV_1.[50] In AATD individuals with COPD, a negative correlation between initial FEV_1 and ELF neutrophil burden has been reported.[51] However, it is unclear whether increased neutrophils have a causal relationship with AATD lung function decline. The contribution of proteases to the etiology of airway obstruction prior to the development of severe AATD lung destruction is even less well established. Here, we show an unexpected negative correlation between initial FEV_1 and neutrophil burden in the ELF of AATD individuals. According to previous reports, ΔFEV_1 levels accelerate as age increases.[52] In agreement with previous reports[53] measuring the FEV_1 during 1 year of follow-up, we observed that in AATD individuals, ΔFEV_1 was independent of age and negatively correlated with the ELF levels of NE and neutrophil burden. The correlation between increased neutrophils and immunomodulators of the lower respiratory tract with ΔFEV_1 suggests a role for early persistent inflammation in the development of lung injury prior to AATD lung function impairment. This observation indicates of a baseline ongoing airway inflammation in AATD individuals, without symptoms or clinical evidence of lung disease.

Our study has several limitations, the sample size is small and is only limited to subjects with normal lung function. It will be important to confirm the relationship between inflammation and lung function in larger cohorts of AATD subjects at different stages of disease and lung function. We also included ex-smokers in our AATD cohort. Even though it was minimal and remote smoking history it could affect our results. Finally we did not have chest imagen to evaluate potential emphysematous changes despite normal lung function. Chest CT densitometry might also be helpful for the early detection of AATD lung destruction.[54]

Conclusions

In conclusion, this study supports a multitude of AAT biological functions including modulation of several pathogenic processes underlying lung destruction. We demonstrate that normal environmental exposures might not only lead to a consistent airway inflammation, but also lead to continued infiltration of inflammatory cells within the AATD airways prior to the clinical evidence of lung disease. Our results suggest that AATD lung inflammation prior to significant lung damage might be modulated by early treatment with AAT replacement therapy and other anti-inflammatory therapies. Furthermore, our data also provide further rationale for the use of NE inhibitors in AATD as well as other lung diseases associated with NE-induced inflammation.

Abbreviations

AAT	Alpha-1-antitrypsin
AATD	Alpha-1-antitrypsin deficiency
ANEC	Anti-neutrophil elastase capacity
BALF	Bronchoalveolar lavage fluid
COPD	Chronic obstructive pulmonary disease
CS	Cigarette smoke
ΔFEV_1	Decline in forced expired volume in 1 s
ELF	Epithelial lining fluid
FEV_1	Forced expired volume in 1 s
IHC	Immunohistochemistry
NE	Neutrophil Elastase
PR3	Proteinase 3

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-023-02343-3.

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Author contributions

MB conceptualized and supervised the project, designed the methodology, recruited patients, collected samples and contributed to the draft manuscript. NK performed airway experiments and contributed to the draft manuscript. NK conducted data analysis and wrote the original manuscript. JL and LR revised the manuscript and data analysis. All authors read and approved the final manuscript.

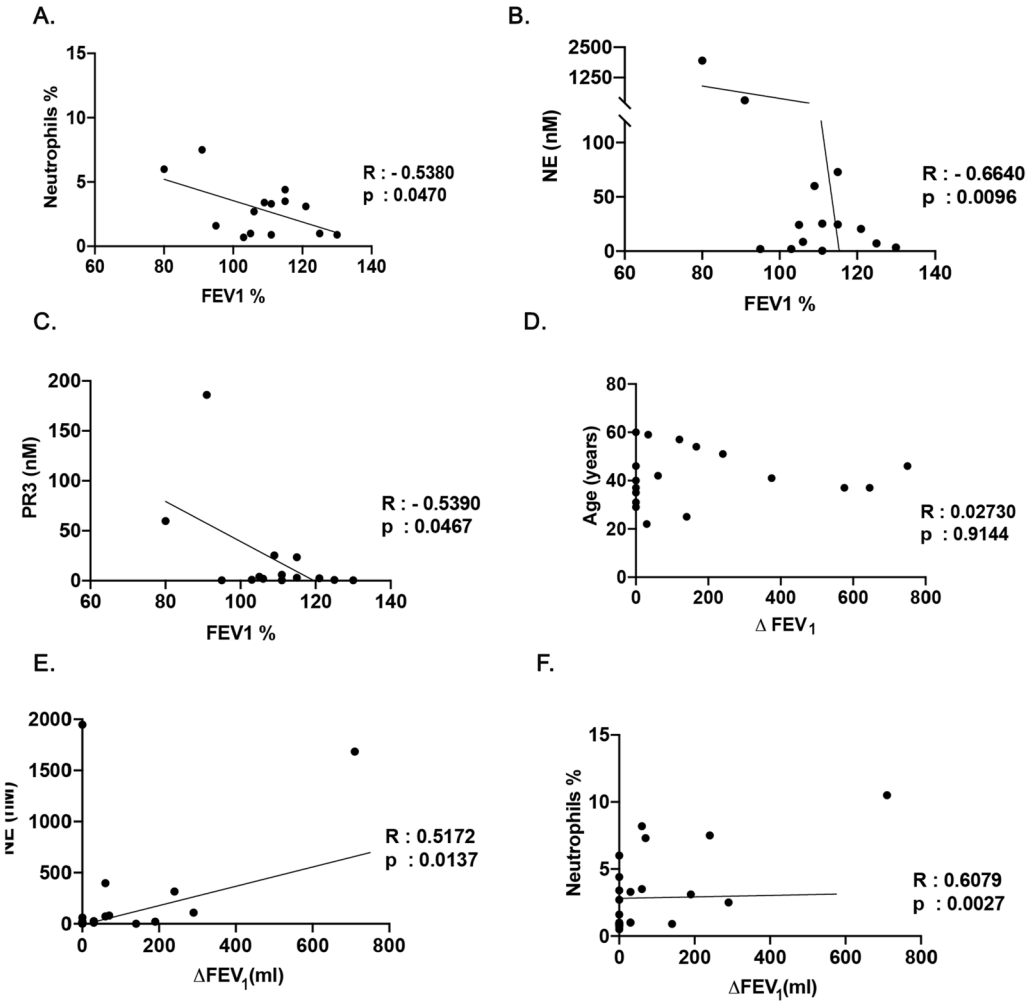

Fig. 5 Correlation of lung function rate of decline and inflammatory state of the lower respiratory tract in alpha1- antitrypsin deficient individuals. **A** The correlation of initial FEV1 with the percentage of neutrophils, **B** the concentration of neutrophil elastase, and **C** the concentration of protease 3 (PR3) in the lower respiratory tract of alpha-1-antitrypsin deficient individuals. **D** The correlation of the rate of decline in lung function (Δ FEV1) with age of individuals α-1 antitrypsin deficiency, and **E** the concentration of neutrophil elastase, **F** as well as percentage of the neutrophils of the lower respiratory tract in the individuals with alpha1- antitrypsin deficiency

Competing interests

The authors declare that the research was conducted in the absence of commercial or financial relationships that could be construed as a competing interests.

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satisfied with their products and services. Results are based on interviews conducted with respondents in 1,716 clinical testing locations in the US, representing 2,169 instruments. As the leading market research and business intelligence provider to the laboratory diagnostic industry, IMV has been a laboratory benchmarking standard for over 25 years. "It's an incredible honor to have the quality of our products and customer service, in both our Hemostasis and Acute Care Diagnostics business lines, recognized among the winners of the 2022 IMV awards," said Bill Crandell, Vice President of Commercial Operations, North America at Werfen. "This is a testament to the hard-work and commitment of the entire Werfen team, from those who develop and manufacture the very best products, to those who provide the very best support at our customers' sites. Their efforts enable us to fulfill our Purpose: to Power Patient Care." The Werfen Hemostasis Diagnostics Management product portfolio is comprised of in vitro diagnostics systems, reagents and information technology solutions used to diagnose and guide treatment of thrombotic and bleeding disorders. ACL TOP Family 50 Series Hemostasis Testing Systems for routine and specialty testing, offers unprecedented pre-analytical quality assurance, risk-management, and laboratory accreditation benefits. The ACL AcuStar is the first specialty testing analyzer to offer full automation of highly sensitive immunoassays, with no special training required. HemoCell™ Specialized Lab Automation, a unique Hemostasis workcell, allows Hemostasis labs to standardize their testing processes, while HemoHub™ Intelligent Data Manager centralizes oversight and access to Werfen testing systems for operational performance, quality management and clinical-decision support. The comprehensive and fully automated HemosI assay portfolio, including routine and specialty testing, is designed for disease state management.

CAIRE Completes Acquisition of MGC Diagnostics

CAIRE Inc., the leading global manufacturer of oxygen therapy and on-site generation systems, has finalized the acquisition of St. Paul, Minnesota-based MGC Diagnostics Holdings, Inc. (MGC). This acquisition strengthens CAIRE's position and focus on diagnostic technologies — furthering expanding its expertise in serving patients throughout the progression of pulmonary disease. Through this expansion of its time-proven portfolio of personal portable and stationary oxygen therapy solutions, and larger onsite generation solutions, CAIRE adds MGC's well-respected brand of non-invasive cardiorespiratory diagnostic systems, accessories, and consumables for the detection, classification, and management of cardiorespiratory disease. "This acquisition provides the means of serving the patient in a more holistic way — improving their quality of care throughout their entire journey. With MGC, we address the needs of patients early in the progression of pulmonary disease with a proven portfolio of equipment that addresses awareness and diagnostic tools for the healthcare provider and clinician. After diagnosis, CAIRE's oxygen therapy portfolio, which covers the entire continuum of care, can be leveraged to manage the patient's disease and ensure the best possible quality of life. This is a win for CAIRE, but most importantly the patient, and quality respiratory care everywhere." said Earl Lawson, CAIRE President and CEO. "We also expect to leverage CAIRE's well-established global distribution and manufacturing footprint to expand patient access to this expanded set of solutions." Established in 1977, MGC is the number two player globally in the cardiorespiratory diagnostics sector. In addition to its St Paul headquarters, MGC has facilities in Belgium, Germany, France, and Australia with more than two hundred employees. The company has a broad portfolio of products anchored by its pulmonary function testing systems, cardiopulmonary exercise systems, spirometers, flow sensors, gas analyzers, and associated consumables. An aging population contributes to continued growth in prevalent populations for conditions requiring cardiorespiratory diagnostic testing. More than 65 million patients suffer from COPD, the third leading cause of death worldwide, and more than 300 million patients suffer from asthma globally. Both these populations continue to grow annually and are responsible for more than $100 billion annually in healthcare spending. "The MGC team is excited about CAIRE's acquisition of MGC. The additional resources that CAIRE and its parent NGK SPARK PLUG CO., LTD offer will enable the MGC business to accelerate its plans for expansion and growth to better serve respiratory patients around the globe. These plans include continued strengthening of the product portfolio and improved access in current and new markets," said Todd Austin, MGC CEO. Acquired by NGK SPARK PLUG in 2018, CAIRE is poised for continued growth as the organization further expands its portfolio of solutions to serve the greater medical and healthcare markets, a part of its overall diversification outside of its core internal combustion engine business. Brookwood Associates acted as the financial advisor to CAIRE in this acquisition.

Paxlovid Has Been Free So Far. Next Year, More Will Pay

Nearly 6 million Americans have taken Paxlovid for free, courtesy of the federal government. The Pfizer pill has helped prevent many people infected with COVID-19 from being hospitalized or dying, and it may even reduce the risk of developing long COVID. But the government plans to stop footing the bill within months, and millions of people who are at the highest risk of severe illness and are least able to afford the drug — the uninsured and seniors — may have to pay the full price. And that means fewer people will get the potentially lifesaving treatments, experts said. In response to the unprecedented public health crisis caused by COVID, the federal government spent billions of dollars on developing new vaccines and treatments, to swift success: Less than a year after the pandemic was declared, medical workers got their first vaccines. But as many people have refused the shots and stopped wearing masks, the virus still rages and mutates. In 2022 alone, 250,000 Americans have died from COVID, more than from strokes or diabetes. But soon the Department of Health and Human Services will stop supplying COVID treatments, and pharmacies will purchase and bill for them the same way they do for antibiotic pills or asthma inhalers. Paxlovid is expected to hit the private market in mid-2023, according to HHS plans shared in an October meeting with state health officials and clinicians. Merck's Lagevrio, a less-effective COVID treatment pill, and AstraZeneca's Evusheld, a preventive therapy for the immunocompromised, are on track to be commercialized sooner, sometime in the winter.

High Dupilumab Discontinuation in Small Nasal Polyposis Case Series

Almost 1 in 4 patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) that was treated with dupilumab discontinued taking the drug because of adverse events (AEs), according to a recent case series. The research, published November 17 in *International Forum of Allergy and Rhinology*, is the first case series to highlight potential risks of dupilumab treatment for CRSwNP. "Of the 58 total patients undergoing

treatment with dupilumab for more than 6 months in the tertiary care clinic, 14 patients (24.1%) experienced AEs that required discontinuation of dupilumab," write lead study author Daniel J. Lee, MD, of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, and colleagues. "The leading causes were dermatologic with skin rashes or pruritus and musculoskeletal with severe joint pain." To investigate dupilumab's real-world safety profile, Lee and his research team conducted a retrospective chart review of patients with CRSwNP who had received subcutaneous injections of dupilumab 2 mL (300 mg) every 2 weeks between November 2018 and February 2022 at one academic rhinology and allergy clinic. The average age of the participants in both outcome groups was around 50 years. The groups were well balanced with respect to gender, as well as smoking and alcohol use, history of autoimmune disease, diabetes, hypertension, asthma, atopic dermatitis, and prior sinus surgery. All participants had undergone prior sinus surgery and had been taking dupilumab for CRSwNP with or without asthma treatment for an average of 7.3 months. Participants who stopped taking dupilumab did so within a median of 4 months of starting treatment; 42.9% (6 of 14) cited severe rash as the main reason for discontinuation, and 35.7% (5 of 14) cited severe joint pain. One person developed a drug-induced systemic lupus erythematosus-like reaction with positive antinuclear antibodies, and another developed angioedema that required medical care.

FLAMA/LABA Combos Tied to Varying Adverse Events in COPD

The risk for severe adverse events for patients with chronic obstructive pulmonary disease was significantly lower among those treated with glycopyrronium/indacaterol or umeclidinium/vilanterol compared with those treated with tiotropium/olodaterol, based on data from nearly 45,000 individuals. Fixed-dose combinations (FDCs) of long-acting muscarinic antagonists (LAMAs) and long-acting beta-agonists (LABAs) remain the foundation of treatment for chronic obstructive pulmonary disease (COPD), but concerns persist about potentially increased risk for cardiovascular events, especially among new users, wrote Ching-Fu Weng, MD, PhD, of Hsinchu Cathay General Hospital, Hsinchu, Taiwan, and colleagues. Data comparing the incidence of severe adverse events among different LAMA/LABA combinations are lacking, they said. In a study published in the journal *Chest*, the researchers reviewed claims data from the National Health Insurance Research Database and mortality data from the National Death Registry, both in Taiwan, from 2010-2019. The study population included 44,498 patients with COPD aged 40 years and older who were new users of any of three available FDCs between January 2015, and June 2019. Patients with concomitant LAMA and LABA in their previous 12 months were excluded. The FDCs were glycopyrronium/indacaterol (GLY/IND), umeclidinium/vilanterol (UMEC/VI), and tiotropium/olodaterol (TIO/OLO). GLY/IND was prescribed to 15,586 patients, 20,460 patients got UMEC/VI, and 8452 patients received TIO/OLO. Baseline characteristics were similar among the treatment groups. The primary outcome of severe adverse events was defined as hospitalization or an emergency department visit with a primary diagnosis of COPD or a secondary diagnosis of a severe AE; the secondary outcome was one of several cardiovascular events including acute myocardial infarction, heart failure, or arrhythmia. The median follow-up period was 6 months for the UMEC/VI and GLY/IND groups, and 60 days for the TIO/OLO group. During the follow-up

period, the incidence of severe AEs was lower in the UMEC/VI group compared with the TIO/OLO group (17.85 vs 29.32 per 100 person-years, hazard ratio [HR], 0.76). Similarly, the incidence of severe AEs was lower in the GLY/IND group compared with the TIO/OLO group (15.54 vs 25.53 per 100 person-years, HR, 0.77). The incidence and risk for any severe AEs was similar between the UMEC/IV and GLY/IND groups. In a sensitivity analysis, the between-group differences decreased when both severe and moderate AEs were included or in an intent-to-treat analysis, the researchers noted. However, effectiveness remained similar for the UMEC/VI and GLY/IND groups, they said. For the secondary outcome of cardiovascular events, patients in the GLY/IND group had a significantly lower rate compared with the TIO/OLO group (2.49 vs. 4.28 per 100 person-years, HR 0.70), but this difference vanished when the follow-up was 6 months or less. No significant differences appeared in cardiovascular events between the UMEC/VI and GLY/IND groups or between the UMEC/VI and TIO/OLO groups.

Fat-Free Mass Index Related to Outcomes in Underweight COPD Patients

Higher fat-free mass was tied to exercise outcomes in patients with chronic obstructive pulmonary disease who were underweight, but not in those who were obese or nearly obese, based on data from more than 2000 individuals. Change in body composition, including a lower fat-free mass index (FFMI), often occurs in patients with COPD irrespective of body weight, write Felipe V.C. Machado, MSc, of Maastricht University Medical Center, the Netherlands, and colleagues. However, the impact of changes in FFMI on outcomes including exercise capacity, health-related quality of life (HRQL), and systemic inflammation in patients with COPD stratified by BMI has not been well studied, they said. In a study published this month in the journal *Chest*, the researchers reviewed data from the COPD and Systemic Consequences – Comorbidities Network (COSYCONET) cohort. The study population included 2137 adults with COPD (mean age 65 years,; 61% men. Patients were divided into four groups based on weight: underweight (UW), normal weight (NW), pre-obese (PO), and obese (OB). These groups accounted for 12.3%, 31.3%, 39.6%, and 16.8%, respectively, of the study population. Exercise capacity was assessed using the 6-minute walk distance test (6MWD), health-related quality of life was assessed using the Saint George's Respiratory Questionnaire for COPD, and systemic inflammation was assessed using blood markers including white blood cells (WBC) count and C-reactive protein (CRP). Body composition was assessed using bioelectrical impedance analysis (BIA). Overall, the frequency of low FFMI decreased from lower to higher BMI groups, occurring in 81% of UW patients, 53% of NW patients, 42% of PO patients, and 39% of OB patients.

Philips Says Tests on Recalled Products Show Limited Health Risks

Dutch health technology company Philips (PHG.AS) said on Wednesday independent tests on its respiratory devices involved in a major global recall had shown limited health risks. The company rocked investors last year by recalling millions of breathing devices and ventilators used to treat sleep apnea, because foam used to dampen noise from the devices might degrade and become toxic, carrying potential cancer risks. "We can state that the whole product complies with safety norms. That is very encouraging news," Chief Executive Roy Jakobs said. Philips said the latest tests indicated that exposure to particulate matter emissions from degraded foam in DreamStation devices was "unlikely to result in an appreciable harm to health in patients", provided the machines had not been treated with ozone-based cleansing products.

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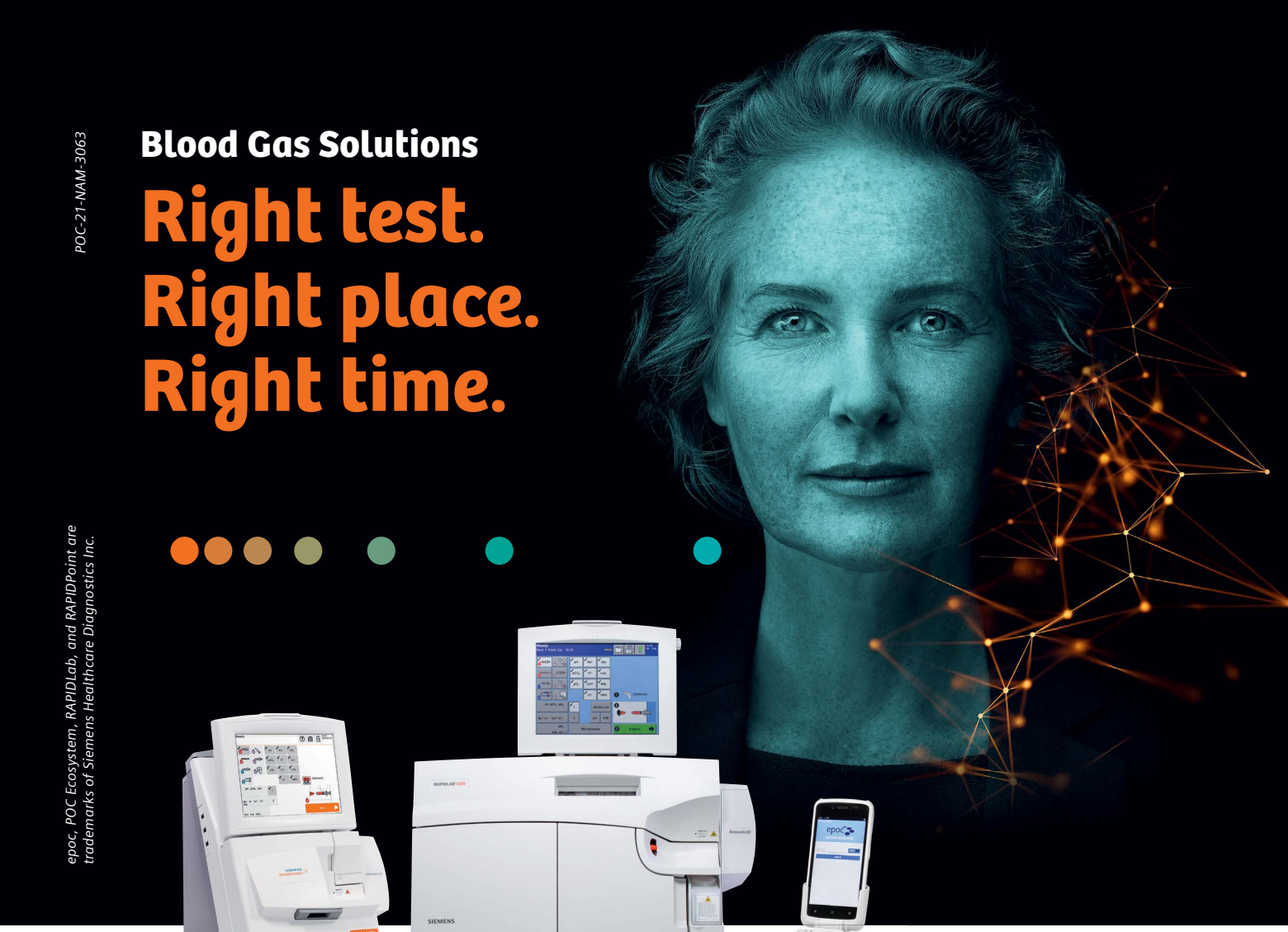

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