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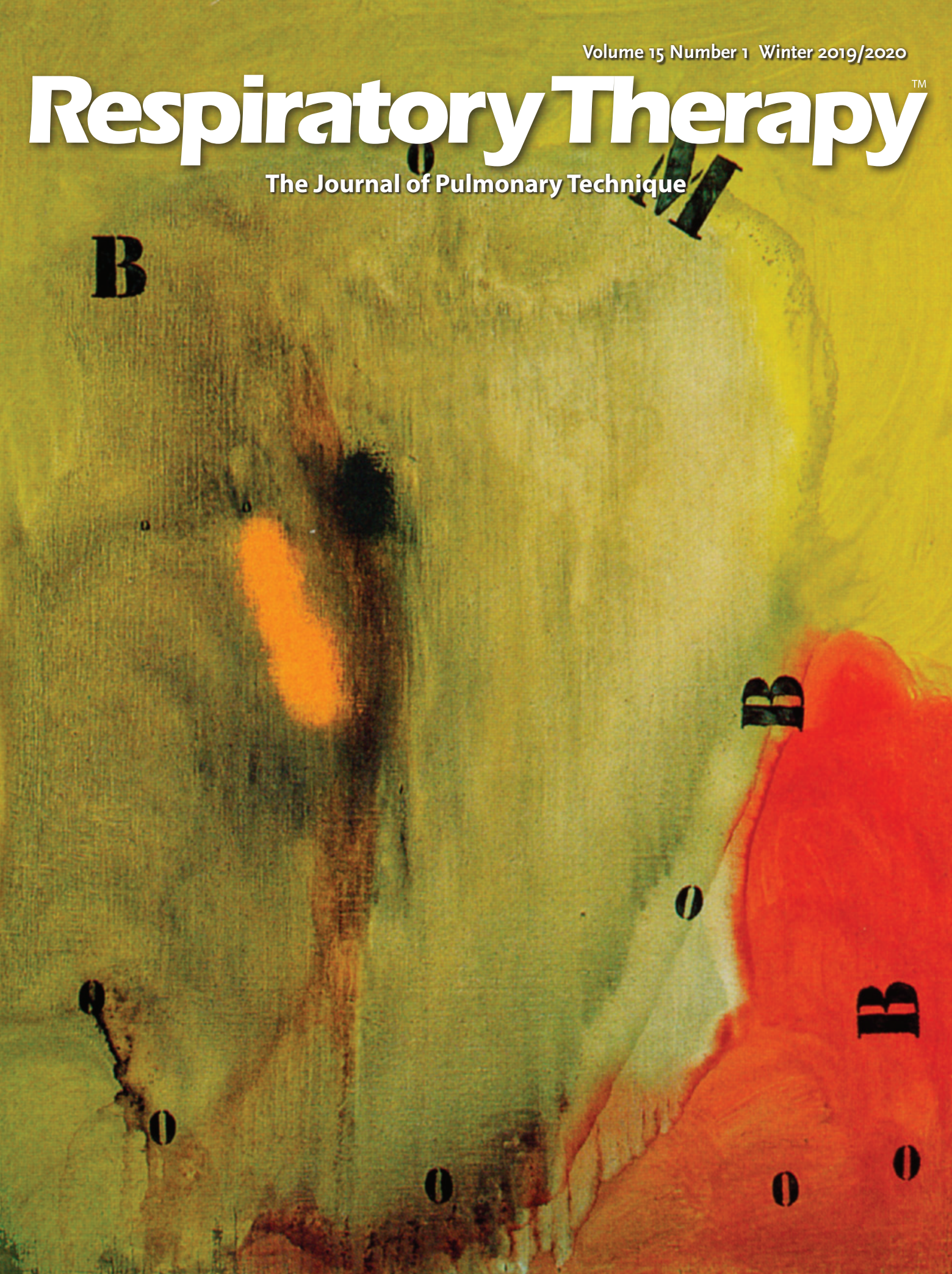
Respiratory Therapy™

The Journal of Pulmonary Technique



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STOP

To Implement into your existing Suctioning Protocol
email: info@NJRMedical.com

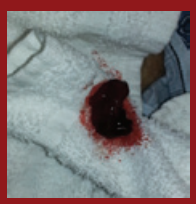
9 NEVERS of NASAL SUCTIONING PROTOCOL

1. Suction Catheter Induced Nasal Trauma (SCINT)
2. Anticoagulants
3. Coagulopathy Issues
4. Colonization in Nares (MRSA)
5. Recent Nasal/Sinus Trauma, Fracture or Surgery
6. Facial or Head Trauma/Basal Skull Fracture
7. Transsphenoidal Neurosurgery
8. End-of-Life Care
9. Occluded Nasal Passages/Deviated Septum

** Screen Patients Before Nasotracheal or Nasopharyngeal Suctioning*
** If answered **YES** to any of the above 9 Nevers, flag patient by placing a sign above bed:*
DO NOT NASAL SUCTION & AVOID NT/NP Suctioning altogether
** Use The No-Bite V™ (suction catheter introducer for the oral airway) as an alternative to nasal suctioning*

THE DANGERS OF SCINT

SUCTION CATHETER INDUCED NASAL TRAUMA



- Nasal Trauma & Pain
- Moderate-to-Serve Bleeding
- Emergent ENT Physician Consults
- Emergent Nasal Packing
- Required Blood Transfusions
- Increased Length of Hospital Stay
- Potential Lawsuit Against Hospital
- Negative HCAHPS & Press Ganey

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News

■ Winter 2019/2020

Monaghan Receives Prestigious Award

Monaghan Medical Corporation (MMC) has received the prestigious American Association of Respiratory Care (AARC) Zenith Award for the fifth consecutive year. The award was presented at the 65th International Respiratory Care Convention and Exhibition in New Orleans, Louisiana. The Zenith Award is a "people's choice" award of excellence voted on annually by members of the respiratory care profession. Recipients are selected based on such criteria as outstanding service, quality, accessibility, truth in advertising and support of the respiratory care community. "Winning the coveted Zenith Award from the AARC is a tremendous honor for which our entire organization is grateful," said Dominic Coppolo, MBA, RRT, FAARC, Vice President Clinical Strategy and Development at Monaghan Medical. "Receiving this recognition from our industry peers for a fifth straight year validates our team's commitment to providing our customers with the very best in respiratory care products and support." AARC is the leading national and international professional association for respiratory care. With more than 47,000 members worldwide, AARC encourages and promotes professional excellence, advances the science and practice of respiratory care, and serves as an advocate for patients, their families, the public and the profession. Monaghan Medical Corporation, headquartered in Plattsburgh, New York (USA), is a leader in the research, development, manufacture and marketing of respiratory devices including the AEROCHAMBER Brand of Valved Holding Chambers, AEROECLIPSE II Breath Actuated Nebulizer, AEROBIKA OPEP device, and the newly released VersaPAP device. MMC's products are developed, tested and validated at the Global Aerosol and Research Center of affiliate Trudell Medical International and are supported by more than 500 peer-reviewed and published articles. To learn more about Monaghan Medical products, visit www.monaghanmed.com.

Ventilator Gets Clearance

Vyaire Medical, Inc.'s bellavista 1000e ventilator has been granted 510(k) clearance from the US Food and Drug Administration (FDA). It is the newest addition to Vyaire's high-end ventilation portfolio offering a comprehensive solution for hospitals with the integration of high flow oxygen therapy and advanced synchrony support for neonatal to adult patients in a single device. Clinicians can rapidly change therapies on a broad range of patients in an effortless way. "We began using bellavista exclusively in 2017, when it was available in Europe. It allows us to ventilate invasive, non-invasive, nasal CPAP and perform high flow oxygen therapy with one device enabling targeted, efficient patient care in any situation" said Vincenzo Cannizzaro, MD, PhD, Deputy Chief Physician of PICU/NICU, University Children's Hospital, Zurich, Switzerland. Designed exclusively around enhancing the caregiver's experience, the bellavista 1000es intuitive touch screen provides advanced graphics to easily visualize the patient's pulmonary status, enhancing situational awareness for the caregiver. Whether its escalating care or weaning a patient efficiently, the bellavista 1000e ventilator simplifies the process by delivering optimal workflows with the goal of reducing operator error and ventilator lengths of stays. "Clinicians, respiratory therapists and bedside caregivers provided critical input in the design of this ventilator and helped us ensure we addressed their challenges in all patient care circumstances," said Lisa Rose, Chief Marketing and Innovation Officer, Vyaire Medical. "The bellavista 1000e is a solution that provides the ultimate versatility in therapy and it can be adjusted quickly depending on patient need in time sensitive situations. These differentiators are critical in a healthcare environment which expects innovative products to improve patient outcomes. Vyaire is dedicated to developing the kinds of systems and products that meet the needs of healthcare providers." Today, there are more than 8,200 bellavista 1000e ventilators in use across 92 countries outside of the United States.

Nihon Kohden Launches New Ventilator System

Nihon Kohden, a US market leader in precision medical products and services, announced the launch of its new NKV-550 series ventilator system that offers a full suite of applications necessary in a critical care setting for patients of all ages — from neonate through adult. The NKV-550, introduced for the first time at the annual American Association for Respiratory Care Congress

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2019 in New Orleans, is an innovative ventilator that features an integrated touchscreen, intuitive user interface, and onscreen help functions. The NKV-550 was developed to seamlessly transition between invasive ventilation, noninvasive ventilation and high-flow oxygen therapy, allowing clinicians to respond to a patient's respiratory support needs without having to change devices. "Every product we bring to market is designed to simplify workflow for clinicians and benefit patients," said Yasuhiro Yoshitake, president and CEO of Nihon Kohden America. "We saw a tremendous need in the respiratory market for a comprehensive ventilator that could respond to any patient situation while also providing excellent usability using modern technology." The NKV-550 is a unique ventilator to offer Protective Control, a feature that uses a second graphic user interface placed outside the isolation room of a contagious patient who is under mechanical ventilation. The respiratory therapists and clinicians can view the ventilator monitors and alarms, adjust ventilation settings and alarm settings, and audio pause the alarm sound, through the second graphic user interface outside the isolation room, as long as the patient is within the sight of the clinician through the room's glass window. When managing a patient who has a communicable disease case and is in isolation, this feature protects both the clinician and the patient because respiratory therapists and clinicians will not lose valuable minutes donning protective gowns, gloves and masks before responding to the needs of an infectious patient. This minimizes a potential hazard many healthcare workers face. An estimated 42 healthcare workers per million employed die each year from infections acquired at work. The NKV-550 was created based on the lung protective approach to ventilation and features the Gentle Lung suite of applications to provide clinically relevant, easy-to-use tools for the open-lung approach to ventilation. The ventilator offers highly customizable screen configurations enabling the ventilator to fit into your paradigm rather than require you adapting to it. The app-based design provides guided processes to help create a more streamlined, systematic way for clinicians to optimize care of their ventilated patients. The NKV-550 also offers on-screen help tools to walk clinicians through critical ventilator troubleshooting. Founded in Japan in 1951, Nihon Kohden is a leading manufacturer, developer and distributor of medical electronic equipment, with subsidiaries in the US, Europe and Asia. The company's products are now used in more than 120 countries, and it is the largest supplier of electroencephalography products worldwide.

'Breathing Company' gets FDA Clearance

Vyaire Medical, Inc., the healthcare industry's dedicated "breathing company," announced the US Food and Drug Administration (FDA) has granted FDA 510(k) clearance for two of its latest Pulmonary Function Testing (PFT) technologies: Vyntus ONE, Vyntus BODY with SentrySuite Software.
The Vyntus ONE is designed to be a convenient PFT station available in a fixed or mobile configuration that is patient-friendly and easy for clinicians to use. Vyntus BODY is engineered to conduct body plethysmography to measure lung capacity and other pulmonary functions for patients of all sizes and mobility, offering larger interior space to accommodate patients of any size without increasing the footprint of the cabin. Both Vyntus ONE and Vyntus BODY include a newly designed Ultrasonic Flow Sensor that represents significant improvements in efficiency and accuracy of pulmonary function testing. All Vyntus technologies run on the SentrySuite Software, which is easy-to-operate and designed completely around the user experience for accurate results and optimal workflow. SentrySuite provides seamless integration and secure connectivity with both the clinical infrastructure and the electronic medical records (EMR) platform. "These new Vyntus products offer a modern ergonomic design, state-of-the-art ultrasonic sensor technology for consistent and accurate respiratory testing as well as more efficient hygiene and maintenance protocols for customers." said Dave Eckley, Vyaire's Chief Executive Officer. "These benefits are absolutely meaningful in today's respiratory diagnostics clinical environment and demonstrate the value of the Vyaire technologies." Vyaire believes this product launch represents the most progressive innovation in the Respiratory Diagnostics field in many years. Vyntus ONE and Vyntus BODY are the continued expansion of the portfolio — including Vyntus CPX, Vyntus SPIRO, Vyntus WALK, and VyntusTM ECG — all of which run on the SentrySuite Software platform. Learn more at vyaire.com.

Telemetry Adapter Now Available in the US

Vyaire Medical has announced the US availability of its smaller, reusable ApexPro FH telemetry adapter for use with the GE ApexPro FH System. Designed with input from clinicians, the new version of the adapter connects to the GE ApexPro FH telemetry system. The smaller design offers a more secure connection making it easier for patients to move about the hospital while receiving ECG monitoring. The adapter can be used in conjunction with Vyaire's Multi-Link X2 ECG portfolio. "The new ApexPro FH adapter demonstrates our commitment to putting customers and patients first. The smaller size improves patient comfort and mobility. The compatibility with our disposable leadwires reduces cross-contamination exposure, because the leadwires can stay with the patient throughout the hospital. Both lead to improved patient outcomes, which is a win for everyone." Joel Brandon, VP Marketing, Vyaire Medical. The ApexPro FH uses one of our Multi-Link X2 solutions that allows for standardization of single patient use leadwires across multiple monitoring platforms including: GE, Philips, Mindray, Nihon Kohden and Spacelabs. Additionally, the new adapter helps optimize patient flow through the hospital allowing patients increased mobility. Infection prevention is a key metric in healthcare systems. By using our single patient use leadwires it can help eliminate the risk of cross contamination often seen with reusable leadwires.

Study Says This Device is 'Feasible'

Vapotherm, Inc., a global medical technology company focused on the development and commercialization of its proprietary Hi-VNI Technology, announced that a paper published in the Journal of Clinical Respiratory Diseases and Care, titled "Assessing the Clinical Effect of High Velocity Nasal Insufflation on Improving Ambulation in Patients with Dyspnea: A Feasibility Study" demonstrated that use of Vapotherm Hi-VNI Technology during ambulation is feasible and showed that patients with dyspnea participating in this study who used Hi-VNI Technology as respiratory support walked farther and recovered faster when compared to standard oxygen treatment. "These results show that the Vapotherm Transfer Unit not only provides support for hospital transfers across all deparments, but also offers an important respiratory support option for clinicians managing inpatients requiring ambulation as part of their treatment," said Joe Army, President and CEO of Vapotherm. "This study offers an additional proof point for clinicians that Hi-VNI Technology may help their patients, not just in general settings as Mask-Free NIV for spontaneously breathing patients, but also during ambulation and recovery." The feasibility study was a prospective cross-over trial that compared oxygen treatment as usual (TAU) to treatment with Hi-VNI Technology—which delivers high velocity nasal insufflation (HVNI)—in 28 patients during ambulation in both inpatient and outpatient settings. The goal was to compare how far and for how long patients could ambulate on Hi-VNI Technology versus the standard TAU. Vital signs and recovery time were measured as secondary outcomes. 25 of the 28 patients were analyzed. Among the inpatients in this study, Hi-VNI Technology during ambulation was not only feasible, but also showed improved patient distance walked by 12.4% and duration of time walked by 8.5%. It also improved recovery time by 32.5%. Use was also feasible among outpatients undergoing ambulation, although outpatients performed worse than the inpatient subgroup studied. These results are very encouraging for further research as well as demonstrating feasibility of using Hi-VNI Technology in respiratory patient ambulation. While this

study was comparing Hi-VNI Technology to oxygen support, previous studies have demonstrated that Hi-VNI Technology is comparable to noninvasive positive pressure ventilation (NiPPV) when treating patients in undifferentiated respiratory distress. The Vapotherm Transfer Unit is a self-contained mobile means of delivering Hi-VNI Technology for patients on the move in the acute setting.

Device Offers Rapid Change in Therapies for Clinicians

Vyaire Medical, Inc.'s bellavista 1000e ventilator has been granted 510(k) clearance from the US Food and Drug Administration (FDA). It is the newest addition to Vyaire's high-end ventilation portfolio offering a comprehensive solution for hospitals with the integration of high flow oxygen therapy and advanced synchrony support for neonatal to adult patients in a single device. Clinicians can rapidly change therapies on a broad range of patients in an effortless way. "We began using bellavista exclusively in 2017, when it was available in Europe. It allows us to ventilate invasive, non-invasive, nasal CPAP and perform high flow oxygen therapy with one device enabling targeted, efficient patient care in any situation" said Vincenzo Cannizzaro, MD, PhD, Deputy Chief Physician of PICU/NICU, University Children's Hospital, Zurich, Switzerland. Designed exclusively around enhancing the caregiver's experience, the bellavista 1000e's intuitive touch screen provides advanced graphics to easily visualize the patient's pulmonary status, enhancing situational awareness for the caregiver. Whether its escalating care or weaning a patient efficiently, the bellavista 1000e ventilator simplifies the process by delivering optimal workflows with the goal of reducing operator error and ventilator lengths of stays. "Clinicians, respiratory therapists and bedside caregivers provided critical input in the design of this ventilator and helped us ensure we addressed their challenges in all patient care circumstances," said Lisa Rose, Chief Marketing and Innovation Officer, Vyaire Medical. "The bellavista 1000e is a solution that provides the ultimate versatility in therapy and it can be adjusted quickly depending on patient need in time sensitive situations. These differentiators are critical in a healthcare environment which expects innovative products to improve patient outcomes. Vyaire is dedicated to developing the kinds of systems and products that meet the needs of healthcare providers." Today, there are more than 8,200 bellavista 1000e ventilators in use across 92 countries outside of the United States. The bellavista 1000e ventilator was introduced to the US healthcare market at the American Association of Respiratory Care Congress (AARC), November 9-12, 2019 in New Orleans.

Some COPD Patients Will Improve on Ventilation

Noninvasive ventilation is a well-known life-sparing option during acute exacerbations of chronic obstructive pulmonary disease (COPD), but its effectiveness for severe, but stable disease has been difficult to establish. "European data are showing that we need to do things differently," said Lisa Wolfe, MD, from Northwestern University in Chicago. "The new thrust is to do two things." The first is to "use higher amounts of pressure support; add backup rates to it," and the second is to "do it specifically in patients with hypercapnia and high hospital admissions," she explained at CHEST 2019 in New Orleans.

Recent European studies have shown that in the right patients, a reduction in chronically elevated carbon dioxide and the delivery of high-pressure support that allows the diaphragm to rest contribute to the effectiveness of ventilation. In a recent review published in Annals of the American Thoracic Society, Wolfe and her colleagues looked at studies of noninvasive ventilation in COPD to better understand why some showed benefit and others did not. In part, the research did not evaluate the right treatment in the right patients, Wolfe reported. "They were looking at relatively low-level pressure support; we see that levels between 8 mL/kg and 12 mL/kg did not really show a benefit."

They now understand that low inspiratory pressure support does not "get rid of carbon dioxide," she explained. "And without successfully doing this, we can't get these people better." In European studies, increased pressure and wider support significantly increased tidal volume; improved alveolar ventilation, gas exchange, and carbon dioxide levels; and ultimately rested the diaphragm. "This is important," Wolfe emphasized. "Increased carbon dioxide allows for the diaphragm to rest. This is where we see a significant improvement." "Effective ventilation appears to improve survival and quality of life only when the chronically elevated carbon dioxide is effectively reduced, not in the setting of acute COPD exacerbation," the researchers write in their review. The European studies also show the benefit of ventilation at home for patients with COPD.

Companies Announced Distribution Partnership

A "monumental distribution partnership" has been announced between Pharma Systems and CAREstream America. Pharma System manufactures the humidification and filtration products that you currently purchase. CAREstream America, based out of Orlando, Florida, offers a variety of premium product and therapy solutions for Aesthetics, Anesthesia, Pain Management, and Respiratory care specialties across the US. Effective January 1, 2020, CAREstream America will become the exclusive distributor of Pharma Systems products in the US. To ensure a seamless transition, the existing product numbers, terms and prices will stay the same. To place an order now with CAREstream America, email orders@carestreamamerica.com, or fax your request to 407-960-2758. If you have any questions, please reach out to our main office at 855-892-3872 or info@carestreamamerica.com.

Antibiotics are Overprescribed for COPD Patients

Antibiotics are overprescribed for chronic obstructive pulmonary disease (COPD), and particularly for mild-to-moderate disease, a large observational study reveals. "Antibiotic treatment brings both risks and benefits for patients," study coauthor Dr Laura Shallcross of University College London said. "Balancing these risks is particularly difficult in primary care, where doctors have limited information, and delaying antibiotics could cause a COPD exacerbation." "A recent multicenter trial showed that antibiotic prescribing can be reduced safely in COPD patients by using a rapid diagnostic (C-reactive protein) test," she noted. "But changing prescribing practice in the absence of rapid diagnostics is challenging, as COPD patients often expect antibiotic treatment, and again, clinicians are keen to avoid triggering exacerbations by delaying antibiotics." Using a large English primary care database, Shallcross and colleagues analyzed data from 19,594 COPD patients (mean age, 71; 46% women) from 157 practices who were followed for a year (2015). Approximately 70%-80% had mild-to-moderate disease (GOLD 1-2 or MRC 1-3). As reported online in the Journal of Antimicrobial Chemotherapy, this cohort represented 2.6% of all patients in those practices, and 11.5% of all prescribed antibiotics. More specifically, 833 patients (4.5%) with severe COPD and frequent acute exacerbations were prescribed six to nine prescriptions

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per year and accounted for 13% of antibiotics. However, individuals with mild-to-moderate COPD and no more than one acute exacerbation received one to three prescriptions per year, accounting for 42.5% of all prescriptions. In adjusted analyses, factors associated with higher rates of antibiotic prescribing were: increasing age (>60 years); female sex (rate ratio, 1.29); and comorbidities including asthma (RR, 1.22;), coronary heart disease (RR, 1.08), diabetes (RR, 1.07), and heart failure (RR, 1.17). Rates were also higher in patients who had received an influenza vaccination (RR, 1.23). By contrast, current smokers received 9% fewer antibiotics on average (RR, 0.91).

Vaping Could Impact Insurance

Global reinsurers are stepping up their warnings to life insurer clients about the potential risks of vaping, putting pressure on underwriters to charge certain vapers higher rates than smokers, or even exclude them altogether. US authorities said that there had been 47 deaths this year from a lung illness tied to vaping. The health concerns about vaping have grown despite evidence showing e-cigarettes help smokers to quit, and has led to bans in some countries including India and Brazil. Reinsurers insure the insurers, and often have large research arms which help their clients by modeling risk. They give broad advice to insurers, rather than specific policy or pricing recommendations, but can potentially refuse to provide reinsurance or can raise premiums if their guidance is ignored. Most insurers have long treated smokers and vapers the same, meaning they can pay close to double the premiums of non-smokers or non-vapers. But three major reinsurers have provided updated advice on vaping in the past three months, with new warnings, while others are considering their approach. The new warnings focus on young vapers and the vaping of liquids containing marijuana ingredient THC, which is legal and prevalent in some US states and has been linked to lung illnesses in the country. The shift in the reinsurance and insurance sector represents a further blow to the vaping industry, which markets its products as healthier alternatives to smoking.

One Inhaler Touted

For patients whose asthma is not well controlled, the addition of a long-acting muscarinic antagonist to the two-drug combination of an inhaled corticosteroid and a long-acting beta2 agonist in a single inhaler improves lung function and reduces asthma exacerbations, according to new research. "This will have an impact on patients. For the first time, we've shown that triple therapy is effective with one inhaler," said investigator Johann Christian Virchow, MD, from Rostock Medical University in Germany. "We know that even when you use the two-drug combination in high doses, we have patients whose asthma remains uncontrolled," he said. The third therapy offers a reduction in exacerbations, "especially for those with bronchoconstriction." Virchow presented results from the triple-therapy study, also published online in the Lancet, at the European Respiratory Society 2019 International Congress. He and his colleagues evaluated the first two double-blind randomized phase 3 studies to compare triple therapy with a two-drug combination for asthma: the Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA (TRIMARAN) trial and the Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium (TRIGGER) trial. Of the 2,592 participants in the two studies, 1579 (61%) were female and 514 (20%) had experienced more than one exacerbation in the previous year. All were 18 to 75 years of age, had an asthma diagnosis for at least 1 year before the age of 40, had a prebronchodilator forced expiratory volume in 1 second (FEV_1) below 80%, had an Asthma Control Questionnaire score of at least 1.5, and had at least one exacerbation in the previous year. In TRIMARAN, patients were randomly assigned to two inhalations twice daily from a single inhaler, for 52 weeks, of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg with or without the long-acting muscarinic antagonist glycopyrronium 10 µg. In TRIGGER, patients were randomly assigned to two inhalations twice daily, for 52 weeks, of beclometasone 200 µg plus formoterol 6 µg plus glycopyrronium 10 µg in a single inhaler or to open-label beclometasone 200 µg plus formoterol 6 µg in a single inhaler plus two inhalations once daily of the long-acting muscarinic antagonist tiotropium 2.5 µg from another inhaler. Improvements in lung function with single-inhaler triple therapy were seen at week 26 in both studies. In TRIMARAN, predose FEV_1 was 57 mL higher with single-inhaler triple therapy than with the two-drug combination (P = .0080), and there was a 15% reduction in the rate of moderate and severe exacerbations (P = .033).

COPD Tools Announced

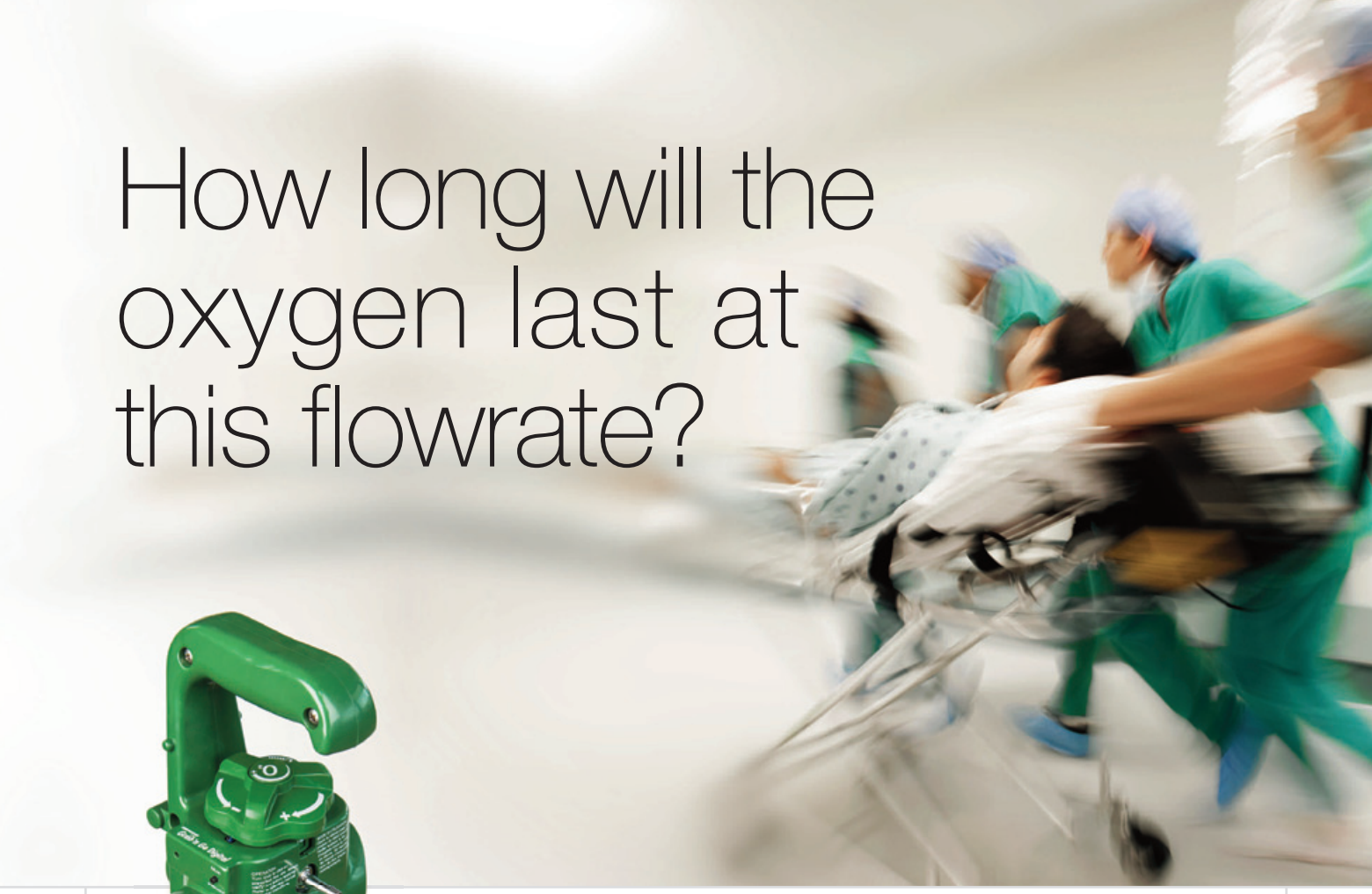
For COPD Awareness Month, ResMed has published an online repository containing educational materials on the condition for patients and healthcare professionals. The resource — resmed.com/COPD — explains what COPD (chronic obstructive pulmonary disease) is, tips for patients living with it, latest research, and leading treatments — including non-invasive ventilation and oxygen therapy, both of which have seen dramatic improvements in recent years in pursuit of helping those living with COPD live fuller, more comfortable lives at home. Patients and healthcare providers can also sign up for alerts when new research or treatment options come out. "COPD is one of the leading causes of death, both across the globe and in the U.S., and that number is projected to increase by more than 30 percent over the next decade," said ResMed Respiratory Care President Richie McHale. "It's more important than ever that we support and educate the growing COPD community with readily available information that can help improve quality of life for millions." In 2015, there were 251 million cases of COPD worldwide. The estimated total prevalence is over 380 million. COPD cost the US healthcare system an estimated $50 billion annually. In 2012, US patients hospitalized for an acute COPD exacerbation cost $14 billion.

Real-time Device Receives CE Marking

Masimo announced that Radius Capnography, a portable real-time capnograph with wireless Bluetooth connectivity, has received CE marking. Radius Capnography connects with the Root Patient Monitoring and Connectivity Platform to provide seamless, tetherless mainstream capnography for patients of all ages. Radius Capnography is the second wireless sensor created by Masimo, joining Radius PPG, or Radius Photoplethysmography, the first tetherless sensor solution to offer Masimo SET Measure-through Motion and Low Perfusion pulse oximetry.

Radius Capnography requires no routine calibration and minimal warm-up time, with fully accurate EtCO2 and respiration rate measurements and continuous EtCO2 waveforms displayed within 15 seconds. Wirelessly connected to Root, Radius Capnography presents a compelling mainstream capnography solution: Cable-free Capnography: The lack of a cable tethering the Radius Capnography sensor and patient to Root improves workflow and reduces the possibility of an interruption in capnography monitoring by minimizing tugging

How long will the oxygen last at this flowrate?



Praxair's *Grab 'n Go® Digital* portable medical oxygen system now features an easy-to-read "time remaining" display, with audible and visual alerts. These alerts are designed to activate if the cylinder pressure drops below 300 psig. With no need to estimate oxygen supply, transports can be more efficient with reduced human error.

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on the breathing circuit. Automated Documentation: Root automates electronic charting of patient data, including the data collected by Radius Capnography, in hospital electronic medical record (EMR) systems, working with Masimo Patient SafetyNet™ or Iris Gateway® to simplify and speed workflow, as well as reduce the likelihood of transcription errors. Maximized Data Visibility and Manipulation: Root's large, multi-touch high-resolution screen provides an easily interpretable secondary display of large, crisp EtCO2 waveforms, improving visibility and assisting clinicians in identifying wave patterns suggestive of airway obstruction or tube dislodgement. Clearly displayed trend data for up to 96 hours helps clinicians review patient progress over time, helping guide ventilation efforts. And the intuitive touch-screen interface allows clinicians to quickly adjust the trend display range and configure alarm settings to meet the needs of each patient. Hassle-free Connectivity: Radius Capnography's cable-free design and quick Bluetooth pairing provide the benefits of reliable capnography and connection to Root without the burden or clutter of additional cables, facilitating easy movement between care areas, as patients move through the hospital, and in busy operating rooms where space is already at a premium.

First Tube-Down Nasal Cradle CPAP Mask Introduced

ResMed introduced AirFit N30, the world's first tube-down nasal cradle CPAP mask with a front-facing tube — a brand-new option for sleep apnea treatment. ResMed's lightest mask yet, AirFit N30 features an adjustable elastic headgear, plus a nasal cradle cushion that sits under the nasal bridge, eliminating soreness in that area. The mask's curved cushion is designed to provide a secure seal regardless of how the wearer sleeps or moves. Together, these innovations help make starting and staying on CPAP therapy easier than ever for more of the 936 million people worldwide living with sleep apnea. "AirFit N30 is about ease of use, helping people ease into therapy and addressing the most common pain points for longtime users," said Jim Hollingshead, president of ResMed's Sleep business. "As the first mask of its kind, AirFit N30 reflects ResMed's continued leadership in sleep innovation — the cornerstone of our company for over 30 years." AirFit N30 joins ResMed's award-winning portfolio of Minimalist CPAP masks designed to be small, light, and easy to use, including the popular AirFit P10 nasal pillows mask and AirFit F30 minimal-contact full-face mask. AirFit N30 is now available in the United States, with other countries to follow.

Kids Hurt by Switching Inhalers

Children with asthma who are required to switch inhaler types to accommodate insurance formulary changes may experience a loss of lung function not seen in children whose inhaler type stayed the same, according to Scott Bickel, MD, from the University of Louisville School of Medicine, who will present the study findings at the CHEST Annual Meeting 2019 in New Orleans. Inhaled corticosteroid (ICS) therapy, a cornerstone of daily asthma management, is delivered by several types of inhalers that require different usage techniques. Insurance formulary coverage often dictates inhaler selection and can change abruptly, requiring children to switch inhaler types with little notice. In this study, moving from beclomethasone dipropionate (BDP) delivered via a metered dose inhaler (MDI) to an ICS delivered by a dry powder inhaler was associated with a loss of lung function. The researchers retrospectively reviewed charts of children ages 6 to 18 with asthma served by the impacted Medicaid plan from a large, university-based general pediatric clinic who had spirometry performed both before (February to July 2016) and after (February to July 2017) the formulary change. Sixty-eight patients were identified on inhaled controller therapy with 98.5% being supported by MDIs prior to the formulary change and 60% afterwards. The investigators found that of the 24 patients switched to a dry powder inhaler, the average FEV1, a measure of maximum air expelled in one second, was 99% predicted prior to the change and 89% predicted after being transitioned to the dry powder inhaler. A statistically significant decline was also seen in FEF25-75%, a measure of small airway function measured by spirometry, where the average was 89% predicted prior to the change and 77% afterwards. Of those who remained on a metered dose inhaler, no statistically significant changes in lung function were observed (FEV1 101% pre-formulary change and 98.9% post). "Changes in insurance formulary coverage are a major reason why patients who are otherwise stable are switched to a different asthma medication," commented Dr. Bickel. "Our findings suggest that when considering formulary changes, insurance organizations should take into account the unique needs of pediatric patients with asthma, ensuring all children have access to the inhaler device that is most appropriate for their individualized care." "This study demonstrates that formulary-dictated changes in inhaled corticosteroids decreases control of asthma and raises the following question: Are changes in formulary driven only by financial concerns appropriate in patients with asthma?" commented Victor Test, MD, Co-Chair of the CHEST Scientific Program Committee and Professor of Texas Tech University Health Sciences Center.

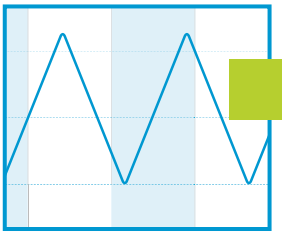
Reintubation Rate Reductions Studied

In ICU patients at high risk of postextubation respiratory failure, noninvasive ventilation (NIV) along with high-flow nasal oxygen applied immediately after extubation reduces the rate of reintubation, a new randomized trial shows. As many as 20% of patient ready to be separated from a ventilator experience extubation failure leading to reintubation, Dr Arnaud Thille of Poitiers University Hospital, in France, and colleagues note in JAMA. Although international guidelines recommend the use of NIV to prevent postextubation respiratory failure, the team adds, in the absence of evidence from large clinical trials most patients in clinical practice are treated with standard oxygen. To investigate further, the researchers studied 641 patients at 30 ICUs who were at high risk of extubation failure. All were older than 65 years or had underlying cardiac or respiratory disease. They were randomly assigned to high-flow nasal oxygen alone or high-flow nasal oxygen with NIV immediately after extubation. After seven days, the reintubation rate was 11.8% in the NIV combination group, significantly lower than the 18.4% seen in the high-flow nasal oxygen alone patients. The rate of postextubation respiratory failure was also significantly lower, at 21% versus 29%, as was the reintubation rate until ICU discharge (12% vs. 20%). The median time to reintubation was not significantly different between groups. Although the ICU mortality rate was lower in the combination group (6%) it was not significantly different from that in patients receiving only nasal oxygen (9%). Dr Niall D Ferguson of Toronto General Hospital, author of an accompanying editorial, said by email, "Despite being less convenient than using only high-flow nasal oxygen for many clinicians, this study inconveniently but probably correctly shows that the combination of NIV and high-flow nasal oxygen provides the best support for patients at higher risk of reintubation." He adds in his editorial that "to get the most of this strategy, clinicians will have to use their clinical judgment to decide which patients within the high-risk

Chronic respiratory patients getting treatment but not feeling better?

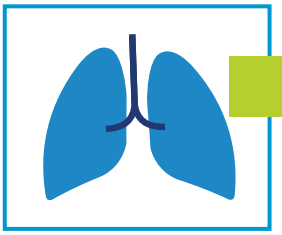
Three great reasons to try the Philips InCourage system:

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



Triangle waveform

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

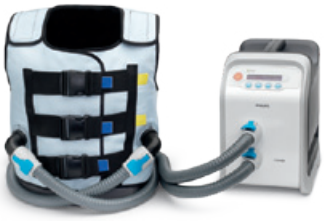


Outcomes

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

Patient results

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



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

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nonhypercapnic group will benefit the most based on individual clinical and physiological characteristics."

Blood Test Helps Spot Risks in Subgroup

A blood test can identify a subgroup of pneumonia patients at increased risk for developing acute respiratory failure or sepsis, according to new research.Pinpointing the host processes dysregulated in CAP patients, "especially in those who develop severe complications, could be crucial for future management of this disease," Dr Francisco Sanz of the University of Valencia and colleagues write in a meeting abstract presented at the European Respiratory Society International Congress in Madrid. To that end, they analyzed clinical data and used real-time PCR to determine microRNA profiles in blood samples from 169 hospitalized CAP patients (mean age, 66.9). Of these, 109 (64.5%) developed complications. A quarter (25.4%) developed acute hypoxemic respiratory failure and 13.6% developed severe sepsis. The mortality rate was 3.6%. The team found that three microRNAs known to be involved in lung and systemic inflammatory processes were helpful in predicting sepsis or respiratory failure. Specifically, microRNA 223 was downregulated in severe sepsis (AUC, 0.78) and microRNA 574 was downregulated in respiratory failure (AUC, 0.77). In addition, microRNA 182 downregulation was highly predictive of both severe sepsis and acute respiratory failure (AUC, 0.83 and 0.76, respectively) in CAP patients. "Our study has improved our understanding of the changes and processes that occur in the body in response to pneumonia by identifying these microRNAs that specifically determine complications, such as sepsis and respiratory failure," Dr Sanz said in a conference statement. "This has implications for prognosis. The potential use of these biomarkers would be at the time of admission of patients in order to anticipate the complications that they could develop. Once it was detected that the patient has a certain profile of microRNAs, more intensive support or monitoring measures could be implemented. The test is fast — it takes between one and three hours — and cheap, and it can be performed with techniques that are available in most hospitals," said Dr Sanz. Although the study was done in the hospital setting, it could be used in the outpatient setting as well, he noted. "In addition, due to the range of ages of the patients in our study, this could be applied to adult patients of all ages, although we cannot extrapolate the results to children," he said. Dr Sanz said, "Before its daily use in clinical practice, our work has to be published and an external validation of it would be very interesting for the confirmation of the results, so its practical application may take some time." Commenting on the study in the statement, ERS President Dr Tobias Welte of Hannover University, in Germany, said, "The innovative approach described in this study could provide a quick and cost-effective method for identifying patients at risk of developing sepsis or respiratory failure, which has the potential to save lives and improve patient quality of life, as well as reduce costs for health care providers. However, this test will have to be compared to guidelines and recommended best clinical practice to confirm its usefulness." The study was funded by Sociedad Valenciana de Neumologia.

New Devices Developed

Masimo announced three additional indices (delta cHb, delta HHb, and delta O2Hb) for O3® Regional Oximetry. These indices provide clinicians with additional visibility into changes in the underlying oxyhemoglobin and deoxyhemoglobin components used to calculate cerebral oxygen saturation, rSO2. With these additions, clinicians will now be able to view the relative contribution of each component to a patient's overall rSO2. O3, available on the Masimo Root Patient Monitoring and Connectivity Platform, is FDA cleared for the monitoring of cerebral oxygenation and may be helpful in situations in which peripheral pulse oximetry alone may not be fully indicative of the oxygenation of the brain. O3 uses near-infrared spectroscopy (NIRS) to monitor and display continuous rSO2 values for each side of the brain. As the degree of oxygenation in cerebral tissue changes, the wavelengths of light absorbed by that tissue and those returned to the O3 sensors also change, forming the basis for the measurement of regional (cerebral) oxygen saturation, rSO2. Until now, rSO2 has been displayed as a single, continuous value for each side of the brain. With these three new indices, O3 can now display information about the changes in the underlying components used to calculate rSO2 values. Delta O2Hb provides an index representing changes in the oxyhemoglobin component of the rSO2 calculation. Delta HHb provides an index representing changes in the deoxyhemoglobin component of the rSO2 calculation. Finally, delta cHb provides an index representing the sum of delta O2Hb and delta HHb. O3 is available as a Masimo Open Connect (MOC-9) module for Root, a powerful, expandable hub that integrates an array of technologies, devices, and systems to provide multimodal monitoring and connectivity solutions. Root's plug-and-play expansion capabilities allow clinicians to simultaneously monitor with O3 and other measurements, such as SedLine brain function monitoring — for a more complete picture of the brain — and SET Measure-through Motion and Low Perfusion pulse oximetry, for expanded visibility of oxygenation status. O3 is available for all patient populations, with sensors in three sizes, for adult (≥40 kg), pediatric (≥5 kg and <40 kg), and infant and neonatal (<10 kg) patients. Joe Kiani, Founder and CEO of Masimo, said, "We are proud to announce these three O3 indices, which we developed in response to requests from clinicians. Now, for the first time, clinicians can monitor not just overall cerebral oxygen saturation but also have access to additional data on the changes in the underlying oxyhemoglobin and deoxyhemoglobin components that make up rSO2 values — data that we hope can help provide additional insight into patient status."

Bronchoscopic Treatment of COPD: Hot News

CSA Medical, Inc., presented positive 12-month results of its feasibility study for the RejuvenAir Metered Cryospray system at the 2019 European Respiratory Society (ERS) International Congress in Madrid, Spain. In the session entitled, "Bronchoscopic Treatment of COPD: Hot News," Dr Justin Garner (Essex, United Kingdom) presented 12-month follow-up data on all patients treated with Metered Cryospray ("MCS") utilizing the RejuvenAir System. The RejuvenAir System is a revolutionary cryosurgical device that applies spray liquid nitrogen to the central airways through a minimally invasive bronchoscopic procedure. The extreme-cold flash freezes damaged surface area lung cells which results in a rejuvenative healing process. Thirty-five patients were enrolled in this safety and feasibility trial (NCT02483637) and all have completed their treatments. The data presented showed clinically meaningful improvements in multidimensional measures of cough, sputum production, breathlessness, and Quality of Life (QoL), as measured by Saint George's Respiratory Questionnaire (SGRQ) and COPD Assessment Test (CAT). MCS is designed to address the underlying causes of Chronic Bronchitis, the over-production of mucus and damaged cilia. The one-year data showed superior scores in QoL measures versus pharmacologic standard of

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care regimens. Dirk-Jan Slebos, MD, PhD of the Department of Pulmonary Diseases, at the University Medical Center Groningen, The Netherlands reported that "Metered Cryospray appears to have a beneficial response with a decrease in cough and mucus production even in our patients who had optimized medical management. The overall improvement in breathing resulted in increased physical activity supporting the potential for RejuvenAir to measurably improve quality of life in chronic bronchitis patients." RejuvenAir Metered Cryospray is safe and well-tolerated for patients suffering from COPD with Chronic Bronchitis.

Multicenter Study Evaluates Trend Accuracy of Noninvasive, Continuous Masimo SpHb and Two Invasive Hemoglobin Testing Methods

Masimo announced that in a multicenter study recently published in the Journal of Clinical Monitoring and Computing, researchers at three institutions — Loma Linda University in California (LLU), the University of California at Irvine (UCI), and Mayo Clinic in Jacksonville, Florida (MCF) — evaluated the trend accuracy of three hemoglobin (Hb) monitoring methods, including noninvasive, continuous Masimo SpHb.

Dr Applegate and colleagues prefaced their investigation by noting that Hb measurement "informs patient-specific perioperative transfusion decisions within the context of symptoms, comorbid conditions, surgical procedure, observed bleeding and hemodynamic performance." They also noted, however, that "the time needed for blood sampling and analysis can cause Hb measurement to lag clinical situations. In surgical settings in which blood loss may not be apparent or be difficult to estimate, continuous rather than intermittent Hb monitoring could provide earlier warning of decreasing Hb." Thus, they sought to determine whether noninvasive, continuous hemoglobin monitoring using Pulse CO-Oximetry (SpHb) might provide useful real-time information about changes in Hb.

The researchers compared noninvasive SpHb measurement and two invasive methods of determining intraoperative Hb changes — arterial blood gas CO-oximetry (ABGHb) and point-of-care hemoglobin using arterial blood (aHQHb) — to laboratory determined hemoglobin changes (tHb) for trend accuracy. SpHb was measured using Masimo Radical-7 Pulse CO-Oximeters with rainbow fingertip sensors at all sites. Based on the institution, ABGHb was measured using either a Radiometer ABL800, Nova Biomedical CCX or PhOX, or Siemens RAPIDLab 1265; aHQHb was measured with a HemoCue HB 301; and tHb was measured using either a Sysmex XE5000 or Coulter AcT-diff or LH 750, also depending on the institution.

The researchers independently enrolled 135 adult patients undergoing non-cardiac surgery in which arterial catheterization was planned and repeated intraoperative blood gas analysis was expected (51 at LLU, 26 at UCI, and 58 at MFC). During surgery, whenever arterial blood analysis was performed, SpHb (as displayed at the time blood was drawn) was recorded, and samples were analyzed within ten minutes using ABGHb, aHQHb, and tHb. On average, patients had 4 samples obtained (ranging from 2 to 13), with a total of 551 blood gas samples analyzed, providing 416 sequential changes in Hb for trend assessment.

Using modified Bland-Altman analysis, the researchers assessed trend accuracy for the three methods compared to laboratory analysis, calculating mean bias (95% limits of agreement) of 0.10 (-1.14 to 1.35) for SpHb, -0.02 (-1.06 to 1.02) for ABGHb, and 0.003 (-0.95 to 0.95) for aHQHb. Defining a change in SpHb, ABGHb, or aHQHb as ±0.5 g/dL and a change in tHb as ±0.25 g/dL, the researchers found that changes in direction agreed with tHb changes in direction as follows: in 94.2% (88.9-97.0%) of SpHb changes, in 98.9% (96.1-99.7%) of ABGHb changes, and in 99.0% (96.4-99.7%) of aHQHb changes.

The researchers concluded, "We found that SpHb, ABGHb and aHQHb changes more than ±0.5 g/dL have similar correlation to the direction but not necessarily the magnitude of tHb change during surgery. The similar agreement in trend direction suggests that clinicians can choose which to use based on availability or preference, although continuous SpHb monitoring may provide useful ongoing Hb trend information. Continuous noninvasive SpHb decreases exceeding -0.5 g/dL may prompt a decision to obtain a confirmatory tHb measurement if low tHb is clinically suspected, but not replace blood Hb measurement in guiding transfusion decision making."

Comparing their results to two previous single-center studies involving changes in SpHb compared to changes in tHb, the researchers noted that their multicenter study produced "similar" results in both cases: one study (of volunteers) found 95.4% SpHb change agreement in 22 samples with tHb <10.0 g/dL, while the other study (of 70 trauma patients) reported bias of -0.05, with limits of agreement of -0.62 to 0.51.

SpHb is not intended to replace laboratory blood testing. Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering, among other factors, patient condition and laboratory diagnostic tests using blood samples.

SPOTLIGHT ON SPIROMETRY

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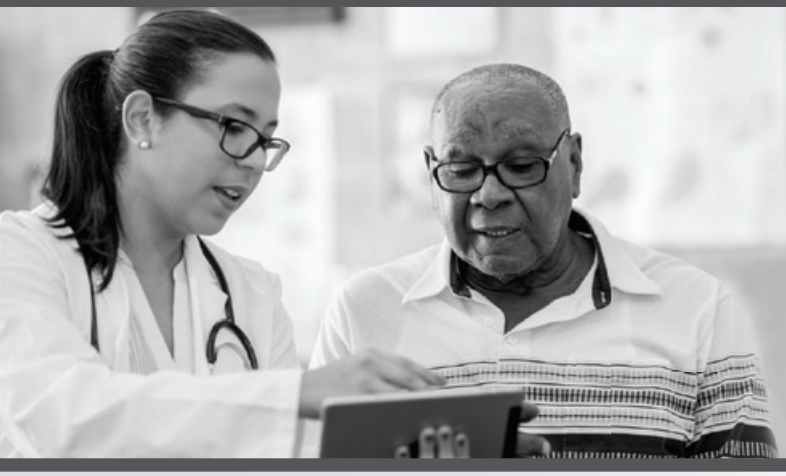

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AIM
AIM assists medical practitioners in assessing inhaler use, whether MDI or DPI, offers the Aerosol Inhalation Monitor. This technique will support more accurate drug delivery and good patient compliance, resulting in better disease management and fewer visits to medical professionals. A summary result is displayed between good and poor technique to assists in training patients to use their inhaler correctly.

Electronic Asthma Monitor
The Vitalograph asma-1 is a simple home use electronic respiratory monitor that measures PEF and FEV1 and may be integrated with smart phone or tablet for ePRO data collection. It offers greater accuracy than mechanical peak flow meters and eliminates the need for paper record cards. asma-1 also come in USB, Bluetooth and for pediatrics.

copd-6
For simple, fast and accurate COPD screening, the copd-6 identifies those at risk of COPD at the pre-symptomatic stage to allow early medical intervention and facilitate better clinical outcomes. This pioneering device screens out those whose FEV1 is normal and who, therefore, do not have COPD without the risk of false COPD negatives, allowing spirometry resources to be focused on those most at risk. copd-6 also come in USB, and Bluetooth.

Lung monitor
Vitalograph lung monitor is an easy to use home monitoring device which records lung function parameters Easy to use device for monitoring of lung function parameters for those with respiratory conditions including cystic fibrosis and transplant patients. The lung monitor measures FEV1, FEV6 and ratio and FEF; the ratio with electronic and hard copy reports. The device is simple to use and stores over 200 test sessions. Lung monitor also come in USB, and Bluetooth.

asmaPLAN and asmaPLAN+
The simple, accurate way to monitor asthma. The patented dual color sliders on the asmaPLAN+ define the management color zones set by the healthcare professional for the asthmatic to follow. The yellow zone will typically be set to start at 80% of the asthmatic's best while the red zone will typically start at 60%. Variability of PEFR of greater than 20% should alert the asthmatic to a possible asthma attack.

myPEF
The only web enabled peak flow meter. The myPEF peak flow meter combines high quality and attractive styling with great value. This robust and easy to clean peak flow meter conforms to the ISO standard for Peak Expiratory Flow Meters. The myPEF is supplied with a unique ID card allowing users free access to a secure website where they can enter their PEF readings, eliminating the need for paper records and supporting data accuracy and effective asthma management. Suitable for use with any web enabled device.

VENTILATION ROUNDTABLE

Getinge

What ventilation products does your company offer?
Servo-u and Servo-i Universal ventilators, Servo-n Neonatal ventilator. All provide Personalized Ventilation with NAVA and Edi monitoring.

What are the new features?
We continuously provide upgrades and updates to our ventilators, and therefore make sure that Servo ventilators can be kept up-to-date and support users changing needs over the lifetime of the ventilator. With the launch of our 2.1 Software we have new features but would like to highlight our New Servo Compass software which visually depicts low tidal volumes and peak pressures so adjustments can be made quickly to keep patients on target. In addition we also launched High-Flow Therapy which delivers a gas flow volume aligned with inspiratory flow rate to help reduce your patient's work of breathing.

Tell us about your company's current or recent R&D efforts.
Our latest software update is due to Getinge's investment in innovations in new therapies functionality and usability.

Discuss the training and support services you offer.
We offer product training to clinicians and staff. For the Biomed side, Getinge certified technical training is also available. Getinge Care Service Plans and technical support is available 24 hours/7 days a week.

Where are your products used? (ie, hospital, home, etc.)
We provide ventilators for Intensive Care Units.

What developments do you foresee for ventilation products and applications?
We believe strongly in Personalized Ventilation, to make sure the ventilation therapy is tailored to the individual patient. To achieve this we develop our NAVA technology, tools that facilitate for clinicians to tailor ventilator settings, and put significant resources in Human Factors engineering to make sure the full potential of our ventilators is easily understood by user's and that they can use it with confidence.

Treatment as individual as your patients

Servo-u and Servo-n put personalized and protective treatment in your hands

With Maquet Servo ventilators from Getinge, you now have the tools and information needed to provide personalized and protective treatment for all of your patients — from neonates, to pediatrics to adults. Servo's unique technology includes:

- Exclusive **NAVA**® technology, with Edi monitoring, promotes patient/ventilator synchrony for truly personalized patient support.
- New **Servo Compass** software visually depicts low tidal volumes and peak pressures so adjustments can be made quickly to keep patients on target.
- New **High-Flow Therapy** delivers a gas flow volume aligned with inspiratory flow rate to help reduce your patient's work of breathing.

Learn more at **getinge.com/ventilation**

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Dräger

What ventilation products does your company offer?
Dräger's ventilation portfolio offers clinicians the latest in caring for patients needed for intensive medical care to individualize care that is needed. Depending on the care area in the hospital. Dräger has a full portfolio of ventilators to suite each patient population.

The Babylog VN500, our dedicated neonatal ventilator, combines our years of experience with the latest technology. Having one machine at the bedside offering NICU clinicians the ability to transition infants between therapies; to and from invasive ventilation, noninvasive ventilation, and/or O2 Therapy all in one device allows the clinician to remain with the tiniest of patients during critical times.

The Evita Infinity V500 is a highly advanced ventilation unit for use in acute care respiratory support for adult, pediatric and infant use. Delivering high performance ventilation capabilities, comprehensive monitoring and effective treatment functions, the Evita Infinity V500 is the ideal choice for respiratory care clinicians and intensivists alike.

The Dräger Savina 300 Select and Savina 300 Classic combines the independence and power of a turbine-driven ventilation system with a wide range of ventilation modes. The large color touch screen and intuitive operating system make operation simple.

Rise up to the challenge in transport ventilation with the Oxylog 3000 plus. Offering high performance such as our signature AutoFlow, integrated capnography and noninvasive ventilation, the compact and robust Oxylog 3000 plus helps you treat and transport your patient safely and provides the feedback you need.

What are the new features?
At Dräger, we work to improve outcomes through:
- Protective therapies that can reduce length of stay in the ICU by reducing ventilation and weaning time.
- Custom-designed, care-centered workplaces that can improve critical care by providing full patient access.
- Connected technologies that consolidate patient data from various devices and send that data where you need it for better informed decisions.
- Data-driven services that can help increase cost-efficiency, reduce technical complexity, and maximize the use and uptime of our devices.

Tell us about your company's current or recent R&D efforts.
Did you know that we now offer customized value analyses free of charge? Examples include an APRV/ARDS Prevention Financial Impact Analysis and an integrated O2 therapy cost of operation analysis. These reports can help your clinical and non-clinical staff evaluate value in respiratory care. Similar programs are available for perioperative care and neonatal care solutions.

Discuss the training and support services you offer.
Dräger supports respiratory care practitioners through a variety of activities.

Online Free CRCE's
Our education and networking website, www.draeger.com/abreathahead, offers complimentary online CRCE's for respiratory therapist on current topics such as adult lung protective ventilation strategies, the latest in neonatal care, evidence-based methodologies and more. In 2019, we added more sessions from live lectures held throughout the year and will continue into 2020.

Live Workshops
Through unrestricted educational grant, Dräger collaborates with SUNY Upstate Medical University to share the latest in mechanical ventilation research and treatment. The audience in attendance consistently attracts respiratory therapist, physicians, and nurses in this Live workshop. We have also been able to Live Stream Day 1 for those that travel is prohibited. 2020 workshops are in the planning stage. Dräger sponsors live educational sessions on neonatal and adult ventilation topics in different areas of the country. These sessions speak to the latest research in adult and neonatal respiratory care, implementing practice change through Evidence-Based respiratory care, benefits of using volume guarantee in neonatal ventilation, and much more. 2020 workshops are in the planning stage.

Reaching the next generation of Respiratory Therapists
Continuing our commitment to respiratory care education, Dräger has donated 99 ventilators to The USA RT Schools. Our goal is to share the latest technologies and approaches to lung protective therapies and neonatal ventilation practices with today's students. This not only helps prepare students to enter the workforce, but it eases the stress of equipment orientation for hospitals.

ICON Hotline – Clinical Support 24/7
Dräger continues to collaborate with Intensive Care Online (ICON) to offer clinical support via a 24/7 hotline. The ICON website is continuing updated with videos, practice guidelines, and training sessions, and so much more.

Where are your products used? (ie, hospital, home, etc.)
Our portfolio of ventilation products is focused in the hospital for all patient population; adult, pediatric, and neonatal, in acute and post-acute settings.

What developments do you foresee for ventilation products and applications?
We believe the best way we can help you achieve your goals is to work together. With our comprehensive portfolio of quality ventilators, anesthesia machines, patient monitoring systems, neonatal care products, and workplace infrastructure designs. Dräger is uniquely positioned to deliver the best for your hospital.

SPOTLIGHT ON BLOOD GAS

Radiometer Offers Benchtop and Point-Of-Care Critical Care Blood Gas Analyzers
Among them: the ABL90 FLEX PLUS. In just 35 seconds, our cassette-based ABL90 FLEX PLUS point-of-care blood gas analyzer can deliver 17 parameters from a sample as small as 65 µL, allowing for a throughput of 44 samples/hour.

The ABL90 FLEX Plus comes with an automated inlet allowing

easier sample introduction and standardized mixing of your blood samples using safePICO syringes and the built-in sample mixer on the analyzer to help reduce preanalytical errors.

Automate and simplify your blood gas sampling and data capture all the way from test order to reported results with 1st Automatic, Radiometer's complete solution for safer and faster arterial blood gas testing.

The ABL90 FLEX Plus is part of the 1st Automatic solution that combines blood gas analyzers, safePICO samplers and AQURE data management to ensure the right result for the right patient at the right time.

Ensure automatic positive patient identification at the bedside, sample integrity, workflow efficiency and greater operator safety with 1st Automatic.

In addition, an Individualized Quality Control Plan is not required for the ABL90 FLEX PLUS blood gas analyzer.

Sil.Flex™ TC Pad

Innovative pad stabilizes trach flange and absorbs pressure at stoma sites

Stoma sites may become sensitive or compromised due to constant pressure or movement of the tracheostomy tube and flange against tender tissue. The Sil.Flex™ TC Pad is designed to cushion the area between the flange and the stoma site, reducing movement and pressure at the site. The contoured surface of the Stoma Pad provides a stable, comfortable interface between the flange and the patient's neck.

Early use of the use of the TC Pad may assist in reducing irritation and tissue breakdown at the stoma site as well stabilizing the tracheostomy tube. Use of the TC Pad may decrease the air leak around the stoma site during trach weaning or during speech therapy by improving the seal between pad and stoma site.

Email us at information@respiralogics.com to use Sil.Flex for your trach patients.

FEATURES

Available in two sizes, accommodating small infants through large adults

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Vivo 65 Improves Long-Term Non-Invasive Ventilation in a 17-Year-Old Patient with Rett Syndrome

Michael Cooper, RT

Introduction

Rett syndrome is a rare genetic neurological disorder that predominantly affects girls. It is characterized by a slow growth of the brain causing a progressive loss of motor skills and speech. Over time, children with Rett syndrome experience increasing problems with the use of muscles that control movement, coordination and communication. Uncoordinated breathing and seizures are associated with the syndrome. Problems with breathing include breath-holding, abnormally rapid breathing called hyperventilation, forceful exhalation of air and swallowing air. These problems tend to occur during waking hours, but other breathing disturbances such as shallow breathing or periodic breathing can occur during sleep. There is no cure for Rett syndrome, all treatments are directed toward relieving symptoms and providing support.

Case Presentation

A 17-year-old female has been followed in the Pediatric Pulmonary Clinic. The patient was diagnosed with Rett's syndrome at age of two and initially exhibited a wide variety of symptoms including physical and mental impairments. Muscle rigidity and severely compromised mobility gradually progressed and resulted in restrictive lung disease with chronic respiratory problems. The diagnosis of chronic respiratory insufficiency was followed by non-invasive ventilation treatment for symptom relief. Non-invasive ventilation is an established treatment modality to improve ventilation by providing ventilatory support through the upper airways, ie by providing the patient with a volume of air through a tightly fitted facial or nasal mask.

Children diagnosed with Rett syndrome are often easily irritable and the patient had frequent crying spells where she would cry or scream for extended time periods. The crying spells made it very difficult to provide effective ventilation. The main limitation of the non-invasive ventilation was related to substantial air leaks during the crying spells, which made it difficult to set an adequate trigger for the delivery of breaths.

The patient received nocturnal, non-invasive ventilation with a full-face mask (Trilogy 100, Philips, Netherlands). The ventilator operated in Average Volume Assured Pressure Support (AVAPS). Over the last year, the ventilator settings were increased multiple times based on an elevated carbon dioxide blood level and a worsening respiratory status. For final settings see Table 1.

Table 1. Trilogy settings

Ventilation Mode	AVAPS
Tidal Volume	400 mL
Breath Rate	15 BPM
IPAP max	35 cmH_2O
IPAP min	25 cmH_2O
EPAP	5 cmH_2O
Inspiratory Trigger	1L/min

Despite escalation of the ventilator settings the CO2 blood level remained elevated with an average of 62.5 mmHg (range: 56-69 mmHg) over the past year, see Figure 1 below. Due to progression of disease the patient required a more efficient non-invasive ventilation. The clinical team made the decision to transition the patient to a Vivo 65 ventilator (Breas, Mölnlycke, Sweden) with the goal to provide more comfortable and better synchronized ventilation. The following ventilator settings were prescribed, see Table 2.

Table 2. Vivo 65 settings

Ventilation Mode	PSV(TgV)
Target Volume	400 mL
Breath Rate	15 BPM
Pressure max	40 cmH_2O*
Pressure min	30 cmH_2O*
PEEP	5 cmH_2O
Inspiratory Trigger	3

*Including Positive End Expiratory Pressure (PEEP)

After transitioning the patient from the Trilogy 100 to the Vivo 65 ventilator, a reduction in CO2 level was seen. The graph below depicts the changes in CO2 levels during the recent year, see Figure 1.

Michael Cooper is a Registered Respiratory Therapist in Chicago, IL, USA.

vivo65
by Breas

THANK YOU BREAS!

(SHOUTING FROM THE TOP OF MY LUNGS)

We care for people – whether patients, healthcare professionals or employees. This philosophy has been the driving force behind Breas Ventilators, BiLevel and CPAP/APAP devices for over 25 years in more than 40 countries around the globe.

Engineered in our founding Swedish offices and now in the USA, Breas delivers leading edge innovations that can provide patient comfort and mobility needed to improve their quality of life. Learn what our exclusive eSync™ technology, ultra quiet operation, long battery life and integrated ventilation monitoring can mean to patients and caregivers alike.

Our Vivo 65 ventilator is a life-support ventilator for use in the hospital, post-acute care institutions and the home environment. Indicated for pediatric* and adult patients, the Vivo 65 treats a broad range of respiratory diseases while providing ease of use to medical staff and care givers.

Innovation for better breathing and quality of life.

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BREAS

*The Vivo 65 is approved only for adults and pediatric patients who weigh 11 lbs / 5 Kg or more.

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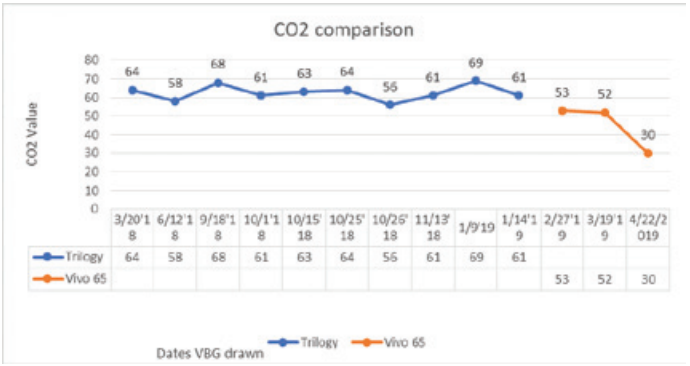

Figure 1. Comparison of CO2 levels after treatment with Trilogy (blue) and Vivo 65 (orange)

In addition, the downloaded treatment report from the Vivo 65 indicated improvements in overall ventilation, magnitude of leaks and work of breathing when compared to the Trilogy 100 report, see table 3 and 4 below. The patient's family reported improvement in quality of life including, better airway clearance and less frequent alarms during the nights.

Table 3. Trilogy, download report

Session	Average values*
Volume Vte (ml)	138
Leakage (L/min)	41.5
Total breath rate (BPM)	19.6
Spontaneously Triggered Breaths	69.4

*from treatment period 12/6/2018 to 01/03/2019

Table 4. Vivo 65, download report

Session	Average values*
Volume Vte (ml)	497
Leakage (L/min)	30.7
Total breath rate (BPM)	16.1
Spontaneously Triggered Breaths (eSync)	27.1

*from treatment period 02/19/2019 to 03/14/2019

Discussion

Carbon dioxide (CO2) is produced as a normal by-product of metabolic processes in cells and the gas normally diffuses into the bloodstream to be exhaled from the lungs. Respiratory failure occurs when the lungs cannot properly remove CO2 from the blood. Hypercarbia, ie high blood level of CO2, is a dangerous condition that if left untreated may cause damage to vital organs. It is therefore imperative to provide effective ventilation to keep CO2 level within a normal physiological range. Normal CO2-values are 35 to 45 mmHg or 41 to 51 mmHg when measured in arterial or venous blood, respectively.

Despite repeated efforts to improve ventilation during the last 12-month period venous CO2 levels remained elevated. It was believed that the most significant reason for suboptimal ventilation was the inability to achieve adequate ventilator/patient synchronization secondary to substantial air leaks during frequent crying spells. An alternative mechanical ventilator with a more sensitive breath triggering mechanism was suggested.

The Vivo 65 ventilator offers a unique patented trigger technology called "eSync". Information from the flow sensor detects the start of patient effort or diaphragmatic contraction, see Figure 2. The Vivo 65 does not require a leak measurement as part of its highly responsive trigger algorithm and therefore is "leak independent". The trigger technology is designed to be sensitive enough to detect very small efforts.

Figure 2. Vivo 65. The eSync triggering algorithm calculates the patient diaphragmatic flow during inspiration using Joules of energy. The minimal trigger of the Vivo 65 is 0.2 L/sec^2 compared to 1-2 L/min for the average home ventilator.

The patient's ventilatory status was optimized by the highly responsive eSync trigger technology. Spontaneously triggered breaths decreased from an average of 69% to 27% and the back up rate setting was reduced from 20 breaths per minute (BPM) to 16 BPM. The Vivo's eSync technology detects the beginning of the patient effort and continues to deliver the precise flow and volume required to maintain the desired settings independent of leaks and without requiring the patient to excessively increase their work of breathing.

It is believed that the improved patient/ventilator synchrony contributed to the reduction of CO2 venous blood levels below normal values (ie 30mmHg) after 2 months.

Although the short-term outcome suggests that treatment with Vivo 65 will reduce the clinical and physiological symptoms of chronic respiratory failure in a young patient diagnosed with Rett Syndrome, continued monitoring of the changes in CO2-levels and oxygen saturation is warranted to ensure long-term success in this difficult case. The end-tidal CO2 monitoring and pulse oximetry functions of the Vivo 65 will facilitate the day-to-day monitoring in the home environment. With the aim to reduce the number of invasive procedures, the non-invasive end-tidal measurement may serve as a complement to the periodic arterial or venous blood sampling.

Conclusion

Overall, the patient's ventilatory status was optimized by the highly responsive eSync system of the Vivo 65 ventilator. The ventilator improved the patient's overall ventilation and airway clearance while decreasing the CO2 blood levels, leaks, patient work of breathing and alarm activation during nighttime hours.

Within a few weeks this remarkable ventilator has improved the patient's quality of life. The patient's family is truly grateful.

The Keys to Switching Over to Positive Pressure Ventilations

James Tanis, MD, and Mark Merlin, DO

The consensus of most emergency and acute care providers is that over-ventilation is probably the most dangerous and harmful consequence of manual ventilations during a resuscitation. Some even refer to conventional adult sized, one and a half to two liter, bag valve mask ventilators (BVM) as "the bag of death"; others have dubbed it one of the "most dangerous tools" in a provider's tool box. Pulmonary physiology can be a lifelong study, but a few simple truths can be explained quite simply.

Traumatize any of the body's tissues or organs enough and it will fail, especially our lung tissue, specifically the alveolus. Under normal circumstances, this is the key to our respiration, the place where the magic of diffusion occurs, oxygen in and carbon dioxide out. It's an impressive system actually, our diaphragm contracts, flattens out, increases the volume of our chest, dropping the intrathoracic pressure and allowing air to fill our lungs; this is the basis for negative pressure ventilation or how we breath as healthy animals. Now in disease states when we are unable to breath on our own or our alveoli are collapsed, filled with junk or destroyed, we then run into real potential problems.

Positive pressure ventilation is usually needed when we are too sick to breathe normally. With positive pressure breaths, we push instead of pull air into our lungs. This is fine if you do it right, like anything else in this world. Push too hard or too much and bad things happen to our pulmonary system. Too much volume, too much pressure, too much variation from normal all lead to damage and destruction of the alveolus. Key things to remember when we need to switch over to positive pressure ventilations:

1. **Always control the rate.** Use of a metronome or the respiration rate on the capnograph will help control our intrinsic need for speed, remember speed kills, especially with fast artificial respiratory rates. Even small volume breaths, times too many per minute, lead to excessive minute volumes and pressures. When left unchecked, lead to over pressured alveoli, increased intrathoracic pressures, barotrauma, hypotension, ischemic cardiopulmonary tissue, ARDS and a death spiral. Normal adult respiratory rates are 12-20 bpm, half that if in cardiac arrest.

2. **Always control the volume.** Use a pediatric 400 or 500 mL BVM, squeeze an adult sized (one-liter) for chest rise or better yet, set the correct tidal volume on a ventilator to act as your BVM during a resuscitation. Tidal volumes are based on a patient's height not weight. Most adults need 6-8 mL per kilogram of IDEAL BODY WEIGHT, which is based on height and gender, [Ideal Body Weight (Devine formula): (IBW) (men) = 50 kg + 2.3 kg x (height, in - 60); (IBW) (women) = 45.5 kg + 2.3 kg x (height, in - 60)]. So, a 6-foot-tall man needs approximately 500mL and a 5-foot-tall lady needs only 300mL tidal volume with healthy lungs, less if diseased, obstructed or ARDS.

3. **Always use PEEP if you are failing to oxygenate the blood.** The number of functional alveoli is directly proportional to the to the pO2. The more open and working air sacks available for diffusion will increase the lungs ability to oxygenate the blood and decrease the CO2. Positive end expiratory pressure (PEEP) is simply the pressure artificially maintained after you exhale to splint the airway open, from the lips to alveoli. Once the alveolus is open it needs to stay open, because each time you collapse and alveoli it is much more difficult to reopen it. Recruitment is the process of opening and maintaining the alveoli open for gas exchange. Increases to FiO2 and PEEP should work together; as you notice hypoxia, increase FiO2 AND PEEP together to optimize your patients.

So, our recommendations, for all of your patients, to keep them safe and moving in the right directions, are to watch your rate, volume and use PEEP early and often during artificial respirations.

James Tanis, MD, EMS Physician, MD1 Program, Emergency Medicine Physician, FEP-Team Health Orlando, Associate EMS Medical Director, Advent Health, Orlando; Mark Merlin, DO, EMS Physician & CEO, MD1 Program, Emergency Medicine Physician, Envision Physician Services, EMS Fellowship Director, RWJ Barnabas Health, Chairman of NJ EMS Council.

Initiatives to Improve Patient Outcomes Following Tracheostomy and Mechanical Ventilation

Melissa Gulizia, BS, RRT, Kristin A. King, PhD, CCC-SLP, Cheryl Tansley, MS, CCC-SLP, Cheryl Wagoner, MS, CCC-SLP, BCS-S

Research has shown that patients with tracheostomy and mechanical ventilation are particularly vulnerable due to the diminished options for mobility, communication, and participation in their care.[1] Not only can this impact a patient's motivation and psychological state, but immobility through bed rest has been shown to cause a rapid increase in muscle atrophy which may further complicate recovery.[2] To combat these issues, the implementation of several protocols may assist with improving patient care, satisfaction, and outcomes.

Early Ventilator Mobilization Program

Early Ventilator Mobilization (EVM) is an initiative designed to increase activity amongst the patient population with ventilator-dependence. There is no evidence that bed rest has any therapeutic value and often worsens outcomes.[2-4]

During bed rest, such as occurs in an intensive care unit (ICU), it has been reported that significant changes can occur in both body mass and strength. In his 2009 presentation, Forte discussed that:

- Muscle mass decreases by up to 5% per week.
- Skeletal muscle strength decreases as much as 20% in the first week.
- An additional 20% loss may occur each subsequent week.
- Weakened muscles generate increased oxygen demand.

Even high intensity bed exercises do not counteract the adverse effects of bed rest. To address these issues with patients who are ventilator-dependent, EVM is a program designed for the physical therapist (PT), occupational therapist (OT), speech-language pathologist (SLP), respiratory therapist (RT), and nursing to be responsible parties in the documentation and mobilization of patients with ventilator-dependence. To increase mobilization, this program includes supine therapeutic exercise, bed mobility, seated balance activities, standing with a walker with assistance, transfers, and upright positioning for meals. All these activities may take place prior to a patient's ability to be out of bed for walking or moving in the hallways.

Melissa Gulizia, BS, RRT, Madonna Rehabilitation Hospital; Lincoln, NE; Kristin A King, PhD, CCC-SLP, Passy-Muir, Inc.; Knoxville, TN; Cheryl Tansley, MS, CCC-SLP, Gaylord Hospital; Wallingford, CT; Cheryl Wagoner, MS, CCC-SLP, BCS-S, Madonna Rehabilitation Hospital; Lincoln, NE.

The selection criteria for patients, who are candidates for EVM, may be those patients who are:

- Minimally able to participate with therapy.
- Stable hemodynamically.
- Receiving acceptable levels of oxygen.
- Medically stable (sufficient perfusion to maintain normal organ function).

Additional, acceptable parameters for determining EVM candidates include:

- Heart rate <110 beats/minute at rest.
- Mean arterial blood pressure between 60 and 110mmHg.
- FiO_2 (Fraction of inspired oxygen) < 60%.
- Maintenance of oxygen saturation >88% with activity.

The early mobilization initiative has led all disciplines to have more accountability for mobilizing patients and improving outcomes. This program allows the team to track performance and to have the ability to adjust treatment plans based on trends seen in a patient's performance. To increase staff communication, a shared documentation site is recommended to note patient performance with increased activity, including frequency and tolerance of mobilization, and all disciplines are responsible for the documentation related to the patient's mobilization. In addition, signs should be incorporated and posted on the doors of EVM candidates to remind all staff to participate in the program and to provide appropriate documentation.

Increasing Use of the Passy Muir® Tracheostomy & Mechanical Ventilation Swallowing and Speaking Valve

The Passy Muir Valve (PMV®) is a speaking Valve that is placed on the end of a tracheostomy tube or in-line with ventilator circuitry. It allows air intake to continue though the tracheostomy tube during inhalation; however, air is redirected out through the upper airway during exhalation. The Valve closes at the end of inspiration and remains closed throughout exhalation, allowing airflow out of the nose and mouth, providing readiness for speech production. Studies have supported that wearing a PMV improves true vocal cord closure; restores voicing and communication; restores smell and taste; improves swallowing, by decreasing aspiration risk and restoring subglottic pressure; improves coughing; restores upper airway sensation; restores PEEP, alveolar recruitment to minimize atelectasis; increases gas exchange and improves saturation levels.[5] It may also expedite the time to ventilator weaning and tracheostomy tube decannulation by rehabilitating

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Table 1. A comparison of HFOT and low flow O_2 (oxygen).

	HFOT	FiO_2	Flow	Humidification
HFOT	Precise	21 – 100%	1 – 40 LPM	At body temperature and 100%
Low Flow O_2	Variable	Variable	Limited	None

respiratory musculature, increasing confidence and motivation, and potentially decreasing the need for sedating medications.[1,6,7]

Healthcare facilities need to develop the right team, so that all staff are on the same page. This can be done by improving the education of staff and providing research to perspective team members, through readings, demonstrations, and webinars. Adopting a "Ventilator Bundle" order set, where the physician chooses the appropriate bundle, allows for physical therapy, occupational therapy, and speech therapy orders for Valve use to generate automatically. Having an order set also reduces the amount of time it would take to obtain the orders to initiate a PMV assessment and assists with getting the team onboard early in the process.

The respiratory and speech-language pathology departments work collaboratively during both evaluation and treatment sessions to improve troubleshooting and education. Respiratory and speech therapists work to place the PMV in-line for new patients, who are on a ventilator, recommended to be within the first 24 hours from admission. A team assessment benefits the patient and facilitates success of Valve use because each person contributes a different aspect to the evaluation. Respiratory therapists have a primary focus on the tracheostomy tube type and size, proper cuff management, settings on the ventilator, patient's vital signs, and safe and proper management of the ventilator and alarms during use of the Valve. The speech-language pathologist focuses on the patient's ability to voice, their speech and language function, access to communication, cognition, and swallowing. Throughout use of the Valve, all team members maintain vigilance on the patient's vital signs and status during use.

Many patients and their loved ones have not heard their voice in several days or even weeks but may with use of the Valve. Communicating with family members, significant others, and staff improves a patient's mood, psychological state, and motivation.[1] Lastly, to assist with communicating among the multidisciplinary team members, speech pathology, respiratory therapy, and nursing share a documentation site to note patient tolerance and progress with PMV use.

Using a High Flow Oxygen Therapy Program

The use of warm mist humidification during the care of patients with tracheostomy aids in secretion management and improving respiratory status (see Table 1). The Vapotherm Precision Flow device allows for delivery of gas flow rates of up to 40 LPM (liters per minute) without discomfort or damage to airway epithelia.[8] Key clinical benefits of high flow oxygen therapy (HFOT) include:

- Humidification at body temperature and saturated – 37°C.
- Delivering consistent, energetically stable, vapor phase humidity.
- Rainout prevention.
- Mitigation of contamination via humidity.
- Mitigation of stoma irritation.
- Better secretion mobilization.

In recent years, HFOT has been used consistently in the Specialty or LTACH units of Madonna Rehabilitation Hospital. Because of this implementation of HFOT with patients following tracheostomy, Madonna Rehabilitation Hospitals earned recognition as the second Vapotherm Center of Excellence in the United States. Following recognition, HFOT use was expanded to include the Acute Rehabilitation and Pediatric Hospitals. Currently, the use of HFOT has been extended to include the long- term ventilator assist unit and the Skilled Nursing Facility level of care. Facility protocols for ventilator weaning and tracheostomy decannulation processes were updated to standardize the safe application of HFOT. In addition, multidisciplinary competencies were developed for staff training that provide for:

- Understanding the indications, contraindications, risks, and guidelines.
- Patient safety.
- Application of HFOT.
- Procedures for safety and use.

The indications for use of HFOT for patients include:

- Humidification of an airway stoma, with or without a tracheostomy tube or larynx tube.
- High oxygen needs.
- A need for high flow therapy.

Patient selection also includes those patients exhibiting increased work of breathing or refractory hypoxemia (generally refers to inadequate arterial oxygenation despite optimal levels of inspired oxygen or onset of barotrauma in mechanically ventilated patients).

Considerations for application of HFOT with a PMV include two options. The first is tracheostomy tube application, which connects a patient to HFOT using a 22mm tubing adapter to their tracheostomy mask or T-piece. It is not recommended to connect the delivery tubing or the tubing adapter directly to a patient's tracheostomy tube (see Figure 1). The tracheostomy tube cuff must be completely deflated when using the Passy Muir Valve (PMV), including in conjunction with HFOT. If the Passy Muir Valve is not being used, the tracheostomy cuff may remain either inflated or deflated, as needed for the patient.

Another option is to use a nasal cannula application. For this option, a nasal cannula may be used during the tracheostomy tube weaning process, when the tracheostomy tube is capped, or with use of the PMV. The nasal cannula application is then utilized for humidifying the upper airway to help jumpstart the natural system and ensure success with secretion mobilization and tracheostomy tube weaning. The flow that is given by the nasal cannula application also helps to flush out the upper airway or deadspace of CO_2; decreases work of breathing; and overall, increases patient comfort and satisfaction.

Positive outcomes at Madonna Rehabilitation Hospital with use of HFOT were observed in numerous areas (see Table 2). Not only have objective changes in care measurements been

Table 2. Use of HFOT and the PMV have led to the following changes in quality improvements for patients.

Ventilator Weaning Rates	Tracheostomy Decannulation Rates	VAP Rate
5.3% increase in weaning rates for 2019 as compared to the previous three years	21% increase in decannulation for 2019 as compared with the previous four-year average	In 2019, 1.55 occurrences per 1,000 vent days versus 2018, 2.01 per 1,000 vent days

observed, but patients' anecdotal reports include improvement in comfort, noise, and overall satisfaction. Staff also reports that HFOT has allowed efficiency of care and participation in therapy, including early mobilization. It also allows the staff to focus on other important patient care needs. Lastly, since the Passy Muir Valve can be used in conjunction with HFOT, communication for the patient is improved and increases their participation in their medical care decisions.

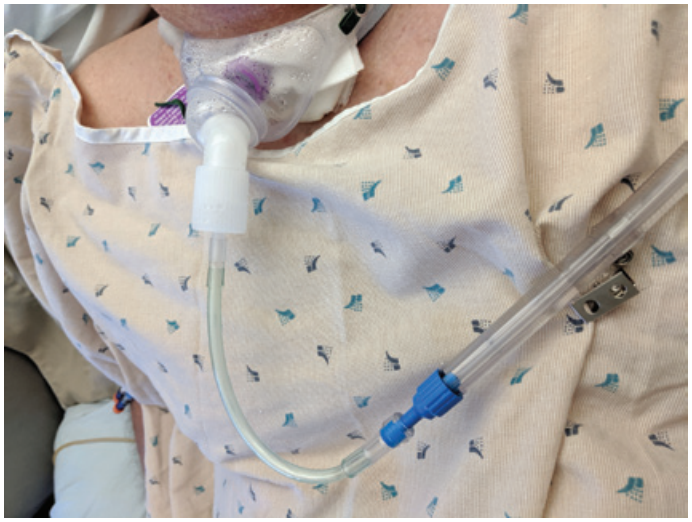

Figure 1. Passy Muir Valve on with tracheostomy mask application of HFOT

Conclusion

Implementing standard protocols and having a multidisciplinary team providing a plan of care has been shown to improve patient outcomes.[9] Establishing protocols that address early mobilization, use of the PMV, use of HFOT, and a standard decannulation protocol, patients may progress to higher levels of function and independence.[10] A patient with a tracheostomy tube and mechanical ventilation has implications for all clinical professions to be involved in their care, and each clinician is essential to the plan of care. The use of HFOT has been shown to enhance secretion management, and all the discussed early interventions have been shown to facilitate weaning. It is through the use of standard protocols in tracheostomy care that facilities have found faster weaning times, which decreases overall lengths of stay and medical costs.

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Outcomes Associated with Implementing the Respiratory Knowledge Portal (RKP) into Daily ICU Rounds: A Retrospective Observational Trial

Michael Pedro MD, Brian Harvey PhD, Steven Cataldo MD, David R Barton BA, RRT, RCP

Introduction

Weaning of mechanical ventilation is the process during which the work of breathing is progressively transferred from the ventilator back to the patient.[1] Failure to wean a patient off of a mechanical ventilator has been shown to prolong the length of time on a mechanical ventilator, prolong intensive care unit *(ICU)* length of stay *(LOS)*, and increase the incidence of Ventilator Associated Events *(VAEs)*.[2-7] The financial impact associated with prolonged mechanical ventilation is also quite substantial. Khan et al 2008 estimated the cost to be $625 per additional day in the ICU.[8] In addition, Zimlichman et al 2013 estimated the cost per VAE to be $41,000.[9]

In order to increase weaning success, societies such as the American Thoracic Society *(ATS®)* and the American College of Chest Physicians *(CHEST®)*, recommend specific weaning protocols which have been demonstrated in randomized controlled trials to reduce the length of time on a mechanical ventilator.[4,10] These recommendations include the daily use of spontaneous breathing trials *(SBT)*, continuous attempts to minimize sedation, and ventilator weaning protocols to decrease mechanical support. Adhering to these protocols have been shown to yield worthwhile results with average decreases in length of mechanical ventilation by 1-4.5 days and ICU length of stay by 1-3.7 days as well as a reduction in VAEs from 9.7% to 5.2%.[3-7]

For an average sized hospital with 1,000 ICU patients per year, the estimated cost savings for reducing ICU LOS and VAEs ranges from $625,000-$2,312,500 and $1,845,000 respectively. Therefore the total estimated cost savings is $2,470,000-$4,157,500.

However, clinician compliance with weaning protocols are not always so straightforward, and outside of these formally controlled trials, real-world evidence doesn't support these great results.[11-13] Factors that have been shown to cause difficulties adhering to protocols are coordinating cross-collaboration between clinical groups *(nurses, RTs, physicians, etc.)* and the absence of accountability resulting in variable practice within the institution. One potential solution is to integrate computerized technology, such as the Respiratory Knowledge Portal *(RKP) (Vyaire Medical, Mettawa, IL)*, into the weaning process in order to make weaning protocols visible across departments and allow managers to hold their staff accountable. It accomplishes this by inputting the institution's best practice weaning protocol into its system, which clinicians from all departments can log into. RKP then outputs near-time information related to the patient's ability to wean, adherence to weaning protocols, and gaps in practice. The objectives of this study were to compare the differences in intensive care unit *(ICU)* length of stay *(LOS)*, time spent on mechanical ventilation, compliance to SBT, and economic savings between non-protocolized weaning, protocolized weaning without computerized technology, and protocolized weaning with computerized technology *(ie: RKP)* at Medical City of Dallas Hospital.

Methods

This was a non-interventional, unblended pre-, post-design quality improvement project that was completed at Medical City Dallas between January 1, 2015 and December 31, 2016 to evaluate the Respiratory Knowledge Portal *(RKP)*. All mechanically ventilated patients in the MICU, SICU, and NVICU between January 1, 2015 and December 31, 2016 were included in the study. The project included three time periods *(Table 1)*: During the first three-month period *("Pre (No Protocol)")* standard of care was followed and no weaning protocol was implemented. For the next 9 months *("Pre (Protocol)")*, MC Dallas' best practice weaning protocol was initiated, but clinicians were blinded to RKP. For the final 12 months *("Post")*, clinicians used RKP to direct care and assist in following the implemented weaning protocol.

Kruskal-Wallis one-way ANOVAs were performed to compare the median ICU length of the stay *(LOS)*, ventilation durations, and compliance to SBT. Chi-square tests were performed to compare proportions between the three groups. Incidence of Ventilator Associated Events *(VAEs)* and Infection- related Ventilator-Associated Complications *(IVACs)* during the entire Pre period *(i.e., January 1-December 31, 2015)* and Post period were compared using Chi-square tests. Estimated cost savings were determined based on the reduction in ICU LOS and VAE incidence. Specifically, we estimated a $625 reduction in variable costs per ICU day[8] and a $41,000 reduction per VAE avoided.[9] Annual saving were calculated based on an estimated 730 mechanically ventilated ICU patients per year.

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Data are presented as median [25th, 75th percentile] unless otherwise indicated.

Table 1. Overview of quality improvement project study periods

Period name	RKP blinded/ unblinded	Weaning protocol?	Start date	End date	Number of patients
Pre *(No protocol)*	Blinded	No	January 1, 2015	March 31, 2015	51
Pre *(Protocol)*	Blinded	Yes	April 1, 2015	December 31, 2015	190
Post	Unblinded	Yes	January 1, 2016	December 31, 2016	328

Results

A total of 615 patients were intubated during the study period. Forty patients had incomplete data and were excluded from the study. Therefore, 575 patients were included in the analysis. 51, 190, and 328 patients were intubated during the Pre *(No Protocol)*, Pre *(Protocol)*, and Post study periods, respectively. Each period had a similar proportion of males *(29 (57%), 110 (58%), and 181 (55%), respectively, p = 0.83, chi-square Test)*.

ICU length of stay (LOS) decreased to 11.2 days after RKP was unblinded in the Post period compared to 14.7 and 14.2 days in the Pre *(No Protocol)* and Pre *(Protocol)* periods, respectively (p = 0.035, Kruskal-Wallis one-way ANOVA, Figure 1). Furthermore, total duration spent on mechanical ventilation decreased from 4.1 and 2.7 days during the Pre *(No Protocol)* and Pre (Protocol) periods, down to 1.7 days in the Post Period *(p = 0.0059, Kruskal-Wallis one-way ANOVA, Figure 2)*. Reintubation rates were similar across the three study periods *(5.9%, 8.4%, and 6.7%, respectively, p = 0.71, chi-square test)*.

To further investigate why patients in the Post period spent less time on the ventilator, we examined the spontaneous breathing trials in more detail. A larger proportion of patients had a successful first SBT in the Post period *(26.5%)* relative to the Pre *(No Protocol) (13.7%)* and Pre *(Protocol) (23.2%)* periods *(Figure 3)*. Further, the portion of SBT within the protocol period increased from 23.5% in the Pre (Protocol) period to 40.0% in the Post period.

> "…an implementation of RKP would reduce annual hospital costs by an estimated $2,051,000."

The initial ventilator settings immediately after a patient was intubated were compared. The initial FiO_2 delivered to the patient immediately following intubation was higher during the Post period *(50.0 [41.5,63.4]%)* compared to the Pre *(No Protocol) (45.9 [40.0,60.3]%)* and Pre *(Protocol) (46.6 [40.2,53.0]%)* periods *(p = 0.0056)*. The initial PEEP settings were similar across the three study periods *(average: 5.4, 5.1, and 5.2 cmH_2O, respectively, p = 0.35)*. Further, the initial MV delivered to patients following intubation was similar for the three study periods *(average: 9.0, 8.7, and 9.0 L/min, respectively, p = 0.20)*.

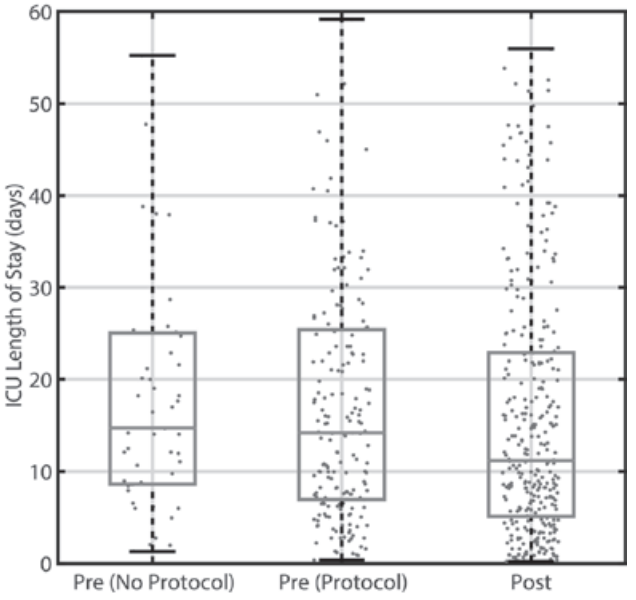

Figure 1. Comparison of ICU length of stay (LOS) for patients intubated during the Pre (No Protocol), Pre (Protocol) and Post study periods. Gray markers represent individual patients. Median (red horizontal lines) ICU LOS were 14.7, 14.2, and 11.2 days during the three study periods, respectively, (p = 0.035, Kruskal-Wallis one-way ANOVA). The 25th and 75th percentiles are depicted in blue.

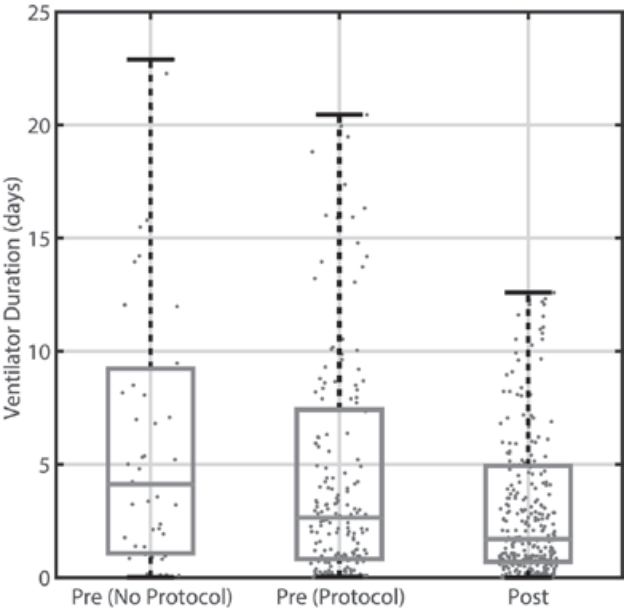

Figure 2. Comparison of duration of mechanical ventilation for patients intubated during the Pre (No Protocol), Pre (Protocol) and Post study periods. Gray markers represent individual patients. Median (red horizontal lines) ventilator durations were 4.1, 2.7, and 1.7 days during the three study periods, respectively, (p = 0.0059, Kruskal-Wallis one-way ANOVA). The 25th and 75th percentiles are depicted in blue.

VAEs decreased from 40 *(i.e., 1 VAE per 6.0 patients)* during the Pre periods *(Protocol and No Protocol combined)* to 29 *(i.e., 1 VAE per 11.3 patients)* during the Post period *(p = 0.005)*. Further, IVACs decreased from 18 *(i.e., 1 IVAC per 13.4 patients)* during the Per periods to only 6 *(i.e., 1 IVAC per 54.7 patients)* during the Post period *(p = 0.0009)*.

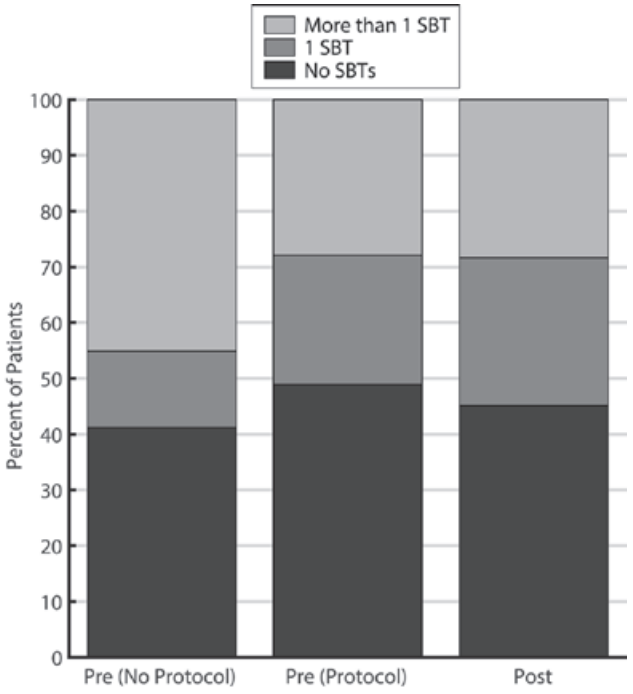

Figure 3. Portion of patients within each of the three study periods who had no spontaneous breathing trials (SBT), exactly one SBT and more than one SBT. The percentage of patients whose first SBT was successful were 13.7%, 23.2%, and 26.5% for the three periods, respectively.

From an economic standpoint, a decrease in ICU LOS of 3.5 days from the Pre *(No Protocol)* period to the Post period translates to an estimated savings of $2,190 per patient and an annual savings of $1,600,000. The reduction of VAEs from 40 to 29 results in an estimated savings of $451,000. Therefore, implementation of RKP would reduce annual hospital costs by an estimated $2,051,000.

Discussion

In this retrospective comparative study there were three major findings. First, the institution of a weaning protocol significantly reduced the total duration spent on mechanical ventilation *(4.1 days Pre (No Protocol) group vs 2.7 days Pre (Protocol) group)*, the ICU length of stay *(LOS) (14.7 days Pre (No Protocol) group vs 14.2 days Pre (Protocol) group)*, and the incidence of VAE and IVACs from 40 to 29 per year and 18 to 6 per year respectively. Second, compliance to the weaning protocol in a real world setting is challenging. This was demonstrated when only 23.5% of the Pre *(Protocol)* group complied to performing a SBT within the protocol period compared to 40.0% in the Post group. Third, the implementation of the Respiratory Knowledge Portal *(RKP)* improved protocol adherence *(40.0% Post group vs 23.5% Pre (Protocol) group)* and further reduced the total duration spent on mechanical ventilation *(1.7 days Post group vs 2.7 days Pre (Protocol) group)* and the ICU length of stay *(LOS) (11.2 days Post group vs 14.2 days Pre (Protocol) group)*. The implementation of RKP also resulted in significant cost savings. The 3.5 days reduction in ICU LOS translates to $2,190 per patient or $1,600,000 annually and the reduction in VAE results in $451,000 of savings. Therefore, the total annual cost savings is estimated to be $2,051,000.

Conclusion

The implementation of a computerized technology improved weaning compliance which substantially increased value for an average size hospital by reducing the incidence of VAE as well as the time on a mechanical ventilator and ICU LOS.

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Understanding Why Not All FDA-Cleared Spirometers Should Be Used for COPD Patients

Alex Stenzler, Martin Stegenga

The gold standard considered by almost everyone who performs Forced Vital Capacity (FVC) spirometry measurements is, "Does the spirometer meet the ATS/ERS guidelines, and has it passed the 24 waveform tests the Task Force created in 1994".[1,2,3] Overwhelmingly, manufacturers tout their FDA clearance and the passing of the 24 waveforms when selling their spirometers. However, there are many spirometers sold in the US, that have all been cleared by the US Food and Drug Administration, that don't really meet all of the requirements of the American Thoracic Society and European Thoracic Society (ATS/ERS) guidelines for spirometry measurements that specifically called out low flow measurements. These spirometers may produce significant errors when testing patients with severe obstructive lung disease. This is particularly important when testing patients with COPD.

We are not the first to point this out. In 2014, Lefebvre and Vandergoten, et al, questioned whether the standard curves of the American Thoracic Society are sufficient.[4] They compared five office spirometers with a 3L syringe at three different flows and against the ATS/ERS waveforms, and then again with waveforms collected from patients and programmed into the same Hans Rudolph 1120 flow-volume simulator. Three of the patient waveforms were from patients with Stage IV COPD.

Testing with the 3L syringe, all spirometers measured the volumes accurately. In the nine different curves from the ATS/ERS waveform set, they reported biases in some of the spirometers, with some measurements falling outside the ATS/ERS requirements. With the patient curves, they found significant errors in measurements where there were steep rise times or low expiratory flows, as seen in patients with severe COPD. They stated that "an ATS/ERS label may be provided to devices that do not deserve it". They proposed that there should be new waveforms used to test spirometers that are more realistic than the original ones.

McCarthy, in his publication on selecting spirometers for home monitoring, reported that many of the spirometers on the market, do not meet the low flow requirements of the ATS/ERS standards.[5] This low flow requirement, separate from passing the 24 waveforms, is that spirometers must be able to measure flows down to 0.025 L/sec. In the 2005 ATS/ERS publication, it specifically states, "The level of minimum detectable flow should be 0.025 L/sec".[2] In the just released 2019 ATS/ERS standard, the wording has changed in the section on determining whether patients reach a plateau to "There is less than a 0.025 L change in volume for at least 1 second (a "plateau")".[3] Therefore, to detect a change of 0.025 in 1 second, the spirometer must be able to measure flows at 0.025 L/sec. Although worded differently, the requirements are unchanged. In McCarthy's publication, there was a link to a video (https://respiratorytherapy.ca/videos/Kevin_McCarthy_Spirometers.php) demonstrating that some turbine spirometers stopped recording at flows significantly above this ATS/ERS requirement.[5]

To understand why spirometers may pass the ATS/ERS waveforms and yet not meet the low flow requirements of the ATS/ERS and produce clinical results as reported by Lefebvre, an understanding of how the waveforms are generated is important. There are multiple manufacturers of waveform generators. These are program-controlled pistons that push air out of the piston in steps defined by a set of instructions that were provided by the ATS/ERS standards Task Force. Each volume step in a unit of time generates a precise flow. As can be seen in Figure 1 below, which is the flow versus time of waveform 17-1 from the set of 24 waveforms, when flows get to the low end of exhalation, there are spikes of flow separated by periods of no flow. The lowest spike of flow is 0.14 L/sec, 5.6 times higher than the minimum flow of the standard. When you average out the spikes of flow with the time periods of no flow, you can reach averages of 0.025 L/sec. However, patients don't exhale with spikes of flow separated by periods of no flow. So, while spirometers that can measure down to 0.14 L/sec can pass the ATS/ERS waveforms, they may not be able to accurately test patients with severe airway obstruction with flows of 0.025 L/sec. This can be a serious deficiency in some spirometers.

We decided to test a range of spirometers for their ability to accurately measure flows at the required low flow threshold.

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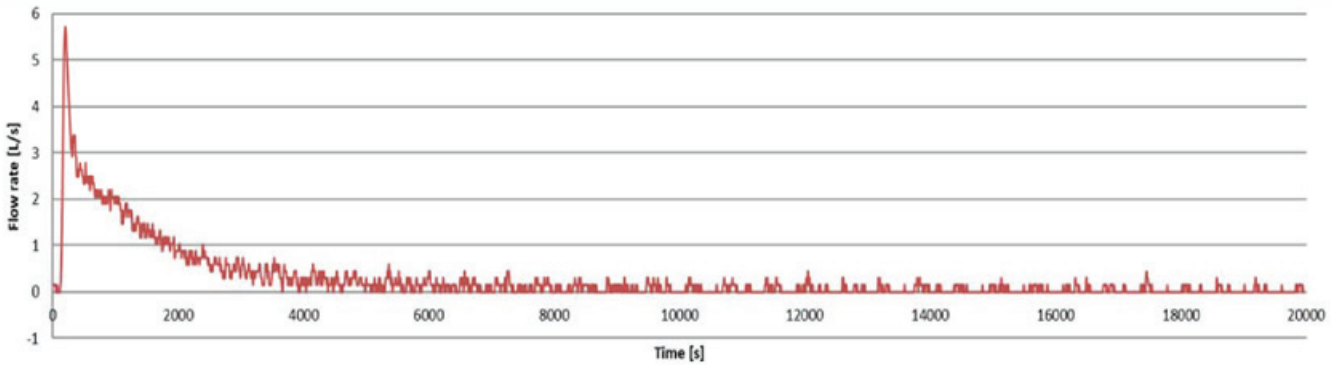

Figure 1. ATS 17-1 Waveform: Flow versus Time

Using a precision driven piston, which is used to test inhaled drug delivery systems (Copley Scientific Model BRS3000, UK) and a fixed flow of 0.025 L/sec (1.5 L/min) with a critical orifice (Figure 2), we compared the spirometers' reported FVC without and with the bias flow. Measurements were performed in triplicate and the average values reported. When the feature existed in the spirometer, we removed the BTPS correction factor.

For the baseline measurement, we set the piston to deliver a volume with a sinusoidal flow pattern of approximately 3 liters within 2 seconds. This produced a peak flow of 2.4 L/sec. We had each spirometer measure this volume 3 times. We then added the bias flow of 0.025 L/sec, teed into the piston flow, and let the low bias flow continue out to 15 seconds. We chose 15 seconds as this is the requirement of the new ATS/ERS standard.[3] The addition of 15 seconds of 0.025 L/sec flow will increase the volume by 0.375 Liters. The actual bias flow for each measurement was measured with a calibrated TSI (TSI Incorporated, MN) hot-wire laboratory flow meter.

We tested eight different spirometers, one of which was tested with its two different flow sensor options (disposable and reusable). They included three ultrasonic spirometers, three turbine spirometers and three pneumotach based spirometers. All spirometers claim to be approved to measure FVC.

Results

Table 1 below presents the results from these tests. Because there may be some bias by each spirometer and because some spirometers have built-in BTPS corrections that we couldn't change for testing with room air, to determine the ability to accurately record the low flow additional volume, we calculated the difference between the baseline measurement and the measurement with the known added flow. The bias flow across all the measurements ranged from 0.0257 L/sec to 0.0262 L/sec for the 15 seconds, accounting for a small potential difference in added volume of 0.007 L (7 mL).

Six of the nine spirometers failed to measure the low flow at 0.025 Liters per second as required by the ATS/ERS standard. The ability to measure the low flow was not technology specific as the spirometers that passed included two ultrasound and one vertical turbine. All of the spirometers seemed to read the 0.025 L/sec bias flow when it was a component of the piston flow, resulting in a higher volume during the bias flow even while failing to measure the flow when it was the only flow component.

Discussion

With an increased interest in monitoring patients in their homes with measurements of FVC, there has been an explosion of new spirometers that supposedly meet the ATS/ERS requirements for FVC measurements. We decided to evaluate both the new spirometers as well as spirometers that have been on the market for some time to determine if they met the ATS/ERS low flow requirements.

We found that the majority of spirometers being sold for the measurement of Forced Vital Capacity, are actually unable to measure the low flows required by the ATS/ERS standard and that this has important implications, particularly when testing

Table 1.

Manufacturer	Spirometer	Technology	Average Baseline Volume (L)	Average Volume with Bias Flow (L)	Expected Volume with Bias Flow (L)[2]	Volume Difference (L)	Percent Error (%)
Inofab Health	SpiroHome	Ultrasound[3]	3.18	3.22	3.57	-0.345	-9.66%
NDD	EasyOne	Ultrasound	2.92	3.36	3.31	0.055	1.66%
Ganshorn	SpiroScout	Ultrasound	2.95	3.43	3.34	0.086	2.59%
Monitored Therapeutics	GoSpiro	Vertical Turbine	3.02	3.44	3.41	0.034	1.00%
NuvoAir	NuvoAir[1]	Disposable Turbine	2.99	3.04	3.38	-0.341	-10.09%
NuvoAir	NuvoAir[1]	Reusable Turbine	3.05	3.11	3.44	-0.333	-9.66%
AioCare	AioCare	Pneumotach	3.29	3.41	3.69	-0.275	-7.46%
Jaeger	FlowScreen	Pneumotach	2.82	2.84	3.22	-0.381	-11.83%
Vitalograph	In2itive	Pneumotach	2.95	3.01	3.33	-0.324	-9.71%

[1] Turbines used by NuvoAir are the MIR disposable and MIR reusable turbines.
[2] The Expected Volume with Bias Flow was determined from the actual Baseline Volume plus the measured volume from the bias flow.
[3] The SpiroHome was unable to trigger a measurement at a peak flow of 2.4 L/sec so the Copley piston was changed to deliver the 3 liter volume in 1 second, producing a peak flow of 4.7 L/sec which successfully triggered the measurement.

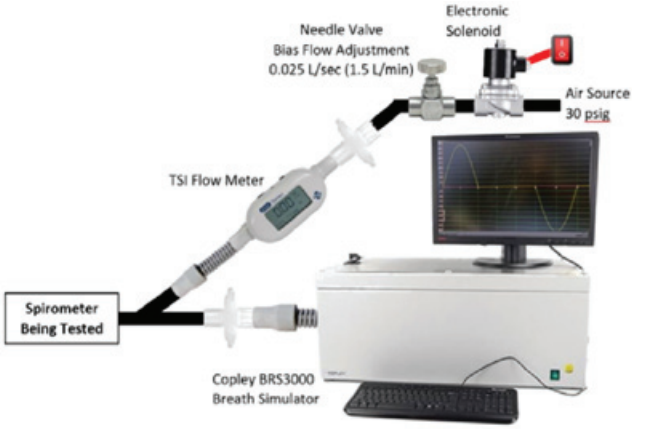

Figure 2. Test fixture

patients with severe obstructive disease. It's not just the error of the measurement that is the concern, but the fact that many of these spirometers stop measuring when flows near the low limit required to identify the End Of Forced Exhalation (i.e., the plateau).

We agree with the conclusion of Lefebvre that many spirometers that have the ATS/ERS label do not deserve it. More importantly, since the introduction of the new ISO 26782 waveform set with more representative waveforms, even spirometers that can pass those tests, do not appear to meet the low flow requirements of the standards.[6] Perhaps spirometer manufacturers need to revisit their technology with a determination to make them useful for patients with severe lung disease so that the healthcare personnel, or the patients who monitor themselves get actionable data and not just numbers.

Conclusion

Physicians and healthcare providers who monitor patients with severe obstructive lung disease should carefully evaluate which spirometers they select for monitoring their patients.

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Two Portable Ventilators Have Their Oxygen Consumption Tested

Chris Campbell

When it comes to a patient's breathing, clinicians want to use the very finest equipment. Finding a cutting-edge ventilator that can deliver optimum results isn't so easy with so many different devices available.

That's why the research of the team of Justin Scott Phillips, Lance Pingul Pangilinan, Edward Karim Saliba, Mark Satomi Siobal and Edna Lee Warnecke involving two devices is so important — it shows one device outperforming another.

The equipment evaluation report is called Oxygen Consumption in Two Portable Ventilators Using a High Pressure Gas Source and the results were published online October 2019 through Respiratory Care. The authors of the report put two portable ventilators to the test.

"The VOCSN (Ventec Life Systems, Bothell, WA) and Trilogy (Philips Respironics, Murrysville, PA) ventilators can deliver oxygen via low or high pressure sources utilizing different circuits," the authors wrote. "We evaluated and compared oxygen consumption from a high pressure gas source using the two ventilators with a null hypothesis that there would be no difference."

Study Methods

The report authors said each device were put through a series of tests.

"A series of three tests were performed for all lung models and circuit configurations," the authors wrote. "Data for the three lung models were averaged for each test configuration and reported as the mean ± SD for both circuits."

The team felt a high pressure gas sources would be an effective way to test both devices.

"The VOCSN and Trilogy ventilators were evaluated using a high pressure gas source (e-cylinders regulated to 50 psi) with both passive (constant leak) and active (exhalation valve) circuits connected to a TTL test lung (Michigan Instruments, Grand Rapids, MI)," the authors wrote. "The three simulated TTL lung models were: normal - Cst 60 mL/cm H_2O and Raw 5 cm H_2O/L/s, restrictive - Cst 30 mL/cm H_2O and Raw 5 cm H_2O/L/s, and obstructive - Cst 60 mL/cm H_2O, Raw 20 cm H_2O/L/s. Using pressure ventilation modes, the peak pressure and rise time were titrated to achieve a tidal volume of 500 mL, as measured by a Certifier FA Plus (TSI Inc, Shoreview MN). Other settings include: frequency 12 breaths/min, PEEP 5 cm H_2O and IT 1.0 second, set FIO_2 of 0.40. Delivered FIO_2 was measured by the Handi + oxygen analyzer (Maxtec, Salt Lake City, UT) at the lung inlet. In addition, the VOCSN pulse dose function was evaluated by titrating its oxygen flow to achieve an FIO_2 of approximately 0.40. We measured the length of time to reduce e-cylinder pressure by 100 PSI for each lung model and test configuration, then calculated the liters of oxygen utilized per minute during each test run."

Research Findings

"Tidal volume delivery and measured FIO_2 remained relatively constant during all lung models, test configurations and circuit types (501 ± 7 mL and 0.397 ± 0.01 respectively)," the authors wrote. "Oxygen consumption using VOCSN with pulse dose oxygen delivery was 1.7 ± 0.7 and 1.7 ± 0.1 L/min, using VOCSN with set FIO_2 was 4.8 ± 0.8 and 2.4 ± 0.1 L/min, and using Trilogy with set FIO_2 was 5.2 ± 1.0 and 4.8 ± 0.9 L/min with passive and active circuits respectively."

Report Conclusions

Based on all of the testing, the authors concluded that the VOCSN satisfied the O2 demand using less oxygen, which allows the tank to last longer.

"Oxygen utilization was lowest using the VOCSN ventilator with pulse dose oxygen delivery with both the passive and active circuits, and with VOCSN using a set FIO_2 with the active circuit compared to the Trilogy 202 ventilator."

Footnotes

- Commercial Relationships: Mark Siobal: Aerogen and Aerogen Pharma
- Support: Disposable and non-disposable equipment (circuits, ventilators, a compressor and oxygen) were supplied by Ventec Life Systems

Chris Campbell is the Senior Editor of Respiratory Therapy.

Effects of Closed-Loop Automatic Control of the Inspiratory Fraction of Oxygen (FiO_2-C) on Outcome of Extremely Preterm Infants – Study Protocol of a Randomized Controlled Parallel Group Multicenter Trial for Safety and Efficacy

Christian A Maiwald[1,2], Hendrik J Niemarkt[3], Christian F Poets[1], Michael S Urschitz[4], Jochem König[4], Helmut Hummler[5], Dirk Bassler[6], Corinna Engel[2], Axel R Franz[1,2]* and FiO_2-C Study Group

Abstract

Background: Most extremely low gestational age neonates (ELGANS, postmenstrual age at birth (PMA) < 28 completed weeks) require supplemental oxygen and experience frequent intermittent hypoxemic and hyperoxemic episodes. Hypoxemic episodes and exposure to inadequately high concentrations of oxygen are associated with an increased risk of retinopathy of prematurity (ROP), chronic lung disease of prematurity (BPD), necrotizing enterocolitis (NEC), neurodevelopmental impairment (NDI), and death beyond 36 weeks PMA. Closed-loop automated control of the inspiratory fraction of oxygen (FiO_2-C) reduces time outside the hemoglobin oxygen saturation (SpO_2) target range, number and duration of hypo- and hyperoxemic episodes and caregivers' workload. Effects on clinically important outcomes in ELGANs such as ROP, BPD, NEC, NDI and mortality have not yet been studied.

Methods: An outcome-assessor-blinded, randomized controlled, parallel-group trial was designed and powered to study the effect of FiO_2-C (in addition to routine manual control (RMC) of FiO_2), compared to RMC only, on death and severe complications related to hypoxemia and/or hyperoxemia. 2340 ELGANS with a GA of 23 + 0/7 to 27 + 6/7 weeks will be recruited in approximately 75 European tertiary care neonatal centers. Study participants are randomly assigned to RMC (control-group) or FiO_2-C in addition to RMC (intervention-group). Central randomization is stratified for center, gender and PMA at birth (< 26 weeks and ≥ 26 weeks). FiO_2-C is provided by commercially available and CE-marked ventilators with an FiO_2-C algorithm intended for use in newborn infants. The primary outcome variable (composite of death, severe ROP, BPD or NEC) is assessed at 36 weeks PMA (or, in case of ROP, until complete vascularization of the retina, respectively). The co-primary outcome variable (composite outcome of death, language/cognitive delay, motor impairment, severe visual impairment or hearing impairment) is assessed at 24 months corrected age.

Discussion: Short-term studies on FiO_2-C showed improved time ELGANs spent within their assigned SpO_2 target range, but effects of FiO_2-C on clinical outcomes are yet unknown and will be addressed in the FiO_2-C trial. This will ensure an appropriate assessment of safety and efficacy before FiO_2-C may be implemented as standard therapy.

Trial registration: The study is registered at www.ClinicalTrials.gov: NCT03168516, May 30, 2017.

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Background

Approximately 0.5% of all neonates (ie, about 25,000 infants per year in Europe) are extremely low gestational age neonates (ELGANs), ie have a gestational age at birth (GA) < 28 completed weeks. The vast majority of ELGANs requires supplemental oxygen in addition to positive pressure respiratory support and frequently experience intermittent hypoxemic and hyperoxemic episodes. Intermittent hypoxemic episodes are predominantly caused by recurrent apnea due to immature development of the respiratory neuronal network (recently reviewed)[1,2] but also secondary to active exhalation during mechanical ventilation.[3] Hyperoxemic episodes are usually a consequence of inappropriate adjustments of FiO_2 (during routine manual control of FiO_2 (RMC) but potentially also during closed-loop automated control of FiO_2 (FiO_2-C)).

Complications of prematurity associated with recurrent hypoxemic episodes

Retinopathy of prematurity (ROP)

Observational data indicated that both, severe and prolonged hypoxemic episodes,[4-6] and wide fluctuations in oxygen levels,[7] increase the risk of ROP. Whereas a better control of SpO_2-levels was associated with a decreased risk of ROP.[8]

Death and neurodevelopmental impairment (NDI)

Observational studies (recently reviewed in)[9] as well as SpO_2 data recorded during the Canadian Oxygen Trial (COT,[10]) suggest that late deaths (ie deaths beyond 36 weeks postmenstrual age (PMA)) and NDI (both cognitive and particularly motor impairment) are linked to hypoxemic episodes, particularly those of more than 60s duration.[6]

Necrotizing enterocolitis (NEC)

The NeOProM (Neonatal Oxygen Prospective Meta-analysis) collaboration reported a lower rate of severe NEC (defined as NEC leading to abdominal surgery or death) in infants assigned to the higher SpO_2 target range (91-95% compared to 85-89%),[11]

which was linked to a lower proportion of time spent with SpO_2 < 80%.

Complications of prematurity associated with hyperoxemic episodes

Considering that breathing room air (ie, FiO_2 = 0.21) leads to a relative hyperoxia compared to intrauterine oxygen partial pressures (PO_2) and oxidative stress in preterm infants, hyperoxia, caused by inadequately high FiO_2, is likely associated with long-term adverse effects.[12]

ROP

The causal relationship between prolonged inappropriate exposure to high oxygen concentrations and ROP has long been established.[13,14] More recently, the NeOProM studies showed increased rates of ROP with the higher SpO_2-target range (91-95%).[11] Finally, implementation of the higher SpO_2-target range based on the results of the NeOProM studies, was associated with an increase in ROP rates in a recent observational study.[15]

Death and NDI

Data from experimental studies in rodents indicate that higher levels of oxygen (eg, FiO_2 0.80 for 2 to 24 h[16-18]) trigger apoptotic neurodegeneration or white matter damage in the brain. These effects have been reviewed by Back et al.[19]

Chronic lung disease of prematurity (BPD)

Hyperoxia enhancing generation of reactive oxygen species triggers inflammatory processes, tissue damage and cell death in the preterm infant's lung, eventually resulting in an increased risk of BPD development (recently reviewed in[20]).

Controlling of FiO_2

To protect ELGANs from the detrimental effects of hypoxemic and hyperoxemic episodes, it can be assumed that PO_2 (and in appropriate simplification SpO_2) must be kept within a narrow target range. To achieve this goal despite the infants' irregular breathing patterns and variations in lung aeration and function, frequent cautious adjustments of FiO_2 are required, which are challenging, time consuming and often impossible due to limited personnel resources.

It has repeatedly been shown that FiO_2-C increases the time infants spent within the SpO_2-target range and reduces the burden of hyper–/hypoxemia while being safe and accurate in short-term studies (reviewed in).[21,22] The effects of FiO_2-C on clinically relevant outcomes measures (such as the hypoxia and hyperoxia-associated complications of prematurity described above) and the safety of its long-term continuous application, however, have yet to be elucidated.

Methods/Design

Trial objectives

The proposed trial was designed and is powered to compare the effect of FiO_2-C in addition to manual adjustments, in comparison with RMC of FiO_2 only, on death, NDI and severe complications of prematurity thought to be related to hypoxia/hyperoxia in ELGANs.

Trial design

This is an outcome-assessor-blinded, randomized-controlled, multicenter parallel group comparison of phase III for superiority (evaluating FiO_2-C in addition to RMC of FiO_2 in comparison to RMC of FiO_2 only) in ELGANs.

In Germany, this study is also considered as a phase IV pharmaceutical trial on safety of the investigational medication 'oxygen' using different modes of administration (decision of the German authority BfArM according to §4 para. 23,1 of the German Pharmaceutical Act). This may not apply to other countries.

Setting

Patients will be recruited in approximately 75 European tertiary care neonatal centers. Recruitment has started in Germany and is intended to expand to additional sites in other European countries, after appropriate approvals will have been obtained.

Patients

Inclusion criteria

- GA at birth 23 + 0/7 to 27 + 6/7 weeks

Exclusion criteria

- Decision not to provide full life support / decision for palliative care only before study entry
- Severe congenital abnormalities (particularly those affecting respiratory, cardiovascular or gastrointestinal function or long-term neurocognitive development, whereas patent ductus arteriosus, patent foramen ovale (PFO), and atrial septal defects type II (ASDII) are not considered a congenital anomaly in preterm infants)
- Postnatal age > 48 h
- Lack of parental consent
- Lack of device enabling closed-loop automatic control of FiO_2 before randomization

Randomization and allocation concealment

Study participants are randomly assigned in a 1:1 ratio to FiO_2-C in addition to RMC of FiO_2 (test intervention) or RMC of FiO_2 only (control intervention).

A web-based randomization tool provided by the Interdisciplinary Center of Clinical Studies at the University Medical Center of the Johannes Gutenberg University Mainz is being used in this study. This program enables bound (into the same treatment group) or free (into different treatment groups) randomization of multiples based on parental choice and the number of available devices enabling FiO_2-C.

A minimization algorithm is applied to preferentially aim for an even distribution of treatment assignment in both GA strata (ie < 26 weeks and ≥ 26 weeks; 1st priority) and both gender strata (2nd priority) within each center.

Blinding

This study is outcome-assessor-blinded, meaning that the personnel performing the ophthalmological examinations throughout the initial hospitalization as well as the personnel performing the neurocognitive evaluation at 24 months corrected age will be blinded to the infants' treatment group assignment. Blinding of doctors, nurses, and parents is not possible with this type of study interventions.

Study intervention

FiO_2-C is provided by commercially available and CE marked infant ventilators with a FiO_2-C algorithm intended for use in preterm infants. The FiO_2-C algorithm must have been tested in human infants and shown to increase the %-time spent in the assigned SpO_2 target range or to reduce the time in hypoxemia or

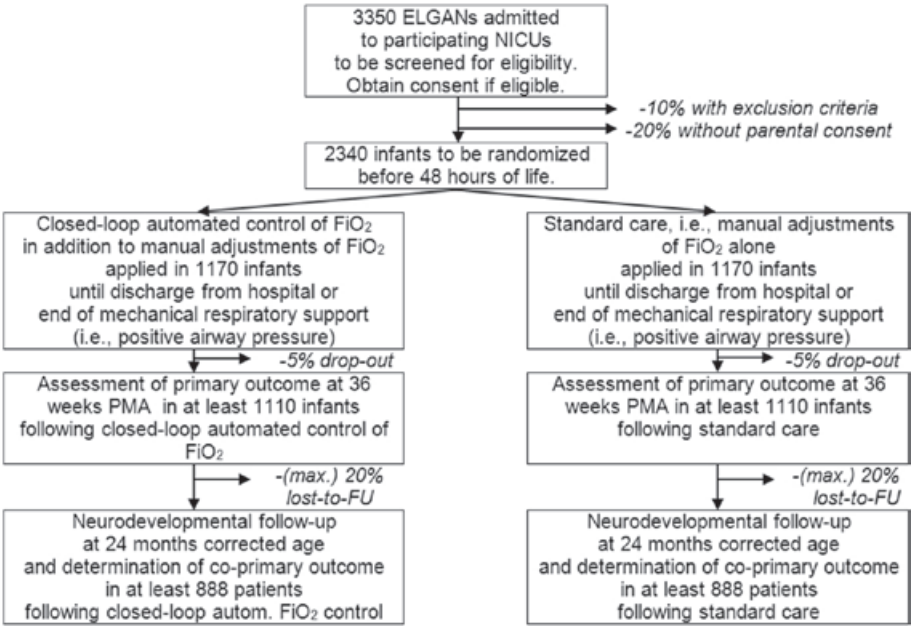

Figure 1. Anticipated Trial Flow

hyperoxemia or to reduce the incidence/duration of hypoxemic or hyperoxemic episodes.

Each FiO_2-C algorithm should be applied in its "optimal mode" (with respect to potentially variable settings provided by the manufacturer such as: averaging time of SpO_2-input, response/wait-time, etc.) based on either evidence in the literature or consensus of the users.

Manual adjustments are encouraged whenever automatic FiO_2 settings seem sub-optimal. In case of FiO_2/ SpO_2-oscillations brought about by FiO_2-C, settings need to be adapted or FiO_2-C has to be temporarily interrupted.

Whenever possible, every study center will use only one type of FiO_2-C algorithm.

Infants in the control group are treated (whenever possible) with the same type of infant ventilator for respiratory support (FiO_2-C turned off) and RMC of FiO_2 is applied by bedside nurse and medical staff throughout the initial hospitalization.

Care is taken in both groups that all staff are informed about the relevance of intermittent hypoxemia and hyperoxemia and trained to execute prudent and careful RMC of FiO_2. This training may include a standard operating procedure for RMC, where the speed of increase/decrease in FiO_2 depends on the magnitude of deviation from the SpO_2 target range as previously described.[23,24]

The intervention should start as soon as possible after randomization and within 48 h after birth. The scheduled end of the study intervention is any of the following (whichever comes first):

- death
- discharge home from hospital
- transfer to another hospital where FiO_2-C is not available (whereas such transfer is discouraged)
- a PMA of 36 + 0/7 weeks
- final discontinuation of positive pressure respiratory support, which does not include limited periods without positive pressure support for weaning. If the infant requires positive pressure respiratory support again for any reason, the infant should again be supported by FiO_2-C (provided a device supporting FiO_2-C is available) until (other) criteria for scheduled end of study intervention are met.
- a PMA of > 32 + 0/7 weeks provided the following two additional criteria of respiratory stability are both met:
  - A) FiO_2 = 0.21 for ≥48 h (for this criterion limited time periods with higher FiO_2 for rescue or for recovery of intermittent hypoxemia will not be considered)
    and
    B) less than 5 intermittent hypoxemic episodes with an SpO_2 < 80% per 8 h shift.

If criteria A) or B) are no longer met, the infant should again be supported by the FiO_2-C device until (other) criteria for scheduled end of study intervention are met.

- a PMA of > 32 + 0/7 weeks if the infant has to be transferred to an intermediate care unit where FiO_2-C is not available

If the infant is re-admitted to intensive care, the infant should again be supported by FiO_2-C (provided a device supporting FiO_2-C is available) until (other) criteria for scheduled end of study intervention are met.

After the end of the study intervention, all study participants will be treated according to the state of the art care and local standards without further requirements or restrictions.

Concomitant interventions and medication

Any concomitant medication that is clinically considered necessary for the patient will be allowed within the study, except for the control group, where closed-loop automatic control of FiO_2 or any other automatic control of airway pressure/respiratory support etc. based on SpO_2 or other vital signals are not allowed.

SpO_2 measurements to guide FiO_2-C

All FiO_2-Controllers should be based on SpO_2-data generated by the same pulse oximeter technology (Masimo). In general, pre-ductal SpO_2-sensor placement is preferred to guide FiO_2-C as long as echocardiography demonstrates a patent ductus arteriosus.

SpO_2-targets and alarm settings

The SpO_2-target range selected by a center for clinical routine has to fulfill the following criteria:

- Study centers need to have a written guideline on SpO_2-target range to ensure that the same SpO_2-target range is applied in both study groups
- The SpO_2-target has to be within the range of 87-95% (may include 87% and/or 95%),
- Care has to be taken that the same SpO_2-target ranges are applied in clinical routine and in both study groups

Documentation of the study intervention

In both study groups, the type of respiratory support, the type of ventilator and the application of FiO_2-C have to be documented daily during the intervention period on a treatment log.

Primary outcome

The primary outcome measure is a composite of death, BPD or NEC assessed at 36 weeks PMA and severe ROP assessed when full vascularization of the retina is documented.

Definitions of components of the primary outcome

Severe ROP

Defined as any ROP stage 3 or higher, or acute posterior ROP, or any ROP in Zone 1, or any treatment for ROP. ROP will be diagnosed at routine ophthalmological examinations, beginning at a PMA of 32 weeks according to international recommendations and local standards until complete vascularization of the retina.[25] The severity of ROP will be graded according to the international classification.[26]

BPD

Defined as requiring positive pressure support or supplemental oxygen at 36 weeks ±2 days PMA, including an oxygen reduction test for infants requiring less than 0.3 FiO_2, representing 'moderate' or 'severe' BPD according to the National Institute of Child Health and Development consensus definition.[27]

NEC

Defined as modified Bell stage ≥IIa[28] until 36 weeks PMA.

Co-primary outcome

The co-primary outcome (tested in a hierarchical design) is the composite outcome of death, language or cognitive delay, motor impairment, severe visual impairment or hearing impairment, all assessed at 24 ±1 months corrected age.

Definitions of components of the co-primary outcome

Language or Cognitive delay: Defined as a language or cognitive composite score at the Bayley Scales of Infant Development 3rd edition[29] of < 85.

Motor impairment: Defined as a Gross Motor Function Classification System (GMFCS) score of 2-5.[25]

Severe visual impairment: Defined as best corrected vision in the better eye yields a visual acuity less than 6/60 m (20/200 ft) according to the relevant doctor's reports/discharge summary.

Severe hearing impairment: need for a hearing aid or cochlear implant.

Any clinical suspicion of previously undiagnosed visual or hearing problems during the FiO_2-C follow-up visit requires a referral to an eye specialist or an pedaudiologist.

If the parents refuse the assessment at the study center or if Bayley test cannot be performed:

Other assessments of neurocognitive and motor development will betaken into account, if parents refuse to attend the follow-up.

Cognitive- and language-composite-scores will then be imputed as follows:

A score "> 85" will be imputed if

- a different cognitive test has been performed elsewhere and scored higher than 1SD below the mean
- the family pediatrician/doctor/health professional caring for the child or the parents rate the infant as "normal"

A score "< 85" will be imputed if

- a different cognitive test has been performed elsewhere and scored lower than 1SD below the mean
- the family pediatrician/doctor/health professional caring for the child or the parents rate the infant as "delayed" or "impaired".

Any such imputation will be described in the final report and the scientific publication.

Secondary outcomes

Key secondary outcome variables are the individual components of the primary (death, severe ROP, BPD, NEC) and co-primary outcome variables (death, cognitive delay or language delay, motor impairment (GMFCS score of 2-5),[30] as well as severe visual or hearing impairment,, the composite scores of the Bayley Scales (3rd edition), the rate of cerebral palsy (CP) according to the criteria defined by the European network 'Surveillance of CP in Europe', and the GMFCS score.

In addition to 'severe ROP' as component of the primary outcome, the 'ROP Severity Score' (also entitled 'ROP activity and structure score')[31] is assessed as secondary outcome, enabling better differentiation and likely being more relevant for functional outcome.

Ethical considerations

The Helsinki Declaration shall be applied to the clinical trial, as well as Good Clinical Practice (GCP). The protocol was submitted and approved by the Ethics Committee of the University Hospital Tübingen as the lead ethics committee. Furthermore, the relevant ethics committees responsible for any of the participating study sites will have to approve participation of the site.

Community engagement

A freely accessible web page for FiO_2-C has been set up (www.fioc-study.eu), providing an overview of aims, partners, study outline, progress and milestones, meetings, findings and news.

Form of consent
Written informed consent from parents or legal guardians is required for participation in the study.

Insurance
Where required by national law, insurance will be obtained for all study patients.

Sample size, power and study duration
The required sample size was calculated for the primary research hypothesis that the implementation of FiO_2-C reduces the cumulative incidence of the composite primary outcome (death, severe ROP, BPD, or NEC).

The co-primary research hypothesis is that FiO_2-C also reduces death or severe NDI (see outcome measures for details). These hypotheses are assessed as a-priori ordered hypotheses, where the co-primary hypothesis will only be tested in a confirmatory manner if the primary hypothesis has been confirmed. Consequently, no correction for multiple testing will be performed.

We assume that,

a) the cumulative incidence of the primary composite outcome of this study is 50% in the control group
b) FiO_2-C reduces the burden of severe hypoxemia/ hyperoxemia by 25-50% and (based on the assumption that (again) 25-50% of the outcome is associated with recurrent hypo–/hyperoxemia) effects a relative risk reduction in this outcome by at least 12.5%.

In summary, we assume a reduction in the primary outcome from 50% (in the control group) to 44% in the intervention group (FiO_2-C).

Sample size calculations were based on a X^2-test, assuming a power of 80% and a significance level of 5%. Based on these assumptions, 1110 infants are required in each treatment group (total 2220 infants). Because all components of this primary outcome will be determined during the initial hospitalization (ie until first discharge from neonatal care), the rate of drop-out before ascertainment of the primary outcome will be low as < 5%. Hence, a total of 2340 infants need to be enrolled and randomized (see Figure 1).

Assuming an incidence of 50% for the co-primary outcome in the control group and a relative risk reduction (RRR) of 25% for the co-primary outcome in the FiO_2-C group, the proposed sample size will have a power > 80% to prove this difference even if up to 20% of randomized infants will be lost to follow-up until 24 months corrected age.

It is estimated that about 90% of all ELGANs will qualify for inclusion into this study without any exclusion criteria. Estimating a participation rate of 80%, approximately 3350 infants have to be screened.

We estimate a recruitment of about 65 patients per month and therefore the recruitment phase of the study will last for approximately 36 months. The individual participation in the study will be about 27 months (between 56 and 91 days of treatment — depending on GA at birth — with an additional follow up to 24 months corrected age).

Data analysis
Analysis of the primary outcome will be based on the intention to treat analysis set, which comprises all randomized patients. Portions of infants with primary endpoint will be compared in a statistical model that accounts for the factors considered by the randomization procedure and the randomization of twins and other multiples. The treatment effect will be reported as a risk ratio and as a risk difference with 95% confidence interval. The co-primary outcome will be assessed only if superiority of FiO_2-C with respect to the primary outcome is confirmed at the 2-sided level of 0.05. This hierarchical testing procedure maintains a multiple type I error of 0.05. All statistical analyses will be described in detail in a statistical analysis plan completed before closure of the database. An interim analysis for efficacy is not intended.

Monitoring safety
An independent Data Monitoring Committee (DMC) is instituted and monitors recruitment, compliance, and safety parameters after 50, 100, 200 and 300 patients have completed 44 + 0/7 weeks PMA, and after every 200 patients have reached this age thereafter.

Safety parameters
Safety parameters monitored by the DMC include:

Early deaths (for the DMC defined as < 44 weeks PMA), late deaths (for the DMC defined as ≥44 weeks PMA), all deaths, BPD, discharge on home oxygen or home positive pressure respiratory support, severe ROP, NEC, (focal) intestinal perforation requiring laparotomy, PDA requiring treatment, intraventricular hemorrhage >grade 2, cystic periventricular leukomalacia. Because the safety parameters include components of the primary outcome, the incidence rates and 95% confidence intervals, these parameters will be 'coded' as "safety parameter A-I".

Furthermore, safety analyses include occurrence and rates of reported adverse events and incidents by treatment group.

Regulatory aspects
Trial sponsor
Sponsor of the FiO_2-C-trial is the University Hospital Tübingen, Geissweg 3, 72,076 Tübingen, Germany. Contact is available at fioc@med.uni-tuebingen.de.

Medical ethics committees
At the time of submission, the relevant ethics committee in Germany approved the study. Applications for approvals are currently underway in additional countries (eg, the Netherlands and Switzerland).

National Regulatory/competent authorities
At the time of submission, the National Regulatory/ Competent Authority of Germany (BfArM) approved the study. Authority approval may not be necessary elsewhere — but this will be determined in collaboration with the relevant ethics committees.

Discussion
Need for a trial
Oxygen is one of the drugs most frequently used in ELGANs and yet, our knowledge on the optimal level of oxygen in arterial blood (or in appropriate simplification the optimal target range for SpO_2) and even optimal technology for monitoring

oxygen levels is incomplete.[32-34] Short-term studies in preterm infants demonstrated that FiO_2-C improved the time within the assigned SpO_2 target range. In these studies, percent time within the assigned SpO_2 target range increased by approximately 10% points to around 70-90% and the improvement was independent of the SpO_2 target range, the FiO_2-C algorithm, and the proportion of time spent within SpO_2 target range in the control-group.[21,22,35,36] It is, however, unclear if more time spent within the assigned SpO_2 target range will also translate into positive long-lasting effects on clinically relevant outcomes. For example, despite higher proportions of time spent within the SpO_2 target range, FiO_2-C might on the one hand side reduce the amplitude of SpO_2 fluctuations, but, at the same time increase the frequency of SpO_2 oscillations and thereby might carry additional risks. This randomized controlled trial will ensure an appropriate assessment of safety and efficacy of FiO_2-C, before it is implemented into standard care.

Discussion of the study intervention period

The study intervention period was chosen because Di Fiore et al. showed that hypoxemic episodes evolve over the first 2 weeks of life and hence starting the intervention within 48 h after birth seems appropriate. This will enable a reasonable time frame to inform parents, even if birth of the infant occurs at night or on weekends, and to enable a meaningful parental decision on participation.

As described by Di Fiore et al.[5] and confirmed by Poets et al.,[6] hypoxemic episodes occurring beyond the 4th week of life are more strongly associated with adverse long-term outcomes than hypoxemic episodes occurring within the first 4 weeks of life. Hence, the study intervention should not end at 32 weeks PMA. Infants with prolonged and frequent hypoxemic episodes beyond this age may benefit most from effective FiO_2-C.

Discussion of chosen population

Because diseases thought to be related to inappropriate use of oxygen such as ROP and BPD essentially only occur in ELGANs, an assessment of efficacy and safety of long-term application of FiO_2-C can only be performed in this patient population.

Discussion of chosen SpO_2-target range

The NeOProM collaboration has shown that the higher SpO_2-target range of 91 to 95% is associated with a decreased risk of early deaths at 18 to 24 months corrected age and NEC, but with an increased risk of ROP.[11] Furthermore, a post-hoc analysis of the BOOST-II data indicated that a higher proportion of time within the assigned target range could enhance this beneficial effect.[37] Consequently, in the FiO_2-C trial the lower limit of the center-specific SpO_2 target range has to be set to ≥87% SpO_2.

Trial status

Protocol version 4: April, 26th, 2018. Recruitment has started in July 2018 and is expected to be finalized in July 2021. The last patient out (after follow-up) will be expected in October 2023.

Abbreviations

ASDII: Atrial Septal Defect II; BfArM - Federal Institute for Drugs and Medical Devices: Bundesinstitut für Arzneimittel und Medizinprodukte; BMBF - German Federal Ministry of Education and Research: Bundesministerium für Bildung und Forschung; BPD: Chronic lung disease of prematurity; CP: Cerebral palsy; eCRF: Electronical case report form; ELGANs: Extremely low gestational age neonates; FiO_2-Controller / FiO_2-C: Closed loop automated control of FiO_2; GA: Gestational age; GMFCS: Gross Motor Function Classification System; NDI: Neurodevelopmental impairment; NEC: Necrotizing enterocolitis; paO_2: Arterial oxygen partial pressures; PFO: Patent foramen ovale; PO_2: Oxygen partial pressures; RMC: Routine manual control; ROP: Retinopathy of prematurity; RRR: Relative risk reduction

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Authors' contributions

CAM drafted the first version of the manuscript. HJN, CFP, MSU, JK, HH, DB, CE, and ARF, as well as all other members of the FiO_2-C study group revised the manuscript and made important contributions. All authors have read and approved the final manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed for the current manuscript.

Ethics approval and consent to participate

The FiO_2-C trial is performed in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice (GCP). Patients can only be enrolled into the study after informed written consent was given by both parents/guardians (by the only parent/guardian in case of single-parent/ guardian families). In case parents are less than 18 years of age, the relevant legal guardian(s) of the child has/have to sign the informed consent.

At the time of publication, the FiO_2-C trial is currently conducted in Germany and may expand to other countries, once ethical and (if appropriate) authority approval has been obtained.

Ethics: Ethics Committee at the University Hospital Tuebingen, reference no. 170/2018AMG1, approved; Authority: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), reference no. 4042695 approved conduct.

Competing interests

C.F. Poets received speaker honoraria from Masimo Inc. and Sentec. All other contributors declare that they do not have competing interest.

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Current Insights In Non-Invasive Ventilation For The Treatment Of Neonatal Respiratory Disease

Dhivya Lakshmi Permall, Asfia Banu Pasha & Xiao-qing Chen

Abstract

Deleterious consequences of the management of respiratory distress syndrome (RDS) with invasive ventilation have led to more in-depth investigation of non-invasive ventilation (NIV) modalities. NIV has significantly and positively altered the treatment outcomes and improved mortality rates of preterm infants with RDS. Among the different NIV modes, nasal intermittent positive pressure ventilation (NIPPV) has shown considerable benefits compared to nasal continuous positive airway pressure (NCPAP). Despite reports of heated humidified high-flow nasal cannula's (HHHFNC) non-inferiority compared to NCPAP, some trials have been terminated due to high treatment failure rates with HHHFNC use. Moreover, RDS management with the combination of INSURE (INtubation SURfactant Extubation) technique and NIV ensures higher success rates. This review elaborates on the currently used various modes of NIV and novel techniques are also briefly discussed.

Introduction

Renewed interest was sparked in NIV modes due to rising incidence of bronchopulmonary dysplasia (BPD) with the use of mechanical ventilation. Despite its benefits in terms of survival of preterm infants, invasive mechanical ventilation for the treatment of neonatal respiratory disease has also elicited an increase in the number of BPD sufferers.[1] The outcomes of BPD are multiple and cause long-term respiratory and neurologic consequences for the patient, leading to a poor quality of life, with increased fatality risk.[2,3] Cerebral palsy, movement disorders, abnormal motor skill development and visual and auditory disorders are other reported consequences of BPD.[4] The current goal is to find the best NIV technique and its optimal settings for respiratory support in RDS management for the different groups of preterm infants.

Modes of non-invasive ventilation

Nasal continuous positive airway pressure (NCPAP)

NCPAP is the most widely used non-invasive ventilation mode in neonatal intensive care units (NICUs).[5] The basis of NCPAP is keeping the airways open and maintaining functional residual capacity (FRC).[6] The mechanism of action comprises an increase in the pharyngeal cross-sectional area, enhancement of diaphragmatic activity, improved pulmonary compliance, and decreased airway resistance which leads to less work of breathing, decreased incidence of apnea and better ventilation-perfusion.[6,7] Newer NCPAP interfaces such as nasal masks, single or bi-nasal prongs have now replaced the older interface models.[6] Chen et al.[5] proposed a new strategy to improve the quality of NCPAP delivery in the NICU. NCPAP kits with a mobile cart and written nursing protocols were used in the NICU to decrease the NCPAP set time, patient discomfort and complications associated with NCPAP. Another aim of this project was to provide the same standard of nursing care to all the patients.

Nasal intermittent positive pressure ventilation (NIPPV)

Several modes of NIPPV have been described in literature, namely nasal intermittent mandatory ventilation (NIMV), non-invasive pressure support ventilation, and bi-level CPAP.[8] It can be further classified as synchronized (patient-triggered) NIPPV (SNIPPV) and non-synchronized (machine-triggered) NIPPV (NS-NIPPV).[8] Application of NIPPV combines NCPAP with additional intermittent breaths above the baseline and the modifiable parameters are positive end expiratory pressure (PEEP), peak inspiratory pressure (PIP), respiratory rate and inspiratory time (Ti).[9,10,11] The periodic breaths increase tidal volume leading to enhanced removal of CO2, sustained alveolar ventilation during episodes of apnea and increased FRC.[8,9] The efficacy of NIPPV is enhanced by the combined usage of early surfactant use in RDS.[12] This mode of NIV has a greater ability to reduce apneic and bradycardic episodes in preterm infants compared to NCPAP.[13] While alterations in pressure and lung volume are not considered to be the actions of NIPPV, proposed mechanisms are: pressure delivery to lower airways, alveoli micro-recruitment, pharyngeal inflation and elicitation of an increased inspiratory reflex (Head's paradoxical reflex).[1,9] Even with the prevalence of NIPPV worldwide, the types of devices used and the mode of delivery vary among countries.[9] Most ventilators can be used to provide NS-NIPPV but SNIPPV can only be generated by Infant Flow SiPAP and Infant Flow Advance, since the Infant Star ventilator is now unavailable.[11] For synchronization, the most frequently used device is the Graseby capsule (GC), which is placed in the subxiphoid area to track the respiratory effort.[9,14] Most studies/units use the short bi-nasal prongs as the interface for NIPPV, although, use of masks and long nasopharyngeal tubes have been reported.[1,11] The popularity of NIPPV is rising since its comparison to NCPAP has demonstrated significant decrease in respiratory failure, re-intubation rates and extubation failure.[15] However, in one of the largest studies by Kirpalani et al.,[16] NIPPV did not prove to be superior to CPAP for

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extremely low birth weight (ELBW) infants born before 30 weeks of gestation for outcomes such as survival with BPD or death.

Bi-level nasal CPAP (BiPAP)

BiPAP has a mechanism similar to NIPPV, and it is usually included within the broad term of NIPPV.[9] It provides cycles of alternating high and low levels of positive airway pressure at preset intervals of time, not synchronous to the infant's breathing pattern.[9,15] The pressure delivered by BiPAP is lower than NIPPV and the higher and lower positive airway pressure levels differ by no more than 3-4 cmH2O.[1,17] Also, with BiPAP, the Ti is longer and cycle rate is lower.[1] Limited tools are available for BiPAP delivery to neonates.[9]

High flow nasal cannula (HFNC)

The latest addition to the NIV family in the NICU is the HHHFNC, which delivers heated and humidified gas through the usage of the HFNC system.[18] The HFNC system consists of small-sized, bi-nasal prongs that do not occlude the nostrils, through which oxygen or a mixture of oxygen and air is delivered at a flow rate of > 1 L/min[19] or > 2 L/min.[11] Preconditioning of gases to mimic the normal upper airway conditions is a crucial characteristic which helps to diminish energy consumption of the body, to avoid proximal airway mucosal dryness and injury.[1,18] Moreover, although not proven, the mechanisms of action of HHHFNC are thought to include: (1) decreased airway resistance and work of breathing, (2) increase the efficiency of gas exchange by the washout of nasopharyngeal dead space in the upper respiratory tract, and (3) supply of positive distending pressure.[1,18,20] Decreased rates of nasal trauma and infant pain scores have been revealed with the use of HHHFNC.[21] Despite the uncertain safety of HHHFNC, surveys demonstrate its increasing use in about two-thirds of NICUs in developed countries, such as the United States, Australia and New Zealand.[21] Its rising popularity is mainly due to its ease of application and maintenance, thus being the preferred NIV mode of physicians and nurses.[18,19] The fact that there is no sealing required also causes less distress to the infants.[19] In spite of the numerous benefits imparted by HHHFNC, the major concern related to this NIV mode is the unavailability of monitoring the pressure it delivers.[22]

Comparison

NCPAP vs NIPPV

In a meta-analysis of 10 trials, with 1061 preterm infants requiring respiratory support for respiratory distress disease, NIPPV proved to be more efficient than NCPAP for the prevention of respiratory failure and for reducing need for intubation.[23] Among the 10 trials, only Ramanathan et al.[24] showed a decrease in BPD incidence and it has been attributed to early surfactant administration prior to the use of respiratory support. Early use of NIPPV instead of NCPAP for preterm RDS patients showed lesser need for mechanical ventilation by 72 h of age and by 7 days of age.[25,26] Tang et al.[27] also found NIPPV to reduce intubation requirement, with a slight decrease in BPD incidence and increase in extubation success. Similarly, Yuan et al.[28] found less intubation in preterm infants supported by NIPPV. NIMV compared to NCPAP as initial treatment for RDS in preterm newborns of < 35 weeks of gestation demonstrated decreased need for intubation and decreased BPD rate with NIMV.[29] Silveira et al.[30] found that for preterm infants of gestational age < 37 weeks and birth weight < 2500 g, failure on NIPPV support compared to CPAP was less likely and the rate of intubation was higher when using CPAP. Moreover, occurrence of apnea episodes was lower in the NIPPV group. The significant effect of apneic episodes reduction with NIPPV compared to NCPAP has been reported by several studies.[13,27,31,32] In a review evaluating the use of NIPPV and NCPAP as post-extubation methods, the results were statistically significant in showing stronger effect of NIPPV in reducing post-extubation failure.[33] Furthermore, synchronized NIMV has proven to be efficient in improving extubation success in very low birth weight (VLBW) infants in the first 72 h post-extubation.[32] As Ramanathan et al.[24] have shown the beneficial association of INSURE followed by NIPPV on BPD, additionally, another RCT[34] compared the use of NIPPV and NCPAP after the INSURE approach in premature infants of < 34 weeks of gestation suffering from RDS in terms of efficacy and complications of the two NIV modes. It revealed significantly lower re-intubation rates, reduced length of hospitalization and decreased BPD rates in the NIPPV group. Oncel et al.[35] compared NCPAP and NIPPV as the primary mode of respiratory support within the minimally invasive surfactant therapy (MIST) for 200 preterm infants with respiratory distress not requiring intubation. They showed the diminished requirement of surfactant and invasive ventilation in the NIPPV group, but no effect on BPD outcome. Li et al.[36] found a significant decrease in the need for intubation in the subset of infants who received surfactant before NIPPV, confirming the beneficial effect of early surfactant therapy. Salvo et al.[37] retrospectively compared NCPAP, SNIPPV and nasal BiPAP to assess their efficiency as initial treatment for RDS in VLBW infants. They found a significantly higher frequency of NIV failure within the first 5 days of life in the NCPAP group as compared to SNIPPV and BiPAP groups, depicting the benefits of using SNIPPV or BiPAP as primary treatment for VLBW infants with RDS. Moreover, there was no difference in the SNIPPV and BiPAP groups.

NCPAP vs BiPAP

According to a small study by Lista et al.,[38] BiPAP was superior to NCPAP in infants with moderate RDS between 28 and 34 weeks' gestational age. Although similar serum cytokine levels were observed in both groups, reduced respiratory support, supplemental oxygen and hospital stay were advantageous outcomes seen with BiPAP support. Furthermore, Rong et al.[39] found BiPAP to be more effective than NCPAP in reducing the intubation requirement in the first 72 h of life for infants of ≤32 weeks' gestational age but BiPAP did not modify the BPD incidence. The use of BiPAP has also demonstrated improvement in gas exchange compared to NCPAP.[40] In comparing nasal BiPAP to NCPAP as post-extubation support in 540 preterm infants, Victor et al.[41] found no additional benefit with nasal BiPAP as post-extubation support.

NCPAP vs HHHFNC

A large RCT involving 432 preterm infants found no difference in terms of efficacy and safety of HHHFNC compared to NCPAP, whether as initial respiratory support or as post-extubation support.[42] Accordingly, the authors support the non-inferiority of HHHFNC when compared to NCPAP. However, the rate of nasal trauma was significant in the NCPAP group. The large HIPSTER trial[21] designed to compare HFNC to NCPAP as early respiratory support for infants with respiratory distress without the use of surfactant, was interrupted since the treatment failure rate was significantly higher in the HFNC group. Nonetheless, a significantly higher frequency of nasal trauma and pulmonary air leaks was observed with NCPAP. One of the recent trials comparing HFNC to NCPAP was also interrupted due to significantly higher treatment failure rate in the HFNC group.[43]

Since high flow therapy fairs better as post-extubation support, surfactant administration might be the key to the success of high flow therapy. In addition, whether high-flow therapy is used as primary or post-extubation support in preterm infants, rescue NCPAP should be available in case of high-flow therapy failure to avoid intubation.[20] Another small RCT with 54 preterm infants with RDS randomised to HFNC or NCPAP as post extubation support after INSURE approach observed an increase rate of re-intubation in the HFNC group compared with the NCPAP group.[44] However, the authors emphasized that the use of higher flow rates of > 4 L/min might resolve this problem. Lavizzari et al.[45] evaluated the efficacy of HHHFNC when compared to NCPAP or BiPAP as the initial treatment for mild to moderate RDS in preterm neonates of > 28 weeks' gestational age. HHHFNC and NCPAP/BiPAP displayed similar efficacy with regard to the requirement of intubation within 72 h since the start of respiratory support. The results of the currently ongoing HUNTER trial in Australia, comparing HHHFNC to NCPAP as primary support in preterm infants with RDS, is awaited to determine if HHHFNC is consistently non-inferior to NCPAP as primary respiratory support.[46]

NIPPV vs BIPAP

In comparing SNIPPV and BiPAP, Salvo and al.[47] concluded that both NIV strategies are valuable in the treatment of early RDS in VLBW neonates. In the study comparing NCPAP, SNIPPV and BiPAP as initial treatment for RDS in VLBW infants, the efficacies of SNIPPV and BiPAP were also similar.[48]

NIPPV vs HHHFNC

A pilot study conducted to compare HHHFNC to NIPPV as the primary therapy for RDS revealed comparable use of both methods as initial treatment for RDS and in terms of preventing intubation in infants < 35 weeks' gestation and birth weight > 1000 g.[49] However, further larger trials are warranted before initiating the use of HHHFNC as a primary treatment for neonatal respiratory disease.

HHHFNC vs BIPAP

The only study to compare HHHFNC and NCPAP/BiPAP was conducted by Lavizzari et al.,[45] showing HHHFNC to have similar efficacy to both NCPAP and BiPAP as the initial mode of NIV support in preterm neonates of > 29 weeks' gestation with mild-moderate RDS.

Synchronised or not

One of the first studies to demonstrate work of breathing reduction in preterm infants with the use of SNIPPV was done more than 10 years ago.[50] Chang et al.[51] also reported reduced inspiratory effort when using synchronized NIMV and Huang et al.[52] supported these benefits of synchronized ventilation. Other reported advantageous aspects of SNIPPV include improved thoraco-abdominal synchrony, reduced need of intubation and lower incidences of desaturations, bradycardias and central apnea.[9,33,53] Decrease in BPD and air leakage was also noted with SNIPPV.[33] The use of SNIPPV on 78 infants of < 32 weeks of gestation as post-extubation support or after NCPAP failure, showed a reduced need for intubation in 74.4% of these preterm infants with respiratory failure.[54] Khalaf et al.[55] demonstrated superiority of SNIPPV over NCPAP for extubation success in RDS patients ≤34 weeks' gestational age. SNIPPV has also shown potential as a favorable mode of respiratory support after the INSURE approach since it decreases the need for mechanical ventilation and limits the requirement of additional surfactant doses. It is thought to enhance the distribution of surfactant in the lungs.[56] Comparison of SNIPPV with BiPAP revealed similar efficacy of both methods.[48] One of the flaws of the SiPAP system remains its inability to respond to all detected breaths at higher breath rates, thus lower peak pressures are delivered as compared with the previously used GC with the Infant Star ventilator.[9,57,58]

Non-invasive ventilation in the delivery room and NICU

The only currently used NIV mode in the delivery room or for stabilization in the first few hours of life is NCPAP, either used alone or with the INSURE technique, thus requiring a brief duration of intubation.[59,60] In comparing early NCPAP to intubation, Morley et al.[61] found no significant decrease in BPD or mortality between the two study groups. The SUPPORT trial[62] compared early CPAP treatment with early surfactant treatment and mechanical ventilation in extremely preterm infants started in the delivery room and although no significant difference was noted in the mortality or BPD rates, the CPAP group resulted in decreased intubation rate, decreased use of postnatal corticosteroid and reduced ventilation time. However, initial application of NCPAP followed by selective surfactant use in extremely preterm infants can decrease the incidence of BPD or mortality rates.[63] A Cochrane review also found decrease incidence of BPD, lesser need for intubation and lesser occurrence of air leak syndromes in infants at risk of or with RDS, treated with early surfactant followed by NCPAP.[64] According to the analysis of four RCTs, one extra infant could survive to 36 weeks without BPD for every 25 babies treated with NCPAP in the delivery room instead of being intubated.[65] Despite the overall decreased risk of BPD with early NCPAP use in the delivery room, NCPAP still has a high failure rate, with a 50% failure in VLBW infants reported.[59,66] The risk factors of NCPAP failure are infants with smaller gestational age, male gender, low birth weight infants, FiO2 > 0.25 at 1 and 2 h of age.[67,68] The cause of NCPAP failure in premature infants is often RDS and it can be predicted by FiO2 ≥ 0.3 in the first hours of life.[69] The timing of surfactant is a key factor for BPD prevention as administration > 2 h after birth, known as late rescue surfactant treatment, has shown decreased efficiency in reducing BPD.[68] Knowing the high-risk group of preterm neonates prone to NCPAP failure might improve the timing of surfactant administration and avoid unnecessary NCPAP therapy.[67] This high NCPAP failure rate finding has led to the use of sustained lung inflation (SLI), which is the delivery of a high peak pressure of 20-25 cmH2O for a duration of 10-15 s using a face mask or nasopharyngeal tube.[66] SLI combined with NCPAP instead of NCPAP alone in the delivery room revealed a reduced need for invasive ventilation in the initial 72 h of life for infants at high risk of RDS.[70] However, no change in the incidence of BPD was observed with SLI use.[70] The ongoing SAIL (Sustained Aeration of Infant Lungs) trial is focused on evaluating the effect of sustained inflation versus standard positive pressure ventilation.[71]

Newer NIV modes

Nasal high-frequency oscillation ventilation (nHFOV), provides an oscillatory pressure waveform to the airways, without synchrony with the infant's breath, aiding to enhance CO2 elimination and alveolar recruitment.[72,73] A study using a term-newborn model showed the superiority of nHFOV in terms of CO2 elimination compared to NCPAP and NIPPV, with thrice the effect of NIPPV.[74] Additionally, it has been reported to significantly decrease CO2 levels, desaturations and frequency

of apnea and bradycardia episodes.[75] The frequent adverse effects observed with nHFOV are upper airway obstruction due to increased secretions, thick, viscous secretions and abdominal distention.[72,76] The formation of extremely viscous secretions in the upper airway has been attributed to usage of low nHFOV frequencies with high amplitudes.[73] A recent study compared nHFOV to NCPAP in preterm infants (28-34 weeks) with moderate to severe respiratory distress post-INSURE.[77] They found a significant decrease for intubation requirement when using nHFOV. Further studies are required to assess and compare various devices and interfaces to deliver nHFOV and to compare nHFOV to the more commonly used NIV techniques. Neurally adjusted ventilatory assist (NAVA) can be provided invasively and non-invasively in spontaneously breathing infants. It is patient-controlled and utilizes diaphragm electrical activity (Edi) to deliver synchronised, pressure-controlled breaths via a ventilator.[78] Central apnea, indicated by the lack of Edi signal, can trigger the back-up ventilation mode of the NAVA system. Since this would resolve the issue of NCPAP failure due to apneic episodes, NAVA would be an ideal alternative method to deliver NCPAP. Moreover, the synchrony achieved using NAVA can allow for earlier extubation.[78] A clinical guideline for the use of NAVA in neonates, by Stein et al., defined NIV-NAVA to be similar to invasive NAVA but ventilation mode delivery is via nasal prongs or single nasal-pharyngeal tube or a mask. NIV-NAVA comprises a leak compensation system which applies to leaks as high as 95%. The benefits of both NAVA and NIV-NAVA are similar, namely better patient-ventilator interaction and synchrony and improved gas exchange efficiency.[78,79] The ease of use of NIV-NAVA will undoubtedly promote its growing use in NICUs worldwide.

Conclusion

In the search for the optimal NIV approach for successful respiratory support in RDS management and BPD prevention, further research and study is still called for. NIPPV is rapidly replacing NCPAP due to its remarkable benefits. NAVA, nHFOV and SNIPPV are promising interventions but they require larger RCTs to confirm their safety and efficacy in various infant groups as compared to more familiar NIV modes. Although the long-term outcomes of NIV-NAVA are still to be determined, it is potentially one of the NIV modes that may surpass the standard respiratory support strategies in the near future.

Abbreviations

BiPAP: Bi-level nasal
CPAPBPD: Bronchopulmonary dysplasia
ELBW: Extremely low birth weight
FRC: Functional residual capacity
GC: Graseby capsule
HFNC: High flow nasal cannula
HHHFNC: Heated humidified high-flow nasal cannula
NAVA: Neurally adjusted ventilatory assist
NCPAP: Nasal continuous positive airway pressuren
HFOV: Nasal high-frequency oscillation ventilation
NICU: Neonatal intensive care unit
NIMV: Nasal intermittent mandatory ventilation
NIPPV: Nasal intermittent positive pressure ventilation
NIV: Non-invasive ventilation
NS-NIPPV: Non-synchronized nasal intermittent positive pressure ventilation
PEEP: Positive end expiratory pressure
PIP: Peak inspiratory pressure
RDS: Respiratory distress syndrome
SLI: Sustained lung inflation
SNIPPV: Synchronized nasal intermittent positive pressure ventilation
Ti: Inspiratory time
VLBW: Very low birth weight

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Contributions

DLP reviewed the literature and prepared the manuscript. ABP revised the manuscript. XQC designed, supervised the project and gave final approval for submission. All authors read and approved the final manuscript.

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Additional information

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Comparison of NIV-NAVA and NCPAP in Facilitating Extubation For Very Preterm Infants

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Abstract

Background: Various types of noninvasive respiratory modalities that lead to successful extubation in preterm infants have been explored. We aimed to compare noninvasive neurally adjusted ventilatory assist (NIV-NAVA) and nasal continuous positive airway pressure (NCPAP) for the postextubation stabilization of preterm infants.

Methods: This retrospective study was divided into two distinct periods, between July 2012 and June 2013 and between July 2013 and June 2014, because NIV-NAVA was applied beginning in July 2013. Preterm infants of less than 30 weeks GA who had been intubated with mechanical ventilation for longer than 24 h and were weaned to NCPAP or NIV-NAVA after extubation were enrolled. Ventilatory variables and extubation failure were compared after weaning to NCPAP or NIV-NAVA. Extubation failure was defined when infants were reintubated within 72 h of extubation.

Results: There were 14 infants who were weaned to NCPAP during Period I, and 2 infants and 16 infants were weaned to NCPAP and NIV-NAVA, respectively, during Period II. At the time of extubation, there were no differences in the respiratory severity score (NIV-NAVA 1.65 vs NCPAP 1.95), oxygen saturation index (1.70 vs 2.09) and steroid use before extubation. Several ventilation parameters at extubation, such as the mean airway pressure, positive end-expiratory pressure, peak inspiratory pressure, and FiO_2, were similar between the two groups. SpO_2 and pCO_2 preceding extubation were comparable. Extubation failure within 72 h after extubation was observed in 6.3% of the NIV-NAVA group and 37.5% of the NCPAP group (P = 0.041).

Conclusions: The data in the present showed promising implications for using NIV-NAVA over NCPAP to facilitate extubation.

Keywords: Airway extubation, Continuous positive airway pressure, Neurally adjusted ventilator assist, Noninvasive ventilation, Ventilator weaning

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Background

Invasive mechanical ventilation (MV) is frequently required in preterm infants after birth to maintain adequate alveolar ventilation and effective gas exchange. However, tracheal intubation and MV in preterm neonates can induce ventilator-induced lung injury (VILI) and airway inflammation.[1,2] Prolonged MV in preterm infants also increases the risk of ventilator-associated pneumonia, increasing the length of hospital stays, mortality, and neurologic impairment.[3] Therefore, noninvasive respiratory modalities have been used in preterm infants to facilitate the transition to spontaneous breathing following extubation.[4-7]

Nasal continuous positive airway pressure (NCPAP) maintains functional residual capacity while improving lung compliance and oxygenation. NCPAP has been widely used in the neonatal intensive care unit (NICU) and has proven to be effective in preventing failure of extubation in preterm infants.[8] However, studies have reported that extubation failure rates ranged from 25 to 35% among preterm infants who were given NCPAP after extubation.[9,10] Nasal intermittent positive pressure ventilation (NIPPV) augments NCPAP by superimposing ventilator inflation on NCPAP.[11] Although synchronized (SNIPPV) or nonsynchronized techniques can be used to supplement the infants' own breathing efforts, it is likely that more effective support can be achieved with SNIPPV.[12,13] To date, pneumatic capsules or flow sensors have been used to detect inspiration for synchronization, but some limitations in clinical practice have been reported.[14-16]

Neurally adjusted ventilatory assist (NAVA) improves synchrony in patients with respiratory support by detecting the electrical activity of the diaphragm and may offer potential benefits in neonatal ventilation.[17-20] Noninvasive ventilation using NAVA as a triggering modality (NIV-NAVA) could be effective, as demonstrated in adult populations.[21,22] To date, few studies of NIV-NAVA in preterm infants have been conducted. Patient-ventilator synchrony and effective diaphragmatic unloading were reported in preterm infants during NAVA-derived noninvasive nasal ventilation.[23] Herein, we aimed to compare NIV-NAVA and NCPAP for the postextubation stabilization of very low birth weight infants.

Methods

This study used a retrospective approach and was approved by the Institutional Review Board of Seoul National University Hospital. The study included preterm infants of less than 30

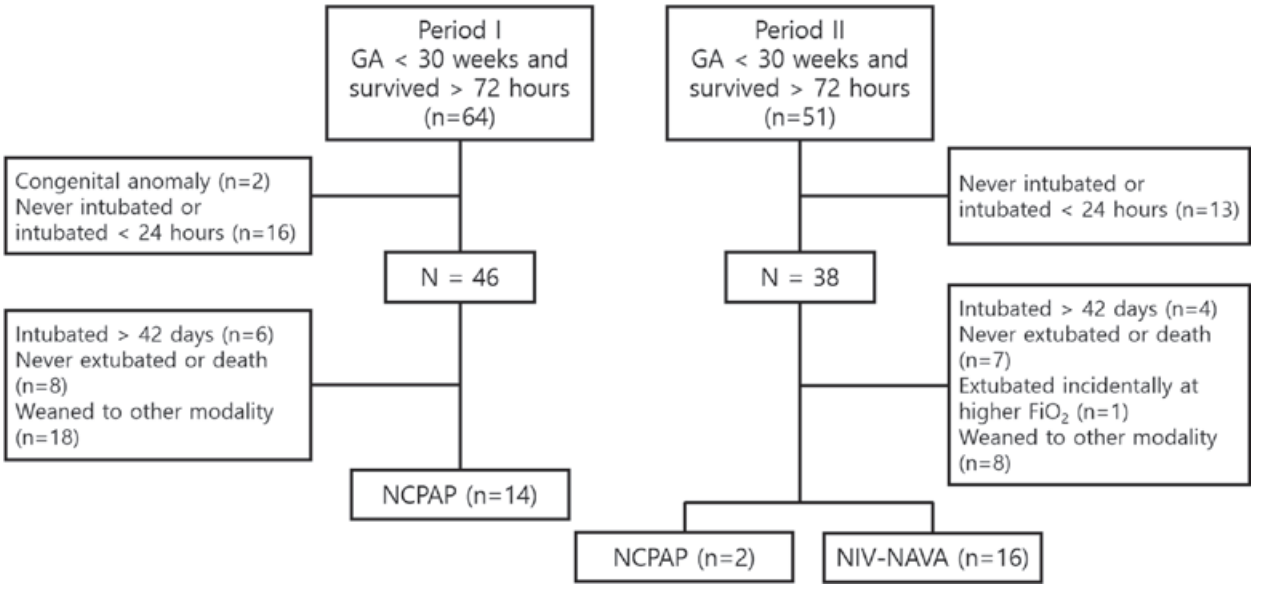

Fig. 1 Selection of the study population during the study period

weeks gestational age (GA) who were admitted to the NICU of the Seoul National University Children's Hospital (SNUCH) between July 2012 and June 2014 and survived more than 72 h. Infants who were on MV for longer than 24 h and were weaned to NCPAP (Infant Flow system, Viasys, Healthcare, Pennsylvania, United States) or NIV-NAVA (SERVO-I, Maquet Critical Care AB, Solna, Sweden) after extubation were eligible for the study. The size of the Edi catheter used during the study period was 6 Fr/49 cm, which could be used for extremely preterm infants.[20] There were no postmenstrual age (PMA) criteria for the use of NIV-NAVA during the study period if self-respiration was well established in the baby. Infants who had major congenital anomalies or who were intubated for longer than 6 weeks were excluded from the study. The study period was divided into two distinct periods, namely between July 2012 and June 2013 (Period I) and between July 2013 and June 2014 (Period II), because NIV-NAVA was applied at SNUCH beginning in July 2013.

The respiratory severity score (RSS = mean airway pressure (cmH_2O) x FiO_2) and oxygen saturation index (OSI = MAP x $FiO_2 \times 100 \div SpO_2$) were used to compare the pre-extubation respiratory conditions between the two groups.[24,25] The RSS has been used to predict extubation readiness or the length of mechanical ventilation in preterm infants, and the OSI has been suggested to be a useful measurement to reliably assess the severity of respiratory conditions in preterm infants when the oxygen index is not available.[26,27] During the study period, extubation was performed if the patient remained stable with a $SpO_2 > 90\%$ for at least 6 h while on the following settings: mean airway pressure (MAP) ≤ 9 cmH_2O, positive end expiratory pressure (PEEP) ≤ 7 cmH_2O and fraction of inspired oxygen (FiO_2) ≤ 40%. In infants who were mechanically ventilated for longer than 15 days, dexamethasone was administered to reduce airway edema. All infants included in the study population were treated with caffeine. A capillary blood gas analysis was performed within 1 h after extubation. Postextubation PEEP was initially set to 5~6 cmH_2O both in the NCPAP and NIV-NAVA groups, and was then adjusted within a range of 4~8 cmH_2O according to the clinician's discrimination. The NAVA level was initially set to 1.0~1.5 $cmH_2O/\mu V$ and adjusted to obtain $pCO_2 < 70$ mmHg. In both ventilation strategies, binasal prongs and masks were used alternatively every 24 h to minimize nasal injury.

The primary outcome of the study was extubation failure within 72 h after extubation, which was defined according to a set of conditions for reintubation and the reapplication of MV.[28] Infants with severe apnea requiring positive pressure ventilation (PPV), ≥ 4 apneic episodes per hour needing moderate stimulation, $FiO_2 > 60\%$, or uncompensated respiratory acidosis (pH < 7.25) were reintubated during the study period. Backup ventilation at a rate of 30/min and pressure of 10-15 cmH_2O above PEEP was applied if Edi was absent or apnea occurred for more than 5-10 s and the upper pressure limit was set to 20-25 cmH_2O.[23]

All statistical analyses were performed with STATA 11.0 (Stata Corp, College Station, TX, USA) using the independent t-test for continuous variables and the χ^2-test and Fisher's exact test for categorical variables. For all statistical analyses, $P < 0.05$ was considered statistically significant.

Table 1 Demographics of the study population

	NIV-NAVA ($n = 16$)	NCPAP ($n = 16$)	*P* value
GA (weeks)	27^{+1} (26^{+5}, 27^{+6})	26^{+5} (25^{+4}, 27^{+6})	0.317
Birth weight (grams)	875 (677.5, 1145)	845 (700, 1030)	0.777
Male	11 (68.8)	7 (43.8)	0.143
C/S	8 (50.0)	7 (43.8)	0.500
Multiple births	12 (75.0)	10 (62.5)	0.352
PIH	4 (25.0)	1 (6.25)	0.166
hCAM	5 (31.3)	10 (62.5)	0.078
PPROM	7 (43.8)	6 (37.5)	0.500
Antenatal steroid	7 (43.8)	12 (75.0)	0.074
1-min AS	3 (2, 5)	3.5 (2, 4.5)	0.802
5-min AS	5.5 (4, 7)	7 (6, 7)	0.122
RDS	14 (87.5)	16 (100)	0.242
PDA	12 (75.0)	7 (73.3)	0.618

Values are presented as the median (interquartile range) or n (%)
NIV-NAVA Noninvasive neurally adjusted ventilatory assist, *NCPAP* Nasal continuous positive airway pressure, *GA* Gestational age, *C/S* Cesarean section, *PIH* Pregnancy induced hypertension, *hCAM* Histologic chorioamnionitis, *PPROM* Preterm premature rupture of membrane, *AS* Apgar score, *RDS* Respiratory distress syndrome, *PDA* Patent ductus arteriosus

Table 2 Clinical characteristics at the time of extubation

	NIV-NAVA ($n = 16$)	NCPAP ($n = 16$)	*P* value
PMA at extubation (weeks)	30 (28^{+6}, 31^{+4})	29^{+4} (27^{+3}, 30^{+4})	0.282
Weight at extubation (grams)	1045 (800, 1325)	1025 (905, 1190)	0.651
	Pre-extubation		
Ventilator duration (days)	21.5 (11.5, 27)	9.5 (4.5, 34.5)	0.365
Systemic steroid use	7 (43.8)	5 (31.3)	0.358
RSS	1.65 (1.49, 2.28)	1.95 (1.68, 2.32)	0.317
OSI	1.70 (1.53, 2.39)	2.09 (1.76, 2.51)	0.274
MAP (cmH_2O)	7 (7, 7.5)	8 (7, 8)	0.212
PEEP (cmH_2O)	5 (5, 5)	5 (5, 6)	0.531
PIP (cmH_2O)	13 (12, 14)	15 (12, 16)	0.180
FiO_2 (%)	0.24 (0.21, 0.31)	0.25 (0.21, 0.30)	0.700
pCO_2 (mmHg)	53.2 (45.0, 58.4)	49.1 (43.7, 65.3)	0.970
SpO_2 (mmHg)	95.5 (94, 98.5)	96 (93.5, 97)	0.760

Values are presented as the median (interquartile range) or n (%)
NIV-NAVA Noninvasive neurally adjusted ventilatory assist, *NCPAP* Nasal continuous positive airway pressure, *PMA* Postmenstrual age, *RSS* Respiratory severity score, *OSI* Oxygen saturation index, *MAP* Mean airway pressure, *PEEP* Positive end-expiratory pressure, *PIP* Peak inspiratory pressure

Results

A total of 64 infants in Period I and 51 infants in Period II who were born at less than 30 weeks of gestation and survived greater than 72 h were admitted (Fig. 1). Two infants from Period I were excluded: one infant had Beckwith-Wiedemann syndrome, and the other infant had Galen malformation of the brain. Sixteen infants in Period I and 13 infants in Period II who were never intubated or intubated less than 24 h were also excluded. After excluding infants who had been intubated for greater than 6 weeks, those who were never extubated or died before discharge, and those who were weaned to other modalities, such as heated and humidified high flow nasal cannula (HHHFNC), there were 14 infants who were weaned to NCPAP during Period I and 16 infants who were weaned to NIV-NAVA during Period II. The 2 infants who were weaned to NCPAP during Period II were categorized as the NCPAP group with the infants from Period I.

The GA and birth weight of the NIV-NAVA group and NCPAP group were not significantly different (27^{+1} vs 26^{+5} weeks and 875 vs 845 g, respectively) (Table 1). The incidence of RDS, maternal histologic chorioamnionitis and antenatal steroid use were also not significantly different between the two groups. At the time of extubation, PMA and weight exhibited no significant differences between the NIV-NAVA group and NCPAP support parameters after extubation, such as PEEP and FiO_2, were comparable between the NCPAP and NIV-NAVA groups with similar pCO_2 and SpO_2. Among those who were reintubated in the study, GA at birth was 26.4 weeks in the NIV-NAVA group and 25.9 (25.3-28.1) weeks in the NCPAP group. In the univariate logistic regression analysis, GA at extubation and the duration of invasive ventilation before extubation were not associated with reintubation (data not shown).

No differences were noted between the two groups regarding the other clinical outcomes, including the development of moderate to severe bronchopulmonary dysplasia (BPD) (Table 4).

Table 3 Post-extubation status of the study population

	NIV-NAVA ($n = 16$)	NCPAP ($n = 16$)	*P* value
PEEP (cmH_2O)	6 (5.5, 6)	6 (5, 7)	1.000
FiO_2 (%)	0.30 (0.27, 0.35)	0.25 (0.21, 0.33)	0.109
pCO_2 (mmHg)	48.5 (44.3, 53.6)	49.7 (40.7, 62.1)	0.695
SpO_2 (mmHg)	96 (93, 97)	96.5 (94, 98)	0.597
Extubation failure ≤72 h	1 (6.3)	6 (37.5)	0.041

Values are presented as the median (interquartile range) or n (%). Post-extubation status was checked 1 h after extubation
NIV-NAVA Noninvasive neurally adjusted ventilatory assist, *NCPAP* Nasal continuous positive airway pressure, *PMA* Postmenstrual age, *RSS* Respiratory severity score, *OSI* Oxygen saturation index, *MAP* Mean airway pressure, *PEEP* Positive end-expiratory pressure, *PIP* Peak inspiratory pressure

Discussion

Extubation failure is often observed in preterm infants because the chest wall and upper airway collapses easily and diaphragmatic strength is poor.[29,30] The present study revealed that NIV-NAVA facilitated extubation better than NCPAP. Following a period of endotracheal intubation and IPPV, NCPAP is effective for preventing extubation failure in preterm infants.[8] This technique appears to improve lung function and reduce apnea and may therefore play a role in facilitating extubation in this population. However, certain populations among preterm infants who were subject to NCPAP experienced extubation failure.[6,31-33]

NIPPV augments NCPAP by delivering ventilator breaths via nasal prongs or a mask. Although it did not improve ventilation in infants who were able to maintain their own ventilation on NCPAP, in infants with a higher baseline $PaCO_2$, ventilation was more effectively increased by NIPPV than NCPAP.[34] Severe apnea and increased $PaCO_2$ were the most common causes of failure in infants receiving NCPAP, and NIPPV achieved a comparative reduction in extubation failure in preterm infants. A recent meta-analysis demonstrated that the incidence of extubation failure and the need for reintubation within 48 h to 1 week was reduced by NIPPV in preterm infants.[12] However, synchronization and the device used to deliver PPV may be important parameters in NIPPV.[13]

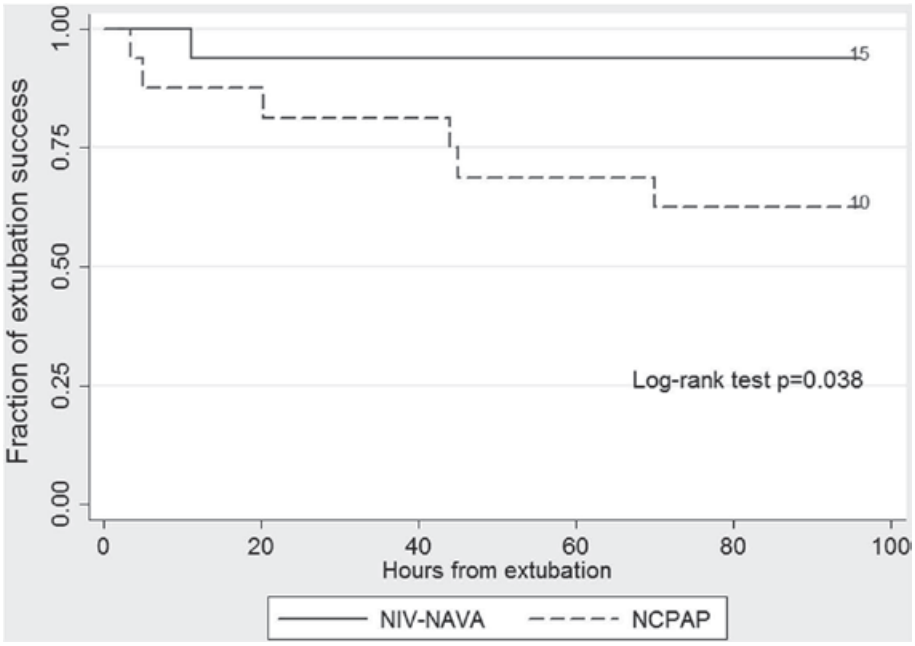

Fig. 2 Kaplan-Meier estimates for extubation success by post-extubation modality

NAVA has been applied in clinical practice during the last decade, but studies have rarely involved neonates, especially the preterm infant population. However, a recent study demonstrated the effectiveness and feasibility of NAVA in this population.[19] Noninvasive support via NAVA improved patient-ventilator synchrony by reducing trigger delay and the number of asynchrony events.[35] Previously, we reported that NAVA improved patient-ventilator synchrony and diaphragmatic unloading in preterm infants during noninvasive nasal ventilation compared with pressure support mode.[23] A recent physiologic study performed by Gibu et al. compared NIV-NAVA and NIPPV and demonstrated that peak inspiratory pressure and FiO_2 were lowered in NIV-NAVA than in NIPPV.[36] Furthermore, both infant movement and caretaker's work were lowered in NIV-NAVA, suggesting that NIV-NAVA was more effective than NIPPV at increasing infant comfort. Because it has excellent synchronization, NIN-NAVA could serve as a substitute for NCPAP to facilitate extubation in preterm infants. Most cases of reintubation in this study were the result of severe apnea or uncompensated hypercapnia. When compared to NCPAP, apnea and hypercapnia were more preventable in NIPPV by generating higher airway pressure to prevent obstructive apnea and triggering sigh in preterm infants.[37,38] Although NIV-NAVA seemed to improve ventilator synchrony and diaphragmatic unloading during noninvasive ventilation compared to other NIPPV, there was no evidence that NIV-NAVA is superior to other NIPPV modalities after extubation.[23,39]

Table 4 Clinical outcomes of the study population

	NIV-NAVA (n=16)	NCPAP (n = 16)	P value
Moderate to severe BPD	10 (62.5)	9 (60.0)	0.589
NEC ≥ stage 2	2 (12.5)	5 (33.3)	0.170
Retinopathy of prematurity	4 (25.0)	6 (40.0)	0.306
IVH ≥ grade 2	2 (12.5)	1 (6.7)	0.525
Periventricular leukomalacia	1 (6.3)	0 (0)	0.516

Values are presented as the median (interquartile range) or n (%)
NIV-NAVA Noninvasive neurally adjusted ventilatory assist, *NCPAP* Nasal continuous positive airway pressure, *BPD* Bronchopulmonary dysplasia, *NEC* Necrotizing enterocolitis, *ROP* Retinopathy of prematurity, *IVH* Intraventricular hemorrhage

Even though there could be concerns regarding the size of the baby when using NIV-NAVA, many studies showed NIV-NAVA was feasible in extremely preterm infants.[23,39] In the present study, NIV-NAVA was also found to be feasible in babies as small as 660 g at extubation or 700 g at birth who were successfully weaned to NIV-NAVA at PMA 28 weeks. A baby who was 500 g at birth was also successfully weaned to NIVNAVA at 770 g. Moreover, Edi catheters can efficiently serve as a feeding tube in these babies and thus an additional feeding tube did not need to be inserted for enteral feeding. NEC was comparable in both groups and there were no intestinal perforations or air leaks after the infants were weaned to NIV-NAVA or NCPAP. Although the rates of neonatal complications are lower in noninvasive versus invasive MV, safety must be considered. Previously, it was suggested that neonates who were mechanically ventilated with either a face mask or nasal prongs had an increased risk of gastrointestinal perforations. However, recent data has shown that NIPPV does not appear to be associated with increased gastrointestinal side effects, and the risk of air leaks was lower in NIPPV than in NCPAP.[40] No differences in the development of air leaks and NEC were observed between the two groups in the present study.

There are some limitations to the present study. This study was a retrospective study with a small sample size, thus making it difficult to draw robust conclusions. There also was a period of overlap when both NIV-NAVA and NCPAP were used as weaning modalities. The study population was highly selected because we analyzed only 50% of the preterm infants born at < 30 weeks of gestation who were intubated for more than 24 h and were extubated thereafter during the study period. Furthermore, the duration of ventilation seemed to be shorter in the NCPAP group, although this result was not statistically significant. While the sample size may have been too small to fully elucidate this difference, a logistic regression analysis for reintubation was performed ad hoc and showed that the duration of ventilation before extubation was not associated with reintubation (data

not shown). The criteria for extubation were well-defined in our unit, and the pre-extubation conditions in both groups including the PMA at extubation, RSS, OSI and the ventilation settings were comparable in the present study. Despite these limitations, this is the first study to compare the clinical responses between NIVNAVA and NCPAP when used to facilitate extubation in preterm infants.

Conclusions

The data in the present study were not robust enough to be conclusive due to small sample size, but showed promising implications for using NIV-NAVA over NCPAP to facilitate extubation. NIV-NAVA could be an effective modality for synchronized noninvasive ventilation following successful extubation from MV in preterm infants.

Abbreviations

HHHFNC: Humidified high flow nasal cannula; MAP: Mean airway pressure; MV: Mechanical ventilation; NAVA: Neurally adjusted ventilatory assist; NCPAP: Nasal continuous positive airway pressure; NICU: Neonatal intensive care unit; NIPPV: Nasal intermittent positive pressure ventilation; NIVNAVA: Non-invasive ventilation using NAVA; OSI: Oxygen saturation index; PEEP: Positive end expiratory pressure; PPV: Positive pressure ventilation; RSS: Respiratory severity score; SNIPPV: Synchronized Nasal intermittent positive pressure ventilation; VILI: Ventilator-induced lung injury

Authors' contributions

SHS, BKL and H-SK conceived and designed the study, collected and analyzed the data and drafted the manuscript. E-KK and YHJ revised the manuscript for critically important intellectual content. SHS, BKL and H-SK finalized the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset generated or analyzed during this study can be made available to interested researchers by the authors of this article upon reasonable request.

Ethics approval and consent to participate

Ethical approval to conduct this study was obtained from the Institutional Review Board of Seoul National University Hospital. Written consent from the caregivers of the neonates could not be obtained due to the retrospective nature of the study. However, all the patient-related information was anonymized.

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