Volume 19 Number 1 Winter 2024

Respiratory Therapy™

The Journal of Pulmonary Technique

Servo-air and Servo-air Lite ventilators

Intuitive, flexible, powerful, and efficient ventilation

Servo-air ventilators are a turbine-based platform, and are designed to enhance patient safety, deliver optimal respiratory support, and be responsive to your patients' needs.

Learn more

Servo-air and Servo-air Lite are registered trademarks of Getinge AB, its subsidiaries, or affiliates in the United States or other countries • Copyright 2023 Getinge AB or its subsidiaries or affiliates • All rights reserved • ⚠ CAUTION: Federal (US) law restricts this device to sale by or on the order of a physician. Refer to Instructions for Use for current indications, warnings, contraindications, and precautions. • MCV00111108 REVA

www.getinge.com

GETINGE

RespiSim
eLEARNING
Fundamental Ventilation Training

Introducing RespiSim® eLearning

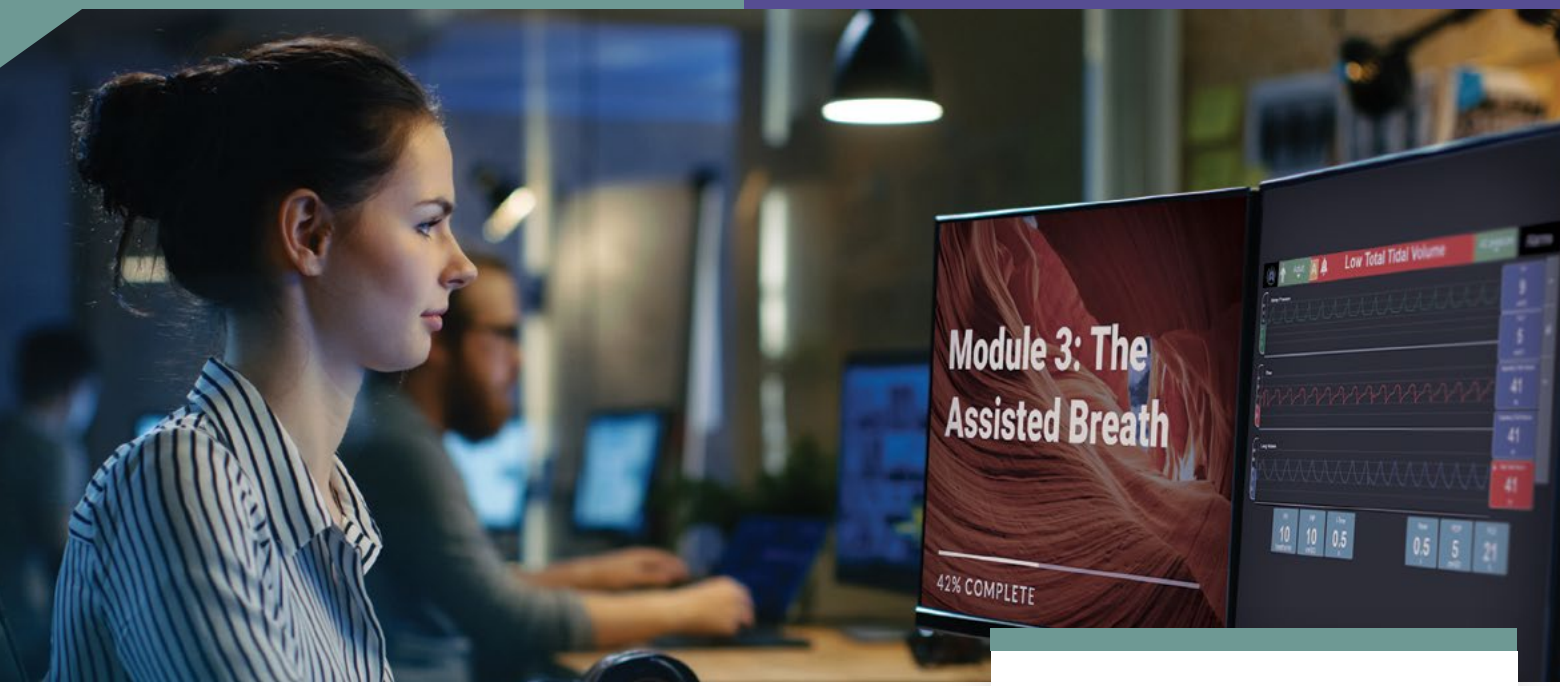
Strengthen learners' understanding of key ventilation concepts with this affordable subscription-based e-learning environment.

RespiSim® eLearning Management System (LMS)

Provide self-guided e-learning content including the acclaimed SEVA™ Curriculum by the Cleveland Clinic.

RespiSim® Virtual Ventilator Software

Demonstrate waveform analysis and the fundamentals of patient-ventilator interaction for a remote or in-person audience.



INGMAR MEDICAL
Respiratory Simulation Specialists

412-441-8228 - Option 2
sales@ingmarmed.com
ingmarmed.com

Scan To Speak With a Product Specialist Today!

Respiratory Therapy
The Journal of Pulmonary Technique

ISSN 2152-355X
Published four times each year by
Goldstein and Associates, Inc.
10940 Wilshire Blvd., Suite 600
Los Angeles, CA 90024 USA
Tel: 310-443-4109 · Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Website: www.respiratorytherapy.ca

Publisher/Editor in Chief
Steve Goldstein
Managing Editor Christopher Hiscox
Senior Editor Chris Campbell
News Editor Vincent Terrier
Associate Editor Jordana Hammeke
Associate Editor Susan Goldstein
Assistant Editor Laszlo Sandor

Circulation, Coverage, Advertising Rates: Complete details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 45 days preceding date of issue.

Change of Address: Notices should be sent promptly to Circulation Department. Provide old mailing label as well as new address. Allow two months for change.

Editorial Contributions will be handled with reasonable care. However, publishers assume no responsibility for the safety of artwork, photographs or manuscripts. All submissions may be emailed to s.gold4@verizon.net. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of information supplied herein or for any opinion expressed. Editorial closing date is the first day of the month preceding month of issue.

©2024 by Goldstein & Associates, Inc. All rights reserved. Reproduction in whole or in part without written permission is strictly prohibited.

Cover: Kleine Welten V (Small Worlds V) (1922) print in high resolution by Wassily Kandinsky. Original from The MET Museum.

Editorial Advisory Board

Mohammed Al Ahmari, PhD, MSc, RRT
AARC Intl Fellow
Director, Respiratory Care Program
King Fahd Military Medical Complex &
Prince Sultan College of Health Sciences
Al-Khobar, Saudi Arabia

Prof. Nicolino Ambrosino, Head,
Pulmonary Unit, Cardio-Thoracic
Department
University Hospital, Pisa; Head, Pulmonary
Rehabilitation and
Weaning Unit
Auxilium Vitae, Volterra, Italy

Muhammad Aslam, MD
Associate Professor of Pediatrics
University of California Irvine
Neonatologist
UCI Medical Center
California, USA

Eliezer Be'eri, MD
Director, Respiratory Rehabilitation Unit
Alyn Hospital
Founder and CSO
Innovent Medical Systems
Jerusalem, Israel

Melissa K. Brown, BS, RRT-NPS, RCP
Faculty, Respiratory Therapy Program
Grossmont College
El Cajon, CA

Prof. Andrea Calkovksa, MD, PhD
Department of Physiology, Jessenius
Faculty of Medicine
Comenius University
Mala Hora, Slovakia

Prof. Enrico M. Clini
Clinica di Malattie Apparato Respiratorio
Dipartimento di Oncologia
Ematologia e Pneumologia
Universita Studi di Modena e
Reggio, Italy

Larry H. Conway, BS, RRT Chief,
Director of Respiratory Care
VA Medical Center
Washington, DC

Edwin Coombs, MA, RRT-NPS, ACCS,
FAARC
Senior Director of Marketing
Portfolio Solutions Training,
Clinical Affairs, & Intensive Care
North America
Draeger, Inc.
3135 Quarry Road
Telford, PA 18969

Dr. Salomay Corbaley, EdD, MBA,
RRT-NPS, AE-C
Program Director Ventilation and Airway
Management
Nihon Kohden
Anaheim CA

Prof. Caglar Cuhadaroglu, MD
Pulmonology Department and
Sleep Center
Maslak Hospital, Facutly of Medicine
University of Acibadem
Istanbul, Turkey

Antonio Esquinas, MD, PhD, FCCP
Director, International School of
Noninvasive Mechanical Ventilation
Catholic University-San Antonio
Murcia, Spain

Dr. Javier Fernandez
Director of Clinical Affairs & Education
Respiratory Division Latin America
Miami, FL

Gerardo N. Ferrero, PT
Clinical Specialist, Latin America
Buenos Aires, Argentina

Louis Fuentes, RRT
Marketing Manager — Ventilation
Maquet Medical Systems, USA
Wayne, NJ

Dr. Miguel Goncalves
Pulmonology Department and ICU and
Emergency Department
University Hospital of S. João School
Faculty of Medicine
University of Porto, Portugal

Joshua F. Gonzales, MHA, RRT-NPS, RRT-
SDS, RCP
Associate Professor
Department of Respiratory Care
Texas State University
San Marcos, TX

Rik Goselink, PT, PhD
Professor, Rehabilitation Sciences
Dean, Faculty of Kinesiology and
Rehabilitation Sciences
Universitaire Ziekenhuizen Leuven/
Katholieke Uniersiteit Leuven, Belgium

Gary L. Hansen, PhD, MS, BS
Director of Scientific Affairs
RespirTech, a Philips Company
Plymouth, MN

Ken D. Hargett, MHA, RRT, RCP, FAARC,
FCCM
Director, Respiratory Care Services,
Pulmonary Diagnostic Laboratory,
Digestive Disease Endoscopy
The Methodist Hospital
Houston, TX

Surinder K. Jindal, MD
Postgraduate Institute of Medical
Education & Research
Chandigarh, India

Brent D. Kenney, BSRT, RRT, RCP, FAARC
Supervisor of Care Coordinators,
Respiratory Care Department
Mercy Hospital
Springfield, MO

Prof. Dr. Naomi Kondo Nakagawa
Department of Physiotherapy,
Communication Science and Disorders and
Occupational Therapy
Faculdade de Medicina da Universidade de
Sao Paulo, Brazil

Scott E. Leonard, MBA, BA, RRT
Director of Respiratory Therapy, EEG,
Neurophysiology
George Washington University Hospital
Washington, DC

Benan Mayrakci, MD
Assistant Professor of Pediatrics
Director of Pediatric
Intensive Care Unit
Hacettepe University School of Medicine,
Ankara, Turkey

Timothy R. McConnell, PhD
Chair, Department of Exercise Science
Bloomsburg University
Pennsylvania USA

Bob Messenger, BS, RRT, CPFT
Manager, Respiratory Clinical Education
Invacare Corporation
Elyria, OH

Kenneth Miller, MEd, RRT-ACCS, NPS,
AC-E, FARRC
Clinical Educator, Dean of Wellness,
Respiratory Care Services
Lehigh Valley Health Network
Allentown, PA

Nawal M. Mofarreh
MBBS, Arab Board-Internal
Medicine I, Cardiac Center-
Al-Thawra General Modern Hospital,
CPR Instructor & Co-Ordinator
Saudi Heart Association in affiliation with
American Heart Association, CPR Center,
Al-Thawra Hospital
Sana'a-Yemen

Richard J. Morishige, MS, RRT, RCP, RAC
Director, Clinical Affairs
Breathe Technologies, Inc.,
Irvine, CA

Pavlos M. Myrianthefs, MD, PhD
Assistant Professor
Athens University
Critical Care Department
KAT Hospital
Athens

Paul Nuccio, MS, RRT, FAARC
Director of Pulmonary Services
Brigham and Women's Hospital & Dana-
Farber Cancer Institute
Boston, MA

Lisa Pappas, RRT, BS
Respiratory Clinical Coordinator, NICU
University of Utah Hospital
Salt Lake City, UT

Hossein Razavi, MD, FCCP
Pulmonary, Critical Care &
Sleep Medicine
St. Helena, CA

Ruben D Restrepo, MD, RRT, FAARC, FCCP
Coordinator of Research Professor
Division of Respiratory Care
UT Health San Antonio
San Antonio, TX

Dr. John H. Riggs, PhD, RCP, FAARC
Director of Respiratory Services
Mission Hospitals
Asheville, NC

Daniel D. Rowley, MSc, RRT-ACCS, NPS,
RPFT, FAARC
Clinical Coordinator
Pulmonary Diagnostics & Respiratory
Therapy Services
University of Virginia Medical Center
Charlottesville, VA

J. Kyle Schwab, MD
Medical Director
Louisiana Sleep Foundation
Baton Rouge, LA

Tushar A. Shah, MD, MPH, FAAP
Division of Neonatology
Cincinnati Children's Hospital
Medical Center
Cincinnati, OH

Chet Sivert Jr, BS
Director of Regulatory and
Clinical Affairs
Electromed, Inc.
New Prague, MN

Alex Stenzler
President, 12th Man Technologies, Inc.
Garden Grove, CA

Dave Swift, RRT
Ottawa Hospital — Civic Site; Campus
Coordinator (Professional Practice) &
Special Care Nursery Charge Therapist;
Respiratory Therapy Team Lead; National
Office of the Health Care Emergency
Response Team (NOHERT); Subject Matter
Expert, Health Canada

Dan Van Hise, RRT-NPS
Marketing Senior Manager
Philips Medical
Andover, MA

TRACOE Twist

atosmedical.us

Twist Plus C

Twist Plus Fen

Twist Plus

Twist & Twist Plus tracheostomy tubes for adults - For the patient, every millimeter counts

We are here to help, contact us today:

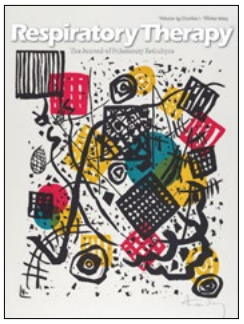
Atos Medical Inc.
2801 South Moorland Road, New Berlin, WI 53151
Tel. +1.800.217.0025
Email: info.us@atosmedical.com

More Info

Atos

Breathing–Speaking–Living

© Coloplast A/S, 2023. All rights reserved. Atos and the Atos Medical logo are trademarks of Coloplast A/S. MC3124, 111323



Respiratory Therapy™
The Journal of Pulmonary Technique

Vol. 19 No. 1
Winter 2024

Table of Contents

News

■ Winter 2024

Shakeup in Pharmacy Market

Monaghan Medical Corporation (Monaghan) and Allergan Sales, LLC have announced a mutual agreement wherein Monaghan will assume the direct management of the AeroChamber brand Valved Holding Chamber (VHC) for retail pharmacy markets. Starting January 1, 2024, Monaghan will take on the complete responsibility for retail pharmacy sales of the AeroChamber brand VHC. Commencing from September 1, 2023, Monaghan will initiate collaborations with pharmacy wholesalers and retail establishments that currently procure the AeroChamber brand VHC through Allergan, manufactured by Monaghan. Monaghan, headquartered in Plattsburgh, New York, is a prominent US-based manufacturer celebrated for crafting exceptional respiratory care products design specifically to treat respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and others. Monaghan's excellence is rooted in innovative product development and design, underpinned by its world-class Aerosol and Research Laboratory.

New Tests May Finally Diagnose Long COVID

One of the biggest challenges facing clinicians who treat long COVID is a lack of consensus when it comes to recognizing and diagnosing the condition. But a new study suggests testing for certain biomarkers may identify long COVID with accuracy approaching 80%. Effective diagnostic testing would be a game-changer in the long COVID fight, for it's not just the fatigue, brain fog, heart palpitations, and other persistent symptoms that affect patients. Two out of three people with long COVID also suffer mental health challenges like depression and anxiety. Some patients say their symptoms are not taken seriously by their doctors. And as many as 12% of long COVID patients are unemployed because of the severity of their illness and their employers may be skeptical of their condition. Quick, accurate diagnosis would eliminate all that. Now a new preprint study suggests that the elevation of certain immune system proteins are a commonality in long COVID patients and identifying them may be an accurate way to diagnose the condition. Researchers at Cardiff University School of Medicine in Cardiff, Wales, United Kingdom, tracked 166 patients, 79 of whom had been diagnosed with long COVID and 87 who had not. All participants had recovered from a severe bout of acute COVID-19. In an analysis of the blood plasma of the study participants, researchers found elevated levels of certain components. Four proteins in particular — Ba, iC3b, C5a, and TCC — predicted the presence of long COVID with 78.5% accuracy. "I was gobsmacked by the results. We're seeing a massive dysregulation in those four biomarkers," says study author Wioleta Zelek, PhD, a research fellow at Cardiff University. "It's a combination that we showed was predictive of long COVID." The study revealed that long COVID was associated with inflammation of the immune system causing these complement proteins to remain dysregulated. Proteins like C3, C4, and C5 are important parts of the immune system because they recruit phagocytes, cells that attack and engulf bacteria and viruses at the site of infection to destroy pathogens like SARS-coV-2. In the case of long COVID, these proteins remain chronically elevated. While the symptoms of long COVID have seemed largely unrelated to one another, researchers point to elevated inflammation as a connecting factor that causes various systems in the body to go haywire. "Anything that could help to better diagnose patients with long COVID is research we're greatly appreciative of within the clinical community," said Nisha Viswanathan, MD, director of the University of California Los Angeles Long COVID program at UCLA Health in Los Angeles. Testing for biomarkers highlighted in the study, as well as others like serotonin and cortisol, may help doctors separate patients who have long COVID from patients who have similar symptoms caused by other conditions, said Viswanathan. For example, a recent study published in the journal *Cell* found lower serotonin levels in long COVID patients compared with patients who were diagnosed with acute COVID-19 but recovered from the condition.

Air in Remote First Nations Houses Tied to Respiratory Ills

Indoor air in four First Nations communities in remote northwestern

REACTHEALTH Ventilatory Solutions

Supporting your patient's journey from hospital to home

React Health ventilators support pediatric to adult patients across the continuum of care, from hospital to home, with a comprehensive set of modes and beneficial features such as:

- **Volume-Targeted Pressure Modes**, auto-adjusting pressure technology with advanced leak compensation to meet patient's changing ventilatory needs
- **High Flow Therapy**, with flow rates of 4 - 60 L/min
- **Reliable, Plug-and-Play, GPS Enabled Remote Monitoring** with React DataLink device and Multi-View Connect platform
- **Portability,** with compact, lightweight design and up to 9 hours of battery life
- **User Friendly** smartphone style touchscreen interface

Invasive and Non-invasive

HFT
High Flow Therapy

Wireless Data Sharing

Record, Trend and Monitor

Hospital to Home

Pediatric to Adult

MADE IN AMERICA

To learn more contact your React Health representative:
ventec-info@reacthealth.com or call 844-698-6276

MKT-00096, Rev A

Ontario contains high concentrations of biocontaminants, mold, fine particles, and other substances that increase the risk of respiratory infections, new research reveals. In a study of the housing conditions and indoor environmental quality (IEQ) in these communities, about 27% of the homes had sustained CO_2 concentrations above 1500 ppm. Although 44% of houses had a heat recovery ventilator (HRV), only 8% were in good working condition. Other issues included biocontaminants such as dust mites and fungal glucan, tobacco smoking, and high concentrations of mold. "One exposure that led up to the children going to hospital was the chemical called endotoxin," study author J. David Miller, PhD, research professor at Carleton University in Ottawa, Ontario, said. "When concentrations are too high, it affects lung function and causes a greater response to allergens. The values in the Sioux Lookout Zone were around 1000 times higher than I'd ever seen in any study in the United States or Canada. That was a big surprise." In their study of four First Nations communities in a remote region of northwestern Ontario, the investigators used statistical methods such as linear regression, mixed models, and logistic regression to assess correlations between housing conditions and biocontaminants and indoor concentrations of fine inhalable particles ($PM_{2.5}$), CO_2, benzene, and formaldehyde.

They investigated 101 homes (40%) in these small communities; each had approximately 1200 residents. Samples were taken, and the homes were inspected by an indoor air quality specialist. To identify factors affecting IEQ, the investigators considered various issues. For example, the houses were crowded, averaging approximately seven people in each. The most common type of fuel for heating was wood (48%), but only 10% of the wood stoves were certified by the US Environmental Protection Agency (EPA) for lower emissions. In 94% of the houses, people smoked commercial tobacco. The mean number of smokers per house was 2.6, and the number of smokers per house was as high as seven.

AHA, AAP Update Neonatal Resuscitation Guidelines

The American Heart Association (AHA) and American Academy of Pediatrics (AAP) have issued a focused update to the 2020 neonatal resuscitation guidelines. The 2023 focused update was prompted by four systematic literature reviews by the International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support Task Force. "Evidence evaluations by the ILCOR play a large role in the group's process and timing of updates," Henry Lee, MD, co-chair of the writing group, said. He noted that updated recommendations do not change prior recommendations from the 2020 guidelines. "However, they provide additional details to consider in neonatal resuscitation that could lead to changes in some practice in various settings," said Lee, medical director of the University of California San Diego neonatal intensive care unit. Lee noted that effective positive-pressure ventilation (PPV) is the priority in newborn infants who need support after birth. And while the 2020 update provided some details on devices to be used for PPV, the 2023 focused update gives guidance on use of T-piece resuscitators for providing PPV, which may be particularly helpful for preterm infants, and the use of supraglottic airways as a primary interface to deliver PPV, he explained. Specifically, the updated guidelines state that use of a T-piece resuscitator to deliver PPV is preferred to the use of a self-inflating bag. Because both T-piece resuscitators and flow-inflating bags require a compressed gas source to function, a self-inflating bag should be available as a backup in the event of compressed gas failure when using either of these devices. Use of a supraglottic airway may be considered as the primary interface to administer PPV instead of a face mask for newborn infants delivered at 34 0/7 weeks' gestation or later.

COVID-19 Antivirals Can Trigger Viral Rebound, Study Finds

COVID-19 antivirals can trigger viral rebound in ambulatory patients, according to an analysis published in *Annals of Internal Medicine*. An observational cohort study compared patients with acute COVID-19 who received 5 days of nirmatrelvir-ritonavir (N-R [Paxlovid]; n = 72) to similar patients who did not receive the treatment (n = 55). All patients were seen in ambulatory settings. Researchers compared rates of reinfection, which was defined as an initial positive test followed by a negative result and then another positive result within 20 days. Rates of increased viral shedding were compared between the two groups as another measure of viral rebound. One in 5 people (15 in 72, 20%) who took N-R had viral rebound compared with just 1 in 55 people who did not. Those who took N-R were older, more likely to be immunocompromised, and had received a greater number of COVID-19 vaccinations (four on average) than did people who did not receive it (three on average). Eight of the 16 people with viral rebound also reported symptom rebound, and two were completely asymptomatic. People who had received N-R and eventually experienced a rebound showed viral shedding for a median of 14 days compared with a median of 3 days among people who did not rebound who were also taking the drug. "For patients with COVID-19 with a low-risk for severe disease, the possibility of prolonged shedding should be factored into the consideration of potential risks and benefits of treatment," the researchers write.

Acute Care Diagnostics

GEM® PREMIER™ 5000 | iQM®2

The Intelligent Analyzer

GEM Premier 5000 blood gas testing system provides automated quality assurance with every whole-blood* sample. Now with next-generation Intelligent Quality Management (iQM2), featuring IntraSpect™ technology, potential errors are detected not only before and after, but also during sample analysis, along with real-time correction and documentation. Plus, it's simple—just change the all-in-one GEM PAK once a month. So regardless of testing location or point-of-care operator, quality results and compliance are assured with every sample.

Real-time assurance and advanced simplicity. Now that's intelligent.

For more information, contact your local Werfen representative.

werfen.com

*Heparinized.

GEM, Premier and iQM are trademarks of Instrumentation Laboratory Company and/or one of its subsidiaries or parent companies and may be registered in the United States Patent and Trademark Office and in other jurisdictions. The Werfen logo is a trademark of Werfen and may be registered in the Patent and Trademark Offices of jurisdictions throughout the world. ©2021 Instrumentation Laboratory. All rights reserved.

werfen

React Health Partners with EnsoData to Utilize Predictive AI to Improve Outcomes for Patients with Sleep Apnea

EnsoData, a leading provider of artificial intelligence (AI) solutions to assist with sleep testing, diagnosis, and treatment, and React Health, a sleep and respiratory device manufacturer based in Sarasota, FL, announced a strategic collaboration to optimize PAP adherence support for patients with sleep apnea. EnsoData's revolutionary adherence prediction AI will be integrated into React Health's recently launched React Health Connect platform. This collaboration will empower referring physicians and DME suppliers with actionable data to provide timely, personalized support to patients who are struggling with therapy adherence. "By partnering with EnsoData, we are making another significant investment in our sleep therapy product portfolio", says Tom Pontzius, President at React Health. "EnsoData's predictive analytics will allow our customers to prioritize and focus on the patients that need intervention the most, and will ultimately provide a more personalized and positive patient experience." "Our PAP compliance AI model has an incredible ability to predict compliance within days of starting treatment," states Chris Fernandez, Chief Research Officer. "We are excited about the transformative impact our technology can have on the multitude of patients who face challenges in treating their sleep apnea. Our goal is to strengthen the bond between healthcare providers and patients, resulting in improved patient outcomes." This partnership signifies a new era in personalized sleep apnea care where predictive clinical AI tools enable timely patient care, increased patient support, and stronger provider-patient connection.

Company Opens New Headquarters

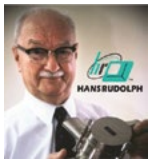
Leading global manufacturer of oxygen therapy and cardiorespiratory diagnostic equipment, CAIRE Inc. has opened the doors on its new Global Service Headquarters in Canton, GA, in a location near its primary manufacturing hub north of Atlanta. The move by the company is designed to advance long-term plans to enhance service and support for home and durable medical equipment providers everywhere. The 29,500-square-foot Canton facility will provide rapid servicing of equipment, as well as fulfillment of specialty service parts and accessories for CAIRE respiratory and specific AirSep brand commercial products. The site has 20 employees, inclusive of the company's US-based technical service team who primarily supports respiratory product customers and end users. The opening, combined with the recent expansion of CAIRE's Authorized Service Network to 23 locations nationwide, is expected to streamline how customers receive critical support to equip their technical service teams with the products they need, and also maintain equipment fleets more efficiently. "As we navigated the challenges of the pandemic, we discovered there was an opportunity to improve the efficiency of our service and support infrastructure. By separating our after-market support from our manufacturing facility, we have the ability to improve the quality and MR-CORP0025 A efficiency of after-market service, and at the same time we can leverage the national footprint and expertise of our Authorized Service Network to serve our customers closer to home which is a win-win for everyone," said Barry Hassett, Chief Commercial Officer. CAIRE's Authorized Service Network, focused on in-warranty product repairs, includes Altra Services Professionals, Oxygen Sales & Service, Inc., Quality Biomedical, and Repair Authority. These providers not only offer convenient physical locations, but several also offer multi-state pick-up and delivery services as an added benefit to customers. "The organizations that make up our Authorized Service Networks have been essential partners in supporting the nation's largest medical equipment providers during a period of serving a large and ever-growing population of oxygen patients. Through our partnership, CAIRE's customers have a wider pool of service professionals that can shorten lead times and deliver potential savings on shipping and freight," said Lanier Hogan, Global Parts and Service Manager.

Telesair Receives FDA Clearance for Bonhawa High Flow Oxygen Therapy System

Telesair, Inc., a technology leader in the respiratory industry, announced that it has received FDA clearance to market its Bonhawa High Flow Oxygen Therapy (HFOT) system, designed to enhance the treatment of patients with respiratory insufficiency. Bonhawa is now the only purpose-built high flow system to receive both the CE Mark/ European Medical Device Regulation and FDA 510(k) clearance. Bonhawa gives healthcare providers and their patients in the US and worldwide an extended flow range, a streamlined disinfection process and an intuitive touchscreen. These attributes collectively offer healthcare workers and institutions greater capabilities and efficiencies. "The best in class Bonhawa system greatly improves patient care while enhancing efficiency for clinicians," said Bryan Liu, PhD, CEO of Telesair. "It represents a significant milestone in that it is a more cost-effective, user-friendly option for treating respiratory conditions.

Get a Stronger Handle on your Pulmonary Testing.

NEW! From Hans Rudolph, an easy-to-install Syringe Handle that simplifies, speeds and strengthens pulmonary equipment calibration.



1) Gives testers the ability to firmly secure syringes for full, smooth piston motions;
2) Ends physical contact with the cylinder, thus eliminates undesirable heat transfer;
3) Protects syringe integrity by stopping slips, drops and other syringe mishaps.

To order, call 913-422-7788 or email HRI@RudolphKC.com

Only applicable for HRI and Vyaire manufactured Syringes. Please specify which manufacturer and number of handles when ordering.

©Copyright 2023, Hans Rudolph, Inc. US Design Patent and EC Design Registrations Pending.

691380-A 2023-07-11

NEOTECH® *Making a Difference*

You Have to Feel It to Believe It!

NeoPulse™

PULSE OXIMETER WRAP

The NeoPulse™ Pulse Oximiter Wrap is made with skin friendly NeoFoam®. A soft material so unique, you have to feel it for yourself.

NeoPulse is lightweight, adjustable, and wicks perspiration, which helps to prevent odors. Designed for comfort and stability.

Available in **3 SIZES**.

©2023 Neotech Products LLC. All rights reserved.

Made in USA

Request your free samples online at neotech-rtj.com

Bonhawa is the only standalone high flow oxygen therapy system designed by experts in ventilation. Our team has decades of experience developing and commercializing revolutionary respiratory solutions and collaborated to create this efficient, easy-to-use system. I am very proud of the organization for achieving both MDR/CE and FDA clearance in less than one year." Telesair's introduction of its lightweight oxygen therapy system to the US further expands the company's existing market access that includes Europe, Latin America, Asia and the Middle East. Liu added that Telesair is actively engaged in developing its first-in-class next-generation home-based platform and is confident in its ability to swiftly introduce its revolutionary technology to the market.

Pfizer, BioNtech Say Flu-COVID Shot Generates Strong Immune Response in Trial

Pfizer and German partner BioNTech said that their vaccine to prevent flu and COVID-19 generated a strong immune response against strains of the viruses in an early- to mid-stage trial. The companies said they plan to start a late-stage trial in the coming months. "This vaccine has the potential to lessen the impact of two respiratory diseases with a single injection and may simplify immunization practices," Annaliesa Anderson, Pfizer's head of vaccine research and development, said in a statement. In the trial, the vaccine candidates were compared to a licensed influenza vaccine and the companies' updated COVID-19 vaccine given at the same visit. The data from the trial showed that the flu-COVID vaccine demonstrated robust immune responses to influenza A, influenza B and SARS-CoV-2 strains, the companies said.

Company Signs Contract for Device

Beyond Air, Inc., a commercial stage medical device and biopharmaceutical company focused on harnessing the power of endogenous and exogenous nitric oxide (NO) to improve the lives of patients suffering from respiratory illnesses, neurological disorders and solid tumors (through its affiliate Beyond Cancer, Ltd.), announced that the LungFit PH system has received an Innovative Technology contract from Vizient, Inc., the nation's largest provider-driven health care performance improvement company. The contract was awarded based on the recommendation of the LungFit PH system by hospital experts who serve on one of Vizient's customer-led councils, and it signifies to Vizient customers unique qualities that potentially bring improvement to the health care industry. Innovative Technology contracts are recommended after review and interaction with products submitted through Vizient's Innovative Technology Program. Vizient customer-led councils identify technologies that have the potential to enhance clinical care, patient safety, health care worker safety or improve business operations of health care organizations. Approved in June 2022, LungFit PH is the first and only 3-in-1 integrated system for inhaled nitric oxide (iNO) generation, delivery, and monitoring, providing unlimited on-demand iNO regardless of set dose or ventilator flow. LungFit PH employs patented Ionizer™ technology to generate iNO from room air within seconds, providing unprecedented speed to care. This point-of-care solution alleviates the logistical and supply challenges associated with traditional iNO systems by streamlining inventory management with a predictable, on-demand supply of iNO generated at the bedside. Clinicians generate what they need whenever they need it. This innovative system is paired with an all-inclusive 24/7 service and support program designed to exceed customer expectations.

"We're very happy and honored to be awarded an Innovative Technology contract from Vizient for our LungFit device. This validates the customer experience and feedback we have received to date," said Steve Lisi, Chairman and Chief Executive Officer of Beyond Air. "Our revolutionary generator-based delivery system is a transformative technology with the potential to change how nitric oxide is used to the benefit of both patients and hospitals, and we are very excited by this opportunity to expand our reach through the robust Vizient customer network." "Congratulations to Beyond Air for being awarded an Innovative Technology contract," said Kelly Flaharty, senior director of contract services for Vizient. "Our member council recommended the LungFit PH system for this contract based on the efficiencies it offers and its potential to make an incremental difference in health care." Vizient represents a diverse membership base that includes academic medical centers, pediatric facilities, community hospitals, integrated health delivery networks and non-acute health care providers and represents more than $130 billion in annual purchasing volume. Through its Innovative Technology Program, Vizient works with hospital experts on its customer-led councils and task forces to evaluate products for their potential to bring real innovation to health care. Vizient may award a contract to products deemed worthy of the Innovative Technology designation outside of the competitive bid cycle.

New RSV Vaccine Will Cut Hospitalizations, Study Shows

The newly approved respiratory syncytial virus vaccine administered during pregnancy substantially reduces the clinical and economic burden of lower respiratory tract disease caused by RSV, according to research presented at Infectious Disease Week (IDWeek) 2023 Annual Meeting. "With RSV maternal vaccination that is associated with clinical efficacy of 69% against severe RSV disease at 6 months, we estimated that up to 200,000 cases can be averted, and that is associated with almost $800 million in total," presenting author Amy W. Law, PharmD, director of global value and evidence at Pfizer, pointed out during a news briefing. "RSV is associated with a significant burden in the US and this newly approved and recommended maternal RSV vaccine can have substantial impact in easing some of that burden," Law explained. This study is "particularly timely as we head into RSV peak season," said briefing moderator Natasha Halasa, MD, MPH, professor of pediatrics, Division of Pediatric Infectious Diseases at Vanderbilt University in Nashville, Tennessee. The challenge, said Halasa, is that uptake of maternal vaccines and vaccines in general is "not optimal," making increased awareness of this new maternal RSV vaccine important.

Masimo ORi Granted De Novo as the First and Only FDA-Cleared Noninvasive and Continuous Parameter

Masimo announced that ORi, a noninvasive, continuous parameter designed to provide additional insight into a patient's oxygen status in the moderate hyperoxic range under supplemental oxygen, has been granted a De Novo by the FDA. Enabled by the multi-wavelength Masimo rainbow Pulse CO-Oximetry platform, ORi is designed for use in conjunction with oxygen saturation (SpO_2) to provide increased resolution of changes in oxygenation under supplemental oxygen. With the De Novo, ORi becomes the first-of-its-kind parameter cleared by the FDA to help clinicians manage oxygen of adults undergoing surgery in perioperative hospital environments. Without ORi, there is no noninvasive way to monitor oxygenation under supplemental oxygen to manage hyperoxia, or higher

BIO-MED DEVICES

TV-100 VENTILATOR

Infant - Pediatric - Adult

One Vent | All Patients | Anywhere

With superior portability, flexibility, and performance,
the Bio-Med Devices' industry leading TV-100 Ventilator offers the latest technology, and provides the modes and performance of a full size ICU ventilator in a compact design that is ideal for transport.

www.biomeddevices.com
BIO-MED DEVICES, INC. 61 SOUNDVIEW ROAD GUILFORD, CT 06437 USA

than normal oxygenation of arterial blood. There is growing evidence that hyperoxia is harmful and can lead to oxygen toxicity, causing oxygen poisoning or pulmonary tissue damage. Currently, clinicians take blood draws that are analyzed to determine PaO_2 levels, the partial pressure of oxygen measured by arterial blood gas devices. However, arterial blood analyses are both intermittent and delayed—leaving clinicians blind to the changes in oxygenation occurring between blood draw results. Masimo ORi addresses these shortcomings by providing continuous insight into the oxygenation of hemoglobin in the moderate hyperoxic range (PaO_2 > 100 and ≤ 250 mmHg). ORi is trended continuously with SpO_2 as a unit-less index between 0.00 and 1.00 to extend the visibility of the oxygenation of patients beyond SpO_2 under supplemental oxygen. By convention, SpO_2 is limited to an upper limit of 100%, but oxygenation can rise into hyperoxia when supplemental oxygen is administered. ORi provides clinicians with additional visibility, as a complement to Masimo SET pulse oximetry, into when oxygenation is increased into, or decreased out of, moderate hyperoxia, in real time. Numerous studies have demonstrated ORi's utility. For example, in a study published in *Anesthesia & Analgesia* of 106 adult patients undergoing scheduled surgery, researchers found decreases in ORi "may provide advance indication of falling PaO_2 when SpO_2 is still > 98%." In another study published in *Intensive Care Medicine*, researchers found that the use of ORi monitoring to titrate oxygen rates "allowed an important reduction of the time spent with hyperoxia compared with the use of SpO_2 alone," in a group of 150 mechanically ventilated adult patients randomized to an ORi or a control group. Joe Kiani, Founder and CEO of Masimo, said, "Since ORi's availability and success outside the US, perioperative clinicians in the US have been waiting for a way to noninvasively monitor patients under supplemental oxygen beyond the limits of SpO_2. We are thrilled that US clinicians can now integrate ORi monitoring—available now on our rainbow SET platform—into their oxygenation monitoring practices, alongside Masimo SET Measure through Motion and Low Perfusion pulse oximetry, and experience their combined benefits." Jesse M. Ehrenfeld, MD, President of the American Medical Association and advisor to Masimo, commented, "I can envision a number of scenarios I encounter in my daily clinical practice as an anesthesiologist where ORi would be invaluable. During patient pre-oxygenation, I often find myself unsure of the adequacy of pre-oxygenation, especially in a patient with a significant cardiopulmonary comorbidity or a patient with diminished oxygen reserve capacity. ORi would solve this problem by giving an easy-to-understand parameter that provides visibility to how oxygenation is changing during the pre-oxygenation process. Additionally, I often find that during the management of a difficult airway, it is never quite clear when to stop, re-establish mask ventilation, and allow the patient to recover. Again, ORi would be very helpful in addressing this issue as it can track the trajectory of the patient's oxygenation status. I am delighted to see ORi receive FDA clearance. It is not often that new parameters are developed which can actually make a real impact in clinical practice." Richard L. Applegate II, MD, Chair of Anesthesiology at Loma Linda University Health, California, stated, "Our studies show that ORi provides advanced detection of low SpO_2 events. This additional time may allow modification of airway management, earlier calls for help, or assistance from other providers. Advanced detection of worsening oxygenation is valuable in operative and critical care settings and ORi use has the potential to provide continuous

A Vizient Innovative Technology Contract Partner

LungFit® PH | ALL YOU NEED IS AIR™

Unprecedented Speed to Care. No Cylinders, No Cassettes.[1]

- Generate and deliver iNO within seconds[1]
- Unlimited, on-demand iNO regardless of dose or flow[2]
- Simplified contracting and savings

Schedule a demo and say goodbye to iNO cylinders. LungFitPH.com/Speed

INDICATIONS FOR USE

The nitric oxide from the LungFit PH System is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents. Refer to the full Prescribing Information within the LungFit PH System Operator's Manual before use.

Visit **www.LungFitPH.com** for full Important Safety Information.

Reference: 1. Data on file. Beyond Air Inc. 2021. **2.** LungFit PH System Operator's Manual. Garden City, NY: Beyond Air Inc. 2022.

© 2023 Beyond Air Inc. All Rights Reserved. Beyond Air® and LungFit® PH are registered trademarks of Beyond Air Inc. All You Need is Air™ is a trademark of Beyond Air Inc.
Printed in USA 11/23

Beyond Air®

monitoring to detect changes in pulmonary function." Ken B. Johnson, MD, Professor of Anesthesiology, University of Utah, commented, "I have been eager for the ORi parameter to be available in the US for a long time as it is a unique innovation with the potential to significantly improve patient care. Observing the ORi trend may help clinicians anticipate hemoglobin oxygen desaturations before they occur. Clinical scenarios where this technology may be useful include airway management that takes longer than expected, prompting rescue breaths before desaturation occurs, and procedural sedation with unanticipated prolonged periods of apnea that can trigger rescue maneuvers before the onset of unwanted desaturation. This index in combination with pulse oximetry shows promise in better managing adverse events related to poor oxygenation and improved patient outcomes." ORi is granted a De Novo by the US FDA to be used in patients undergoing surgery as an adjunct to SpO_2 for increased monitoring resolution of elevated hemoglobin oxygen saturation levels (e.g., due to administration of supplemental oxygen). The ORi feature is indicated for the monitoring of hemoglobin oxygen saturation levels in patients 18 years and older (adults and transitional adolescents) on supplemental oxygen during no-motion conditions perioperatively in hospital environments.

New Data Lowers Estimate of Long COVID's Impact: CDC

An estimated 18 million adults in the US have had long COVID, and half of them are still dealing with the condition, new national survey data shows. Results from the CDC's National Health Interview Survey in 2022 found that 6.9% of adults self-reported they had COVID symptoms for at least 3 months after testing positive or being diagnosed by a doctor as having COVID-19. The estimate is much lower than previous CDC survey data, which has consistently reported that approximately 14% to 15% of US adults have had long COVID. The CDC also newly reported that 1.3% of US children have had long COVID, and 0.5% of children having symptoms lasting at least 3 months at the time of the survey in 2022. The agency lists 19 possible long COVID symptoms, including fatigue, shortness of breath, a pounding heart, brain fog, and changes in smell or taste, as well as symptoms worsening with physical or mental effort. The 2022 survey results were analyzed by demographic factors such as income, gender, age, and race or ethnicity to see if groups of people are affected differently by long COVID. Wealthy people were the least likely to report having long COVID, while people whose family incomes were well below the federal poverty level were the most likely to have long COVID. Women were more likely than men to ever have long COVID or currently have the condition. People ages 35 to 49 years old were most likely to report having the condition.

Pneumonia, Not Just Inflammation, May Cause Severe COVID

As we continue to live with COVID-19, patients and doctors will learn more about the reasons infections can range from asymptomatic to very serious. Many researchers and doctors believe inflammation is the cause of severe COVID. This is due to the virus causing a "cytokine storm" that can adversely affect the organs in a patient's body, including the heart and lungs. New research from Northwestern University and the University of Wisconsin, however, is pointing to bacterial pneumonia as the cause of many severe COVID deaths. Deceased COVID patients studied were not shown to have experienced inflammation at all.

GENTEC® Patient Care
Quality Medical Gas Products for Your Supply Chain
Medical Flowmeters | Connectors & Accessories | Blenders | Medical Gas Regulators | Suction Regulators | Venturi Suction Regulators
GENTEC gentechealthcare.com @genstartech

Instead, the researchers, using machine learning to analyze data, found that half of the severely ill COVID patients who required a ventilator had bacterial pneumonia as a secondary infection. They did not find evidence of a cytokine storm in these patients; instead of dying from organ damage or failure due to COVID, they died of pneumonia. Critically ill patients who recovered from pneumonia were more likely to live," said Benjamin D. Singer, MD, senior author of the study, professor of pulmonary medicine, and a Northwestern Medicine pulmonary and critical care doctor in Chicago. Other researchers don't debunk the idea of cytokine storms in COVID, however. Cytokines are chemicals that are released when a person's immune system overreacts to an infection. Too many cytokines are toxic and can cause organ failure. In COVID-19, cytokines have been thought to release inflammation that can circulate through the body and cause death.

Pilot Study demonstrates Vapotherm HVNI technology is more effective than standard oxygen therapy

Vapotherm, Inc., a global medical technology company focused on the development and commercialization of its proprietary Vapotherm high velocity therapy products, which are used to treat patients of all ages suffering from respiratory distress, today announced the presentation of an Investigator-initiated clinical trial, "High flow humidified oxygen as an early intervention in children with acute severe asthma—a feasibility randomized controlled trial" at the European Respiratory Society International Congress 2023. The study was conducted through the Brighton and Sussex Clinical Trial Unit at University Hospitals, Sussex, England under the direction of Drs Hector Rojas-Anaya and Paul Seddon. Children who presented to the Emergency Department with acute, severe, asthma exacerbations that did not respond to initial pharmacologic treatment were randomized to either HVNI or standard nasal oxygen therapy. Eighty-six percent (19/22) of children treated with standard oxygen required escalation of therapy, while only 61% (17/28) of children treated with HVNI needed further escalation. In addition, children treated with HVNI met hospital discharge criteria in a median time of 29 hours, compared to a median time of 37 hours for those treated with standard oxygen.

"Anytime a child with severe asthma can get well faster and avoid more invasive care it is a victory. We are excited and proud that our technology was utilized in this study and in the care of these children." said Dr Jessica Whittle, Chief Medical Officer of Vapotherm. Almost 5 million children in the USA, and 1 million children in the UK have asthma, according to the CDC and NHS. Asthma is estimated to cost $56 billion according to the Asthma and Allergy Foundation of America. Studies of acute asthma and other emergent conditions are limited, in part, by the challenge of obtaining informed consent. This study demonstrated the feasibility of pediatric emergency studies utilizing coordinated care and delayed informed consent. "These numbers show that we have an enormous opportunity to help children all over world breathe better and have better lives with our technology," said Joe Army, CEO of Vapotherm.

FDA Clears Nova's Stat Profile Prime Plus Analyzer for Micro Capillary Sample Mode

Nova Biomedical announced that the US Food and Drug Administration (FDA) has granted 510(k) clearance for a micro capillary sample mode on the Stat Profile Prime Plus Critical Care analyzer. Prime Plus now performs an 11-test panel including pH, PCO2, PO2, Na, K, iCa, iMg, Cl, glucose, lactate, and hematocrit with just 90 microliters of capillary

blood, or a complete 22-test profile on just 135 microliters of blood. The micro capillary sampling mode adds to Prime Plus blood conservation capabilities for critical care diagnostic testing and is available as a standard feature on all Prime Plus analyzers. Stat Profile Prime Plus provides the most modern and clinically effective critical care test menu including pH, PCO2, PO2, SO2%, Na, K, iCa, iMg, Cl, TCO2, glucose, lactate, creatinine, urea, hematocrit, hemoglobin, MCHC, estimated plasma volume, CO-Oximetry panel, and 34 calculated results in a simple, compact analyzer. Prime Plus combines maintenance-free, replaceable cartridge technology for sensors and reagents with patented, maintenance-free, whole blood CO-Oximetry technology. Blood loss for laboratory testing of critically ill patients has been shown to be a major contributor to severe anemia and increased administration of blood products, which is furthermore associated with prolonged hospital stay and increased mortality rate. According to Terry Austin, Sales Product Line Manager for Prime Plus analyzer, "Prime Plus microsample volume and comprehensive test menu provide a major blood-saving benefit for diagnostic testing of critically ill patients. Prime Plus delivers gases, electrolytes, glucose, lactate, hematocrit, or any subset of these tests on just two drops (90 microliters) of blood. A basic metabolic panel of electrolytes, glucose, lactate, creatinine, urea, and hematocrit is available on 135 microliters, 1/50th the volume of blood needed for the same tests in the central laboratory." The use of small-volume microcapillary blood collection tubes with Prime Plus eliminates sample overdraws, dead volume, and sample waste of syringe or vacuum tube devices. Prime Plus comprehensive test menu enables scheduled bundling of tests to eliminate multiple sample draws, use of multiple sample containers, and amount of blood drawn for critical care testing.

SPOTLIGHT ON BLOOD GAS

GEM® Premier™ 5000 Blood Gas Testing System

The GEM® Premier™ 5000 blood gas testing system from Werfen is the Intelligent Analyzer for point-of-care and centralized laboratory testing. Results for Arterial Blood Gas (ABG), Electrolytes, Glu, Lac, Hct, tHb, O2Hb, COHb, HHb, MetHb, sO2, tBili can be obtained from a single sample. Inte-grated Intelligent Quality Management 2 (iQM®2)—an active quality process control program de-signed to provide continuous monitoring of the analytical process, before, during, and after each sample measurement—assures real-time, automatic error detection, automatic correction and au-tomatic documentation of all corrective actions. Maintenance-free, multi-use, self-contained GEM PAK cartridges incorporate all components needed for testing. The GEM Premier 5000 with iQM2 is a complete solution for enhanced efficiency and patient care.

VENTILATION ROUNDTABLE

Breas

What ventilation products does your company offer?
Currently, Breas US offers two invasive and non-invasive life support ventilators. The legacy Vivo 65, and our flagship device the Vivo 45 LS launched in January 2021.

What are the new features?
The Vivo 45 LS is arguably the smallest and lightest life support device on the market. It is the only life support device on the market that offers "integrated" humidity for patients receiving non-invasive therapy. The Vivo 45 LS offers unique triggering algorithms called e-Sync, and unique auto-EPAP algorithms in addition to high flow nasal therapy. Breas also launched the EveryWare Cloud connectivity solution in January 2021, and the functionality and uniqueness of this solution has allowed our customer base to better manage ventilation compliance and operational effciency of their devices.

Tell us about your company's current or recent R&D efforts.
Breas is always striving to bring innovation and quality to the ventilation industry. As previously mentioned, Breas launched a unique Auto EPAP algorithm along with High Flow Nasal Therapy, 30 LPM O2 bleed to achieve 100% FiO2, and lastly the integrated humidifier and heated wire circuit. All these R&D projects are designed to improve patient compliance and comfort as well as expand the Vivo 45LS therapeutic options. Breas has also released an external battery called XPAC which provides Breas' ventilation customers up to 18 additional hours of battery life to now extend battery life to >24 hours. Breas has more exciting projects in development and will be excited to announce these in the future.

Discuss the training and support services you offer.
Breas philosophy is to offer product focused sales and clinical training support to our customers either virtually or face to face at no cost to our customers. Tutorial training videos are also available in the "Education by Breas" website.

Where are your products used? (ie, hospital, home, etc.)
Breas ventilation products are intended to be used in home care, institutions such as sub-acute and long-term care facilities and hospital transitional care departments and portable applications such as wheelchairs and gurneys. Both the Vivo 65 and 45LS may be used for both invasive and non-invasive ventilation.

What developments do you foresee for ventilation products and applications?
As previously mentioned, Breas works closely with our customers related to incorporating feedback on clinical and operational improvements. Often new features can be incorporated into existing devices with simple firmware updates, but also looking at cutting edge new features that may require new platforms to advance ventilation therapy.

Hamilton

Responses provided by Darron Pinkney, Marketing & Customer Success Manager, Hamilton Medical

What ventilation products does your company offer?
Hamilton Medical is a world-leading manufacturer of intelligent ventilation solutions, accessories, and consumables covering a wide range of patient groups, applications, and environments. Our user-friendly ventilator portfolio covers the complete continuum of care, from ground to sky, transport to ICU, and neonates to adults.

Dale
Medical Products

The Dale BreezeLock® Endotracheal Tube Holder

- Provides reliable stabilization of endotracheal tubes (sizes 7.0-10.0mm) following intubation.
- The low profile design and cushioned neckband are soft and comfortable on the face and neck.
- It can be used in supine or prone position.
- Slide allows easy repositioning of ET tube placement.
- Allows easy access for oral care.
- Prevents kinking or flattening of tube.
- Minimizes unintentional ET tube movement and helps prevent accidental extubation.

QUALITY YOU CAN COUNT ON

For a free sample call 800-343-3980
or visit dalemed.com/samples

Represented Nationally by:
MTMC

Dale and BreezeLock are registered trademarks of Dale Medical Products, Inc.
©2023 Dale Medical Products, Inc. All rights reserved.

EMPLOYEE OWNED 100% AND OPERATED

AD-115 Rev C

For a complete list of our products, visit https://www.hamilton-medical.com/en_US/

What are the new features?
Innovation is at our core. This is what drives us to keep developing intelligent ventilation solutions that promote safer care for critically ill patients and make life easier for the people who care for them.

Our list of features include:
- Adaptive Support Ventilation (ASV)
- Patient ventilator synchrony with IntelliSync®+
- P/V Tool® for assessing lung recruitability and recruitment
- Transpulmonary pressure monitoring

For more information on our features, visit https://www.hamilton-medical.com/Products/Technologies.html

Discuss the training and support services you offer.
New VenTrainer App – Advance your ventilation knowledge with VenTrainer, the free virtual training app for clinicians. Dive into an immersive, easy-to-set up learning experience and:
- Explore our ventilators and their features with an interactive 360° animation
- Use the app to enhance the training experience for you or your team members
- Monitor how your ventilation strategy affects the patient outcome in real time, thanks to the physiologic patient model
- Simulate real-life ventilation with a GUI that displays real-time monitoring values

For more information on our VenTrainer, visit https://www.hamilton-medical.com/Academy/VenTrainer.html

Hamilton Medical e-Academy – Discover a wide range of e-learning resources about mechanical ventilation and ventilators. Our e-learning modules are designed for current and future users of Hamilton Medical ventilators and cover the most commonly used features and functions.

For more information on our e-Academy, visit https://www.hamilton-medical.com/en_US/Academy.html

Where are your products used?
Our products are used by healthcare professionals in hospitals and EMS settings.

Nihon Kohden

Responses provided by Khanh Nguyen, Associate Product Manager, Nihon Kohden OrangeMed

What ventilation products does your company offer?
NKV-550 Series Ventilator System – The NKV-550 is a comprehensive ventilator for neonatal to adult patients, allowing easy transitions between invasive and non-invasive ventilation and high-flow oxygen therapy. It uses an intuitive App-based Graphic User Interface (GUI) that is customizable to fit the workflow of institutions and users. Guided, advanced maneuvers are available as an optional Gentle Lung® Suite. It is the only FDA-cleared ventilator with a second, fully functional GUI user interface, allowing clinicians to respond quickly to changing patient conditions.

NKV-440 Ventilator System – From neonates to adults, the NKV-440 ventilator easily transitions patients between invasive and non-invasive ventilation, and high flow oxygen therapy. Sharing the same easy to understand user interface as the NKV-550 ventilator, the NKV-440 includes an integrated HEPA-filtered turbine, and support for pneumatic and Aerogen nebulizers. The design is a cost-effective choice for high to mid-acuity hospitals with care areas lacking compressed air.

NKV-330 Ventilator System – A single-limb turbine-based invasive or non-invasive ventilator that can transition to high-flow oxygen therapy. The dual HEPA filters add layers of protection for clinicians, patients, and the ventilator as we face the challenges of respiratory infectious diseases. NKV-330 sets a precedent in non-invasive ventilation with built-in SpO_2 and $EtCO_2$ monitoring.

What are the new features?
Nihon Kohden cap-ONE Mask – The first non-invasive ventilation mask capable of mainstream capnography. The innovation helps reduce the need for multiple blood gases for CO_2 trending while the patient is on NPPV therapy.

cap-ONE $etCO_2$ sensor – is an ultra-compact and lightweight (only 4g) mainstream volumetric $etCO_2$ that is designed to integrate with different Nihon Kohden respiratory patient interfaces such as ETT inline adaptor, nasal cannula, and our unique cap-ONE non-invasive masks. Its anti-fog membranes enable uninterrupted $etCO_2$ measurement during aerosol nebulization. It is compatible with all Nihon Kohden ventilators and patient monitors.

Protective Control® is a fully functional, second user interface identical to that on the ventilator. Protective Control was developed to help minimize the clinician's exposure to biological hazards. It also helps reduce the exposure of the patient in reverse-isolation to hazardous pathogens. Using the second user interface, the clinician can view the ventilator monitors, alarms, and adjust ventilation and alarm settings outside of the hazardous environment while the patient remains in view.

Gentle Lung® Suite comprises four lung protection tool Apps with guided steps to allow clinicians to focus on the patient's hemodynamic statuses during lung recruitment maneuvers. The innovative Recruitability Assessment (RA) App provides an innovative tool for clinicians to obtain the insight into the recruitability of the patient's lungs to help determine if a recruitment maneuver would be beneficial to the patient. The Recruitment Maneuver (RM) App is a guided, stepwise PEEP recruitment maneuver. PEEP-Titration (PEEP-T) App helps clinicians find the PEEP providing the best compliance. Finally, the Transpulmonary Pressure App, only available in the NKV-550 ventilator, provides a way to monitor lung compliance independent of chest wall compliance.

Tell us about your company's current or recent R&D efforts.
We take pride in our responsive customer service and are dedicated to lung protection ventilation and providing clinically relevant solutions to optimize the care of our patients.

Discuss the training and support services you offer.
Technical service training is provided by our knowledgeable technical service team. Clinical training is provided by our

NIHON KOHDEN

NON-INVASIVE VENTILATION WITH CONTINUOUS OPERATION.

NKV-330

- Single-limb functionality
- Multiple NIV and high flow oxygen therapy modes
- Rapid in-house patient transportation
- Easy reconfiguration for new care settings

HELP PATIENTS BREATHE EASIER

Learn more about the NKV-330 by scanning the QR code or visit **us.nihonkohden.com**

Important Safety Information:

CAUTION: Federal (United States) law restricts this device to sale by or on the order of a physician.See Instructions for Use for full prescribing information, including indications, contraindications, warnings, precautions, and adverse events.

MKT-01261 [A]

ventilation team, comprised of experienced respiratory therapists.

Where are your products used?
Our versatile ventilator systems serve a range of acute critical care to long-term subacute facilities.

- The NKV-550 ventilator is an excellent choice for all critical-care facilities.
- The NKV-440 ventilator is a smart option for facilities that require advanced neonatal through adult applications but may lack compressed air in care areas.
- The NKV-330 ventilator is a non-invasive option for acute-care hospitals and long-term subacute facilities.

Getinge

Responses provided by Henry Szymanski, RRT, Marketing Product Manager, Critical Care at Getinge

What ventilation products does your company offer?
Getinge is Servo ventilation. The Servo name is well known and has been leading innovation in ICU ventilation for more than 50-Years. We offer a complete line of mechanical ventilators to address the needs of adult through neonatal patients requiring high levels of support to patients recovering needing lower levels of support such as NIV or HFT. Most recently we have launched the Servo-air and Servo-air Lite ventilators. The Servo-air platform is our first turbine driven ventilator that can be configured for a variety of clinical needs. The Servo-air Lite is focused on NIV and HFT. We are proud to have this flexible platform in our portfolio. The Servo-air and Servo-air Lite deliver the level of performance and reliability expected from a Servo ventilator. Our philosophy has been to focus on the ventilator and ease of use, and allow the clinicians to select the patient circuits and interfaces that best meet their needs and the needs of their patients.

What are the new features?
As mentioned above, the newest ventilator in the Servo portfolio is the Servo-air Lite. We are very excited to get this in the hands of our customers. We're confident it will meet their needs and bring a new level of quality and reliability into this category of ventilators. Early feedback from customers has been very positive.

Though not a new technology, we are seeing a high level of interest and adoption of our Edi/NAVA technology. We believe that a growing body of work related to diaphragmatic injury and dysfunction is driving interest in monitoring diaphragmatic activity and using NAVA to support ventilated patients.

Tell us about your company's current or recent R&D efforts.
Getinge is constantly working on and investigating technologies to better monitor and support patients requiring any level of respiratory support.

Discuss the training and support services you offer.
Getinge provides education and support to our customers at 2 levels. First, our Getinge Ventilator Sales and Clinical team is among the top in the medical device industry. Our team know their products, know the environment in which our products are being used, and have a high-level of understanding of how to safely and effectively use our technologies to support patients. This team is deployed around the country and provide immediate and frontline support to our customers.

Second, is our Getinge Educational Institute. Getinge offers formal education content and programs for all our products. Throughout the year Getinge also broadcasts a series of educational webinars presented by both internal experts and clinicians on the use of our products and current topics related to mechanical ventilation.

Where are your products used?
For years Servo ventilation was focused on high acuity patients in the ICU. Getinge continues to develop technologies for high acuity needs but has adopted a broader focus to reach more patients, patients beyond the doors of the ICU. As we perfected the performance of non-invasive modes on our ventilators we launched the Servo-air. Now with the Servo-air and Servo-air Lite our ventilators are used throughout the hospital and sub-acute settings.

What developments do you foresee for ventilation products and applications?
There remains significant room for improvement in patient ventilator interaction and synchrony. Our Edi/NAVA technology is on the leading edge of addressing this problem and we will continue to leverage this area.

There is a huge amount of data coming from the patient, the ventilator, and other devices around the bedside that can be integrated and leveraged to guide clinical decisions and improve patient care. There is a lot of exciting work being done at various levels of clinical decision support using data analytics and I believe this is where there will be technologies developed that actually move the needle in improving patient care.

Help is here for RTs: Automating De-escalation of Care Decisions in the ICU

Kathryn Butler, MS, RRT-NPS

"Is this patient ready to be extubated?" If you're a respiratory therapist (RT) in the ICU, you are, without a doubt, familiar with this question. You scan the central station monitor and can quickly see which patients are flagged for eligibility, meaning they meet all of the data-driven elements for an extubation readiness trial (ERT)/spontaneous breathing trial (SBT).

Whether the patient was ready isn't the primary point here. To reduce mechanical ventilation time, respiratory therapy departments are striving for frequent ERT/SBTs, which is a challenge in any situation, but especially when RTs are too thinly spread. Enter Etiometry's clinical intelligence platform, which can be accessed via EHR and anywhere there's a hospital VPN. It collects all available patient data, visualizes it on one screen, provides estimation of risk that a patient could deteriorate, automates clinical pathways, and then automates reports to efficiently inform quality improvement initiatives and verify your site's protocol effectiveness.

In this case, the decision for an ERT/SBT can be made quickly and with confidence, as you have a holistic view of the patient condition: SpO2, Tidal Volume, Respiratory Rate, Heart Rate, Blood Pressure, EtCO2, Ph, PaCO2, PaO2, etc. on one screen. Etiometry software augments clinical intuitiveness with real and trended data that's being continuously collected.

In a recent study, a clinical pathway was automated within Etiometry to provide a foundational framework to transform an ERT/SBT workflow to help deliver standardized care, reduce variation and improve quality. The platform was customized to each unit's protocols. The care teams were able to track all their patients within one portal and see when a patient might be for an ERT and/or extubation without additional bedside assessments. When the patient was eligible, the RT was alerted. The platform then automatically tracked performance when the vent settings were changed.

Kathryn Clark, RRT-NPS, is the Director of Clinical Development at Etiometry and has a decade of experience in critical care procedures, training clinicians, and award-winning clinical research. She is responsible for developing, coordinating, and implementing Etiometry's FDA cleared analytics and automated pathways functionality into clinical workflows worldwide. Prior to Etiometry, she worked with hospital leadership to establish clinical practices, policies, and protocols for the opening of Sidra Medicine in Qatar. Ms. Clark's experience spans across pediatric, adult, and cardiac patients at Boston Children's Hospital, Tampa General, and beyond.

The outcomes of this study are eye-opening: a 19% reduction in hospital length of stay and a 22% decrease in mechanical ventilation time.[1] This new workflow streamlined patient tracking — eliminating the need for bedside assessments solely to gauge readiness for an ERT. The automation alleviated the workload, allowing more time for personalized patient care, which can go a long way for reducing clinician burnout — especially with so many sites being short-staffed.

The Etiometry platform's ability to help care teams adhere to ERT/SBT guidance is important because these protocols are complex and the data available in most cases are sparse, as mechanical ventilation parameters are typically only documented at certain points throughout the day. We've seen how helpful the platform is in building confidence in newer clinicians, as they are using aggregated data and site-specific protocols to support their escalation and de-escalation of care decisions.

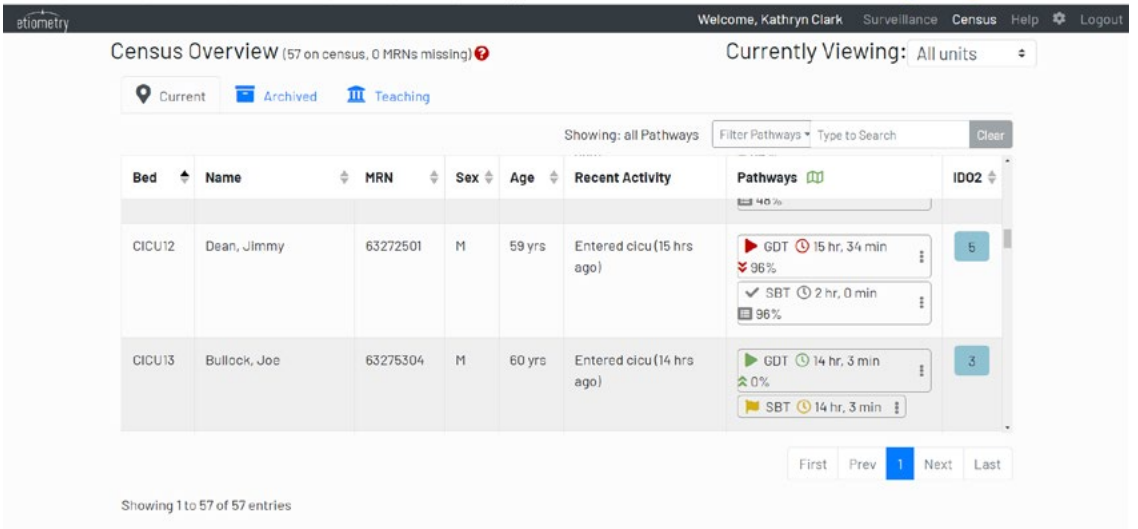
But the platform goes beyond mere flagging eligible patients. Think how you can utilize these insights during rounds, pre-rounding, shift changes and calibrating care team communication.

And let's not overlook the significance of 19% less time spent in the hospital.[1] This reduction not only signifies improved patient outcomes but also potentially frees up beds, optimizing hospital operations and bolstering financial health.

A clinician's testimonial perfectly encapsulates the system's simplicity and effectiveness: "Getting the information for an ERT takes only one click. You get all the data you need on one screen so you can look at everything — easy."

Automating the ERT workflow is all about enhancing patient care and promoting safe and efficient ICU liberation. It's also about simplifying processes, and ultimately, reducing the stress on clinical staff, which is more important than ever in this labor market. It's no secret that there aren't enough RTs to go around, yet the demand is increasing while many are set to retire in the next few years. [2] Expected to do more with less is everywhere, but if you're an RT in critical care and your patient load is higher due to being short-staffed, there's more at stake when lives are concerned.

The ERT pathway is only one use case for clinical pathway automation. Picture a similar scenario for using Etiometry for vasoactive medication weaning, tracking acute kidney injury



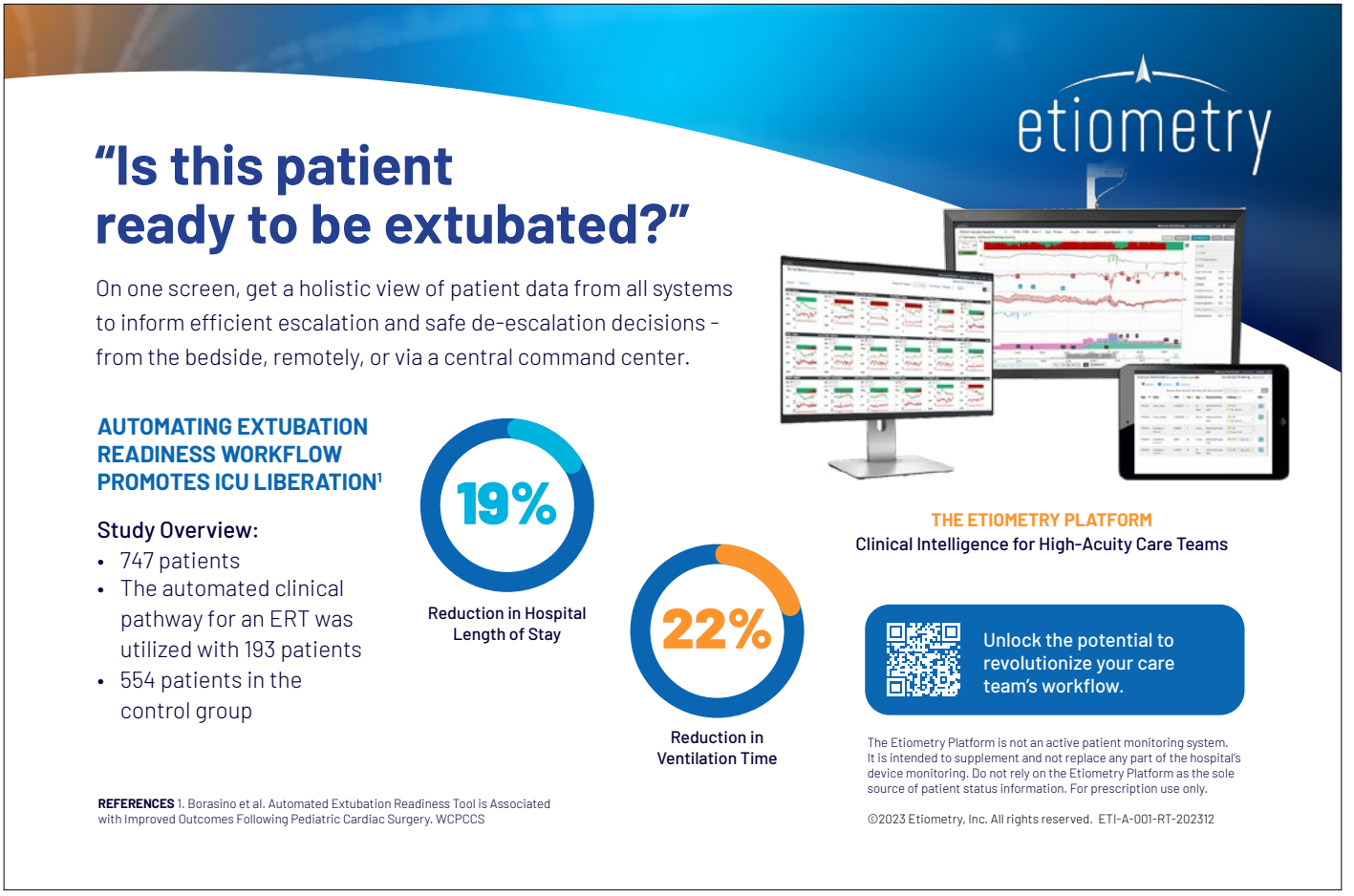
The Etiometry Clinical Intelligence Platform flags patients eligible for a spontaneous breathing trial (SBT) and informs the care team status of goal directed therapies (GDT).

(AKI) and managing acute respiratory distress syndrome (ARDS) patients. Get your personalized view at Etiometry.com/getyourview.

References

1 Borasino, S. et al. (2023) Automated Extubation Readiness Tool is Associated with Improved Outcomes Following Pediatric Cardiac Surgery. WCPCCS.

2 Why We Need More RTs—and How to Help, https://www.morerts.com/growing-need/



A Discussion About Using Nocturnal Pulse Oximetry to Detect or Exclude Obstructive Sleep Apnea (OSA)

In this feature, Dr. Claudio Rabec, a Critical Care Pulmonologist & Sleep Disorders Specialist at the Centre Hospitalier et Universitaire de Dijon, Université de Bourgogne, France, is being interviewed by Euda Arrieta, clinical and training and education manager at Nonin Medical, Inc.

Respiratory Therapy publishes interviews with clinicians and healthcare providers about the actual application of specific products and therapies.

Introduction

Euda Arrieta: It is my great pleasure to introduce you to our distinguished guest for this Nonin Academy *Interview with the Expert*, Dr. Claudio Rabec.

Dr. Rabec is an international expert in the sleep medicine field, recognized for his research contributions related to diagnosing and treating sleep disorders. Dr. Rabec is fellow of the American College of Chest Physicians (ACCP) and currently a staff member of the Pulmonary and Critical Care Division at the Centre Hospitalier et Universitaire de Dijon, in France. During this interview session with Dr. Rabec, we will dive into the important topic of nocturnal pulse oximetry, a vital tool for home sleep testing.

Obstructive sleep apnea (OSA) remains a significant concern, often undiagnosed and unappreciated in its consequences. During this interview with Dr. Rabec, we will explore the insights and the potential benefits of the overnight pulse oximetry as a simple, accessible, and non-invasive method to screen sleep apnea.

For this discussion, we will ask Dr. Rabec a series of questions, submitted by physicians from around the world.

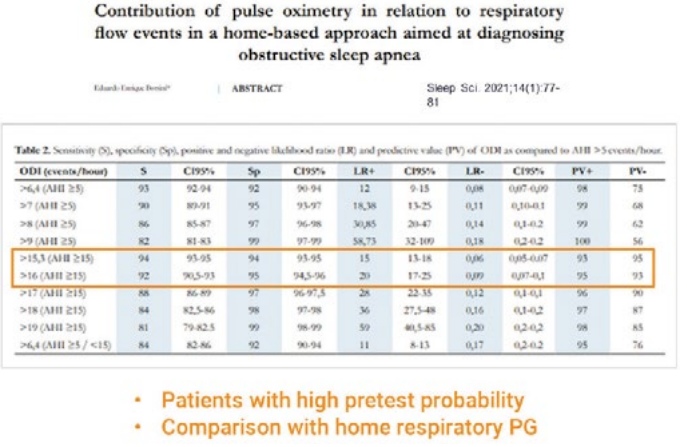
Dr. Rabec: Thank you very much, Euda. I am very glad to be here and thank you for this kind invitation. I am looking forward to discussing various concepts about nocturnal pulse oximetry in breathing sleep disorders.

What important inputs should we consider for oxygen saturation interpretation in patients suspected as having sleep apnea?

Dr. Rabec: There are several important inputs used to interpret nocturnal pulse oximetry. Two key inputs are the threshold, which is used to define a desaturation dip, and the oxygen desaturation index (ODI), which is the number of desaturation dips/hour.

There is some controversy between experts about the relevant percentage of oxygen fall when interpreting oxygen saturation data. However, most papers and most experts use a 3% or 4% threshold to interpret fall in oxygen saturation.

ODI is referring to how many desaturation dips in an hour are significant in terms of screening or diagnosing breathing sleep disorders. Here again there is some controversy between the experts about an exact number. There are multiple indexes that have been developed to help determine what intervals of desaturation dips are significant. In the literature we mainly find values ranging from 10 or 15 desaturation dips in an hour, up to 30 desaturation dips in an hour.



Contribution of pulse oximetry in relation to respiratory flow events in a home-based approach aimed at diagnosing obstructive sleep apnea

Eduardo Enrique Borsini* | ABSTRACT | Sleep Sci. 2021;14(1):77-81

Table 2. Sensitivity (S), specificity (Sp), positive and negative likelihood ratio (LR) and predictive value (PV) of ODI as compared to AHI >5 events/hour.

ODI (events/hour)	S	CI95%	Sp	CI95%	LR+	CI95%	LR-	CI95%	PV+	PV-
>6,4 (AHI ≥5)	93	92-94	92	90-94	12	9-15	0,08	0,07-0,09	98	73
>7 (AHI ≥5)	90	89-91	95	93-97	18,38	13-25	0,11	0,10-0,1	99	68
>8 (AHI ≥5)	86	85-87	97	96-98	30,85	20-47	0,14	0,1-0,2	99	62
>9 (AHI ≥5)	82	81-83	99	97-99	58,73	32-109	0,18	0,2-0,2	100	56
>15,3 (AHI ≥15)	94	93-95	94	93-95	15	13-18	0,06	0,05-0,07	93	95
>16 (AHI ≥15)	92	90,5-93	95	94,5-96	20	17-25	0,09	0,07-0,1	95	93
>17 (AHI ≥15)	88	86-89	97	96-97,5	28	22-35	0,12	0,1-0,1	96	90
>18 (AHI ≥15)	84	82,5-86	98	97-98	36	27,5-48	0,16	0,1-0,2	97	87
>19 (AHI ≥15)	81	79-82,5	99	98-99	59	40,5-85	0,20	0,2-0,2	98	83
>6,4 (AHI ≥5 / <15)	84	82-86	92	90-94	11	8-13	0,17	0,2-0,2	95	76

- Patients with high pretest probability
- Comparison with home respiratory PG

Figure 1

Figure 1 shows data from a paper published by Borsini and coworkers that analyzes different oxygen saturation indexes compared with the apnea hypopnea index. They established that the most accurate ODI threshold to identify patients with an apnea-hypopnea index (AHI) greater than 5 events/h is between 15.3 and 16. That range shows a positive and negative predictive value that is above 90%. However, there are two important limitations of this study to note 1) the population of selected patients had high pretest probability, and 2) the comparator was home respiratory polygraphy, known to underestimate AHI.

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

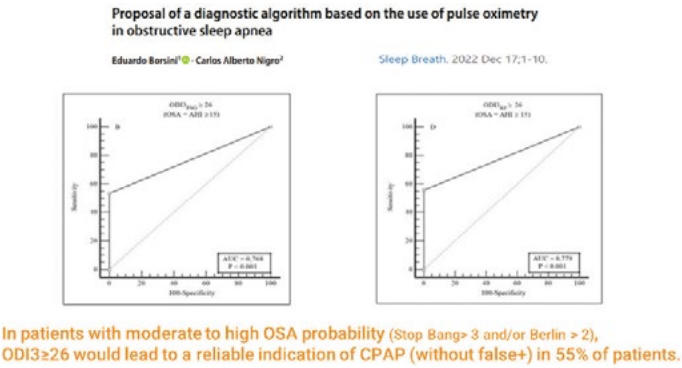


Figure 2

Results of another publication by the same group are shown in Figure 2. In this paper they define that in patients with moderate to high probability of OSA, an oxygen desaturation index of 3% (ODI3) higher than 26 times/h will lead to a reliable indication of CPAP, without a false positive in 55% of patients.

Based on this data, the authors proposed an algorithm (Figure 3) for screening and managing OSA, by integrating validated specific questionnaires (Stop Bang, Berlin), nocturnal pulse oximetry, and PG/PSG. This algorithm, more cost-effective than the approach currently used (i.e., systematic PG/PSG) had an accuracy of more than 90% in predicting sleep apnea qualifying for CPAP treatment.

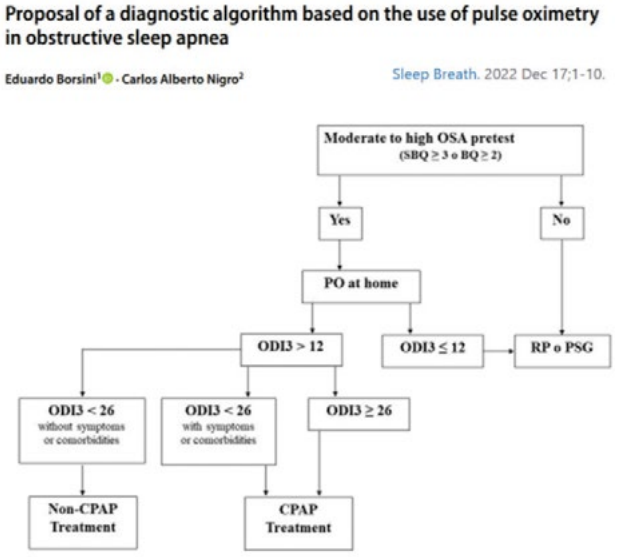


Figure 3

Can you talk about the effects of comorbidities and pulse oximetry interpretation?

Dr. Rabec: Comorbidities do not often impact the quality of data obtained when performing nocturnal pulse oximetry. The exception to this is obesity because the accuracy and feasibility of oximetry is less good due to potential signal loss.

Conversely, comorbidities do impact the decision-making process. If we look again at Figure 3, as the presence of comorbidities impacts the prognosis of OSA it has a major influence in the threshold of ODI used to indicate CPAP.

This is a very important issue, because sleep apnea is not a unique disease, but a syndrome. Comorbidities and clinical symptoms have a considerable effect in the decision-to treat or not OSA.

How is technology impacting the diagnosis of Obstructing Sleep Apnea (OSA)?

Dr. Rabec: In the past, polysomnography was the standard tool to evaluate patients suspected as having breathing sleep disorders. But polysomnography has several limitations. First, we need to hospitalize the patient, which is expensive. The second problem is the number of sensors. The third one is the cost of the device and the impossibility of testing more than one patient per night. Recent progress showed that is possible to simplify the diagnosis. Some of the developments include new available tools, complex algorithms, and more recently the use of artificial intelligence to improve and simplify the diagnosis of sleep apnea at home.

Another important issue is the night-to-night variability in terms of apnea hypopnea index in patients. Technology is helping us move beyond the limitation of evaluating only one patient per night in the hospital, which is a situation that does not exactly simulate real-life sleeping conditions, to evaluate patients at home during several nights. These new appliances can be used in combination with currently available tools, like pulse oximeters.

Can you speak to the importance of pulse oximetry in patient follow-up?

Dr. Rabec: I think that it's very important to emphasize that pulse oximetry is a crucial tool, not only to detect hypoventilation and sleep apnea, but also to monitor patients once they have been diagnosed. If a patient is being treated with a respiratory device, it is crucial to utilize pulse oximetry in order to know a patient's oxygen saturation. Oxygen saturation is a crucial tool to help physicians detect abnormalities and to evaluate treatment efficacy.

In my experience with patient follow up, oxygen saturation helps us understand the patient's condition and long-term treatment options.

Closing

Nocturnal pulse oximetry is essential as a diagnostic tool to screen for OSA in patients who are high risk. It helps physicians prioritize patients for polygraphy and polysomnography and it is a main tool in the decision-making process to indicate home ventilation or long-term oxygen therapy. Further studies are needed to define the role of nocturnal pulse oximetry as a diagnostic tool to confirm or to exclude sleep apnea and to introduce CPAP in our patients.

Additionally, nocturnal pulse oximetry is a main tool in assessing the efficacy of CPAP treatment and other respiratory devices.

View the full video interview on Nonin.com/resource/nocturnal-pulse-oximetry-for-osa

Staying on Top of Respiratory Technology and Techniques in the NICU

Ongoing Clinical Education and Training Key to High Quality Care and Healthy Patient Outcomes

Winnie Sywulak, BS, RRT-NPS and Anduin Anderle, RN

As medical technology continues to advance, offering innovations in both diagnostics and therapeutics, it is more important than ever to ensure clinicians have the training they need to use equipment effectively and safely—and in a world of clinical staffing shortages, efficiently.

Two areas where technology is rapidly evolving to meet patient needs is in respiratory care and the neonatal intensive care unit (NICU). The COVID-19 pandemic has demonstrated the importance of effective and safe ventilation. When it comes to babies born prematurely, respiratory support and NICU care converge as NICU teams work to help preemies' immature lungs develop outside of the womb.

In this article, we look at how clinical education and training is critical to high-quality outcomes in respiratory care and the NICU environment.

Keeping Pace with Healthcare Innovation

In 2021, the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) approved or authorized 103 novel (new) medical devices. Overall, the CDRH oversees 236,000 regulated devices from 25,000 device manufacturers.[1]

With each new technology that enters a hospital comes the need for staff education and training. Patient safety is at risk when clinical staff do not understand how to properly use a device. But keeping up with education in a rapidly changing world is not easy, as the authors of a recent article published in *The Online Journal of Issues in Nursing* state:

> "Advancing the mission of nursing education for a future that we cannot yet fully conceive is a daunting task, but leading and promoting change is not discretionary. Today, awash in accelerated knowledge creation and sweeping innovation, professionals in the healthcare and higher education find themselves facing isomer-like challenges to provide value, positive outcomes, access, and affordability for their consumers—or become obsolete."[1]

Memorial Hermann Health System in Houston experienced "an instance of actual patient harm due to staff unfamiliarity with a medical device," which prompted the health system to "design a 'fail-safe' process to analyze and scale training for use of medical devices, with a risk assessment tool predicting the potential severity and frequency of harm to patients."[1]

Under the fail-safe process, educational rigor, tracking, and accountability management are scaled to the level of device risk. Its objective is to "ensure the competence of clinical staff in the operation of all approved new and updated medical devices." Based on its success, the process became an approved procedure and practice standard at Memorial Hermann Health System.[1]

Research has shown how proactive, ongoing education and training is key to patient care and safety. Case in point: a urology unit in a large acute NHS hospital introduced a new training program, including a "time out" training day "that covered medical device and mandatory training, alongside evidence to support nurses' revalidation and a forum for peer support." Following program implementation, medical device training competency among urology staff increased from 65% to 97% across all staff groups, including nurses and healthcare assistants.[2]

Challenges to care delivery in the NICU

NICU teams are tasked with caring for the smallest, most fragile patients with under-developed bodies, including lungs unprepared to breathe on their own. Neonatal respiratory distress syndrome (RDS) is the leading cause of death in

Winnie Sywulak, BS, RRT-NPS, is the Senior Marketing Manager for Dräger's Respiratory Care Solutions in North America. Anduin Anderle, RN, is the Marketing Manager for Dräger's Neonatal Care & Thermoregulation Solutions in North America.

premature infants.[2] While tremendous strides have been made in neonatal respiratory care over the decades, NICU teams still struggle with supporting pre-term babies' fragile lungs to prevent long-term health consequences.[3]

Respiratory equipment manufacturers continue to advance in ventilation technologies and treatments aimed at improving both short and long-term outcomes for premature infants. But the complexity of some advancements may overcome the benefits for clinicians using them at the bedside.

"Understanding the complexities of care given to any neonate requiring mechanical ventilation is essential to deliver safe and effective care," states the author of Understanding Neonatal Ventilation: Strategies for Decision Making in the NICU. "The range of modes and parameters in ventilation practice can pose a challenge for both the novice nurse and for those more experienced who require an update of knowledge."[3]

Healthcare organizations striving for value-based care must ensure their clinical teams are leveraging devices, including ventilators, effectively and safely to improve outcomes and reduce complications. Neonatal ventilators featuring smart applications and monitoring tools can help clinicians facilitate decisions, but only in conjunction with adequate instruction and support.

Supporting NICU teams through technology, education and training

There are many considerations when pursuing improved mechanical ventilation education and training among NICU staff members, including respiratory therapists (RT) and nurses (RN).

When a new mechanical ventilator is introduced to the NICU, the manufacturer will provide initial in-servicing and training on device usage. Equally important is the availability of ongoing education to reinforce best practices and train users on new techniques.

In a world of healthcare staffing shortages, where caregivers must do more with less, it is critical to make continuing education opportunities convenient and accessible. This is particularly true of the respiratory therapy field, where growing demand for RTs has drastically outpaced the number of current RTs, and myriad factors will exacerbate the shortage in the years to come (e.g., decreased RT program enrollment, 92,000+ RTs retiring by 2030, etc.).[3]

One option for NICUs is to encourage their RT team members to take part in online Continuing Respiratory Care Education (CRCE) courses that promote effective and safe use of neonatal mechanical ventilation. Through its "A Breath Ahead" platform, Dräger offers free online courses accessible 24/7 where RTs can earn CRCE hours to further develop their skills and meet licensing requirements. In 2021, the platform had more than 72,000 complimentary CRCE-accredited course completions by respiratory professionals.[3]

Neonatal respiratory care CRCE course topics on A Breath Ahead include the following related to mechanical ventilation, among many others:

- Use of Airway Pressure Release Ventilation (APRV) in pediatrics and neonatology
- The theory, clinical application, and operating principle of Mandatory Minute Ventilation (MMV) in neonates
- Caring for severe bronchopulmonary dysplasia (BPD) patients
- Volume-Targeted Ventilation in neonatal care

"CME (continuing medical education) is crucial to the prosperity of health care providers — it allows a practitioner to learn and discover viable ways to improve on the patient care they deliver and effectively manage a career in the ever-changing landscape of the medical industry," says the American Association of Continuing Medical Education.[3]

Conclusion

Technological advancements in healthcare delivery broaden the reach of what clinicians can achieve when caring for patients. Looking at mechanical ventilation, it is incredible to see how far oxygen delivery has come since Heinrich Dräger patented the very first ventilator, the "Pulmotor," in 1907. Today, NICU teams provide a level of precision in respiratory support that was unimaginable 100 years ago, enabling extremely low birth weight (ELBW) and extremely-low-gestational-age neonates (ELGAN) to survive and thrive.

With advancement comes responsibility — of ventilator manufacturers to educate and train NICU clinicians on effective and safe use of their devices — and for NICU clinicians to continue to refine their knowledge and skills based on the latest research and literature.

Fortunately, there are many continuing education opportunities available to NICU teams, including RTs, from in-person conferences and events to webinars and presentations.

Healthcare leaders should encourage their NICU clinicians to pursue these opportunities for individual professional development, but most importantly, to minimize the risk for errors and provide patients with the highest quality care available.

References

1 Center for Devices and Radiological Health (CDRH), 2021 Annual Report, https://www.fda.gov/media/155793/download

2 Kavanagh, J.M., Sharpnack, P.A., (January 31, 2021) "Crisis in Competency: A Defining Moment in Nursing Education" OJIN: The Online Journal of Issues in Nursing Vol. 26, No. 1, Manuscript 2, DOI: 10.3912/OJIN.Vol26No01Man02, https://doi.org/10.3912/OJIN.Vol26No01Man02

3 Hercules P, Shabot MM, Ryan T, Ratcliff S. Optimizing Fail-Safe Use of Complex Medical Devices. AACN Adv Crit Care. 2019 Spring;30(1):25-39. doi: 10.4037/aacnacc2019400. PMID: 30842071.

4 Hercules P, Shabot MM, Ryan T, Ratcliff S. Optimizing Fail-Safe Use of Complex Medical Devices. AACN Adv Crit Care. 2019 Spring;30(1):25-39. doi: 10.4037/aacnacc2019400. PMID: 30842071.

5 Shields R, Latter K. Improving the uptake of medical device training to promote patient safety. Nurs Stand. 2019 Aug 31;35(1):31-34. doi: 10.7748/ns.2019.e11219. Epub 2019 May 30. PMID: 31736285.

6 Dyer J. Neonatal Respiratory Distress Syndrome: Tackling A Worldwide Problem. P T. 2019 Jan;44(1):12-14. PMID: 30675087; PMCID: PMC6336202.

7 Davidson L, Berkelhamer S. Bronchopulmonary Dysplasia: Chronic Lung Disease of Infancy and Long-Term Pulmonary Outcomes, J Clin Med. 2017 Jan; 6(1):4. https://www.ncbi.

nlm.nih.gov/pmc/articles/PMC5294957/
8 Petty J. Understanding neonatal ventilation: strategies for decision making in the NICU. Neonatal Netw. 2013 Jul-Aug;32(4):246-61. doi: 10.1891/0730-0832.32.4.246. Erratum in: Neonatal Netw. 2013 Nov-Dec;32(6):415. PMID: 23835544. http://www.academyofneonatalnursing.org/Ventilation/UnderstandNeoVent.pdf
9 Why We Need More RTs – and How to Help, https://www.morerts.com/growing-need/
10 2022 Global Neonatal Devices & Neonatal Care Industry report, Frost & Sullivan, https://www.draeger.com/Library/Content/Draeger-Award-Write-Up-2022.pdf
11 What is CME, American Association of Continuing Medical Education, https://aacmet.org/cme/what-is-cme/

Alternative Screening Tools to Identify COPD Patients

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. This article is a follow-up interview with Alex Stenzler, the Chief Science Officer of Monitored Therapeutics, a telehealthcare company. He is also the President of 12th Man Technologies and was the former Vice-President of Advanced Technologies for Viasys Healthcare, Cardinal Health and CareFusion 207, Inc.

I'd like to follow up from our last interview and further explore spirometry testing in the primary care physician (PCP) office. Before going into the interview, please remind our readers who Monitored Therapeutics is and what it does.

Alex Stenzler: Monitored Therapeutics (MTI) is a disease management company focused on collecting physiologic data from remote sensors. MTI services three segments of the healthcare market. The primary segment we serve is the disease specific monitoring needs of healthcare institutions. For example, we monitor pre and post lung transplant patients for a number of institutions where we alert caregivers to sudden drops in lung function allowing them to intervene earlier. We also monitor patients with asthma, COPD, interstitial lung disease and cystic fibrosis.

We have a clinical trials group that serves our second segment for the pharmaceutical industry. Our solutions are utilized worldwide in studies remotely monitoring lung function as an endpoint from patients at home, as we manufacture one of the very few diagnostic spirometers that has been tested and certified for home use.

The third segment brings our revolutionary avatar-assisted, lab-quality spirometry GoClinic platform into the primary care physician space, allowing patients with lung disease to be diagnosed earlier and then managed with home monitoring and supported by educational materials right on their smartphones. The GoClinic is the starting point of an effective respiratory continuum of care, allowing clinicians to easily test, evaluate, and effectively manage their patient's lung health.

In our last interview you discussed diagnostic spirometry measurements in the PCP office as the best location for identifying patients with chronic lung disease. However, there are reported simpler ways to identify patients with COPD using a series of questions and the measurement of just Peak Expiratory Flow. Are you familiar with that approach?

Alex Stenzler: Yes. This is a relatively new alternative screening tool introduced for primary care offices called the COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk or "CAPTURE" that was developed with support from the NIH. This was designed by a national group of researchers to identify adults with COPD symptoms severe enough to treat, but who haven't received a diagnosis. The study was conducted at seven U.S. clinical research network centers from October 2018 to April 2022; the trial analysis involved adults, ages 45-80. They screened 4,325 people using the CAPTURE algorithm and then had all 4,325 people do formal diagnostic spirometry testing to confirm the presence of COPD or identify normal lung function.

Do you believe this "CAPTURE" program will be effective?

Alex Stenzler: While this might seem like a simple way to screen for COPD, it turned out to not be very effective. Let me share a table that contains the results from that study. With a population size of more than four thousand participants, it was a sizable endeavor. Note that the CAPTURE program missed fifty-seven participants who actually had COPD based on diagnostic spirometry measurements. However, more importantly, it mis-diagnosed 479 participants, indicated as having COPD, while they were actually normal and who, with only CAPTURE screening, would have been referred for a pulmonologist evaluation.

	CAPTURE			
Spirometry Diagnosis	Accurately Diagnosed as Normal	Mis-Diagnosed as Normal	Accurately Diagnosed with COPD	Mis-Diagnosed with COPD
COPD	3736	57	53	479

Not only were these normal participants burdened with the thought that they had lung disease while waiting for an appointment with overburdened pulmonary practices, but further overburdened the pulmonologists with unnecessary referrals at a significant cost to them and insurers. Additionally, 47% of the participants who were diagnosed with COPD by the gold standard of spirometry had only mild COPD that probably could have been adequately managed by the PCP with limited guidance. The researchers do admit that the CAPTURE program has a low sensitivity (32.1%) as evidenced by the high false positives.

Therefore, we continue to strongly believe that the triage for patients with respiratory diseases is best and most cost effectively performed in the PCP office using a diagnostic spirometer, assuming that the quality of the data can match the quality of data performed in the pulmonologist's office or

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

hospital laboratory. I've included the references to the CAPTURE publications at the end for your readers.

They used Peak Flow meters in CAPTURE. Do you believe therefore that Peak Expiratory Flow is inadequate as a diagnostic or screening tool?
Alex Stenzler: The CAPTURE researchers specifically explored the diagnostic accuracy of Peak Flow Meters and noted that Peak Flow had a low sensitivity, reinforcing the importance of using diagnostic spirometry and not a Peak Flow Meter in the PCP office. While a Peak Flow Meter may have some uses, diagnostic spirometry is the only test to accurately detect lung disease.

If all the PCP offices you identified in our previous interview begin to perform spirometry testing, the number of bills to payers for testing will increase significantly. Do you believe there will be pushback from the payers that reimburse the physicians for the tests?
Alex Stenzler: I am certain that all payers are concerned with the potential for overuse of any test. Considering that close to 80% of people with COPD are undiagnosed, a program to identify them will certainly increase the number of spirometry tests performed. However, since early diagnosis is expected to reduce the slope of disease progression through earlier disease management, it would be anticipated that the total long-term cost of care for this population overall and therefore payer costs, will be lower.

How can you assist the PCP with identification of the appropriate patients to screen for lung disease so they don't abuse the system and risk an adverse payer response?
Alex Stenzler: As a starting point, MTI has collaborated with pulmonologists on a suggested list of "Indications for Spirometry" so that the PCP office would consider these when deciding to perform tests. These include individuals who are:

1. Older than 40 years of age with a history of smoking.
2. Or Have dyspnea and/or chronic cough or sputum production.
3. Or have a history of recurrent lower respiratory tract infections.
4. Or have a history of exposure to risk factors such as chemical or particulate exposure.
5. Or have a history of wheezing, shortness of breath, chest tightness, and cough that vary in intensity over time.

These are clear indications. Once a PCP has decided to perform spirometry testing, MTI has the patient fill out a more detailed respiratory history questionnaire. The respiratory history questionnaire collects relevant exposure information, exacerbation history, symptoms, and potential interventions currently being used to treat their symptoms. This information is then included in the report generated by the platform and made available to insurers if requested.

Obviously, if the spirometry detects lung disease, then the test was justified. However, if the test results are normal, and there was no history to suggest a need for the test, that will also be obvious.

What do you think will be the impact on chronic disease management by screening at PCP offices?
Alex Stenzler: The first principle regarding the importance of screening is that if you don't know the disease is there, you can't manage it. I firmly believe that if we can identify lung disease early, and most importantly, where the patients are most likely to be seen, we can have a significant impact. Getting gold standard spirometry in the PCP office is the key to effecting this impact.

How will MTI's remote monitoring programs interplay with the respiratory disease evaluation screening at the PCP office?
Alex Stenzler: MTI's semi-automated workflow platform for the PCP guides the staff through all of the steps for patient respiratory history, disease severity questionnaires, as well as pulse oximetry and pre and post bronchodilator spirometry. It then generates a report for the PCP that includes all the collected information and provides an ATS/ERS clinical impression. Depending on the patient's specific disease and severity, the PCP has the option of referring the patient for a range of remote support elements including education, medication monitoring or physiologic monitoring. If patient specific threshold criteria are met as identified by the ATS, it will advise the PCP to consider referring the patient for a pulmonologist evaluation. This approach integrates the PCP screening program directly with the MTI remote monitoring programs.

It seems like a more holistic approach to chronic disease. Is that a reasonable interpretation of your goals?
Alex Stenzler: Most respiratory diseases, unlike many other diseases, cannot be cured, and the best outcome is to alter the slope of decline with early identification that is supported with proper medication adherence, education, remote monitoring and behavior modification. We believe that if we don't provide all of these management aspects, it will not return the long-term outcomes we seek. On the other side, if we can successfully deliver all of these components in a disease management platform, we can have significant impact for these patients, lower overall healthcare costs, and improve the quality of life for them.

Will you be willing to come back in a year to give us an update on how the program progresses?
Alex Stenzler: I would very much like to speak with you again in a year and inform your readers as to our progress in changing the lives of people with chronic diseases.

References

1 Fernando J. Martinez, MD, MS, et al., Discriminative Accuracy of the CAPTURE Tool for Identifying Chronic Obstructive Pulmonary Disease in US Primary Care Settings. JAMA. 2023;329(6):490-501
2 Fernando J. Martinez, MD, MS, et al., A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2017 Mar 15;195(6):748-756.

Making our world more productive

Comprehensive Solution For Nitric Oxide Inhalation Therapy

Complete with 24/7 support – peace of mind for critical care providers.

National Reach, Local Service

NOXIVENT® (nitric oxide) gas for inhalation, along with the NOxBOXi® delivery system, offered with customizable, consumption-based billing, is backed by Linde's national network, responsive support and reputation for medical gas distribution.

The NOxBOXi nitric oxide gas delivery system is reliable, accurate and easy to use. System features include:

- Real-time, closed-loop monitoring with auto-adjusting alarms
- Pre-packaged, configured circuits ready for use with validated ventilators
- Disposable circuits, including the NOxFLOW module, for easy clean up
- Auto-cylinder changeover with alerts, helping you avoid therapy interruptions

Our Commitment

- Integrated gas delivery system for inhaled nitric oxide therapy
- 24/7 service and support
- Simplified billing process
- Reliable and responsive distribution network
- Established reputation for quality and customer satisfaction

A summary of the prescribing information, including indication and other important safety information, is on the adjacent page. For the full prescribing information, visit www.noxiventus.com.

Call 1-844-445-4633 today for a complimentary requirements evaluation.
www.noxiventus.com

Making our world more productive

NOXIVENT® Indication and Important Safety Information

Indication

Noxivent® is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

Important Safety Information

Contraindications
Noxivent is contraindicated in neonates dependent on right-to-left shunting of blood.

Warnings and Precautions
Rebound: Abrupt discontinuation of Noxivent may lead to worsening oxygenation and increasing pulmonary artery pressure.

Methemoglobinemia: Methemoglobin levels increase with the dose of Noxivent; it can take 8 hours or more before steadystate methemoglobin levels are attained. If methemoglobin levels do not resolve with decrease in dose or discontinuation of Noxivent, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide: Monitor nitrogen dioxide (NO2) levels. Nitrogen dioxide may cause airway inflammation and damage to lung tissue.

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

Adverse Reactions

The most common adverse reaction of Noxivent is hypotension.

Drug Interactions

Nitric Oxide donor compounds may increase the risk of developing methemoglobinemia.

Administration

Use only with a calibrated, FDA-cleared NOxBOXi® Nitric Oxide Delivery System (NODS). Refer to the NODS labeling for needed information on training and technical support for users of this drug product with the NODS.

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

Distributed by Praxair Distribution, Inc., a Linde Company
10 Riverview Dr. Danbury, CT 06810
Phone 844.445.4633, www.noxiventus.com

The Linde logo, the Linde wordmark NOXIVENT, NOxFLOW, NOxBOXi and MAKING OUR WORLD MORE PRODUCTIVE are trademarks or registered trademarks of Linde Inc. or its affiliates. The information contained herein is offered for use by technically qualified personnel, at their discretion and risk, without warranty of any kind.
© Copyright 2021, Linde Inc.

Non-invasive Respiratory Support

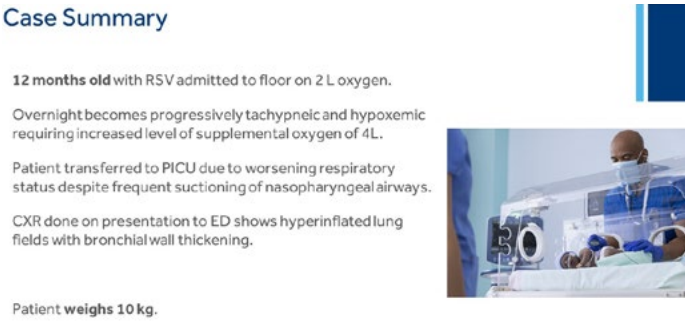
In this feature, Respiratory Therapy adapts educational webinars delivered by clinicians and healthcare providers about the actual application of specific products and therapies. The webinar adapted below was presented by Raymond Nkwantabisa, MD MSc FAAP.

Once again, thank you so much for having me and happy Respiratory Week to all the RTs in the audience. RTs hold a very special place in my heart because I remember as a resident, there were so many nights I was on call without the attending in-house. Those were the dark days. My RTs were always coming to my rescue with regards to what to do with these patients with respiratory illnesses.

We've come a long way with non-invasive modes of respiratory support. Because I remember in the early 2000s when I was a fellow in critical care, a lot of the bronchiolitics who came in were intubated. Now, most of those patients actually are able to make it out of the hospital without intubations.

For the next 30-40 minutes, what I'd like to do is to have this conversation reviewing the path of physiologic underpinnings for the different levels of respiratory support that is used. We'll go over the indications, the benefits, and the limitations of these various modes of non-invasive support, and then we'll touch base on how do you know when your patient isn't doing too well on non-invasive and maybe you should start thinking of potentially intubating the patients?

I think the best way to approach this is to use a case scenario that is fairly common to most RTs in the audience, especially as we go into the winter months. What I'm going to do is I'm going to use this case.



It's a kid who came through our ICU and use this case to highlight some of the key teaching points and principles that we need to be aware of whenever we decide to use non-invasive respiratory support. The case is a 12-month-old with RSV who comes to the hospital through the ED, ends up on the floor. It's when two leaders initially doing well and then progressively start getting worse. The floor starts to ramp up the level of nasal cannula support and when they hit 4 liters, they call the ICU to let us know that, "Hey, we've done everything we can. We've suctioned, and still we're not doing much better. The X-ray that was done in the ER just shows hyperinflated lungs with some mild peribronchial wall thickening, but no focal infiltrates.

This kid weighs about 10 kilos, and so the ICU decides to go ahead and accept this kid. The kid comes to the ICU and is just as described, very tachypneic, retracting. It started on high-flow at 6 liters, 40%. This is through the night and by the morning, we are up to 10 liters, 40% FiO2. This is usually the time that people will try some bronchodilators, plus or minus, because typically you get the sign-off from the ED saying that, "Oh, the kids seem to respond to albuterol," so you give it a shot, but things are still not getting any better.

You keep ramping up your high-flow, and now you're at 15 liters. At this point, you decide to repeat the X-ray. What you see is now you're beginning to see some scattered areas of opacities. You get a blood gas that shows that your ventilatory status is slowly beginning to worsen with your CO_2 now climbing up in the high 50s with a little bit of a base deficit. By this time, your patient or the baby looks quite agitated, is huffing and puffing. You go up to 20 liters, your FiO2 is at 70%. Typically, these are parents who have been up a few nights before the baby ends up in the ICU. You find yourself in a situation where you're dealing with a parent who hasn't slept for a few days and a child who is very agitated. You get calls from your nurse at the bedside saying, "Hey, can you do something to make the situation a little better? Because mom is on the edge." You throw in a little bit of sedation, maybe a little bit of Precedex. We load those just to keep the baby a little calmer. But despite these efforts, your patient is still quite tachypneic and things are not getting any better.

Your patient's oxygen saturations now start to drip down to the low 90s. You decide that, well, we're not making much headway with non-invasive, so you decide to try full-phase BiPAP support. You put the kid on the BiPAP of 10/5, but you still have a pretty high oxygen requirement. You're now up to almost 80% on your FiO2. You repeat a couple of gasses after you have being on BiPAP and you're not seeing much headway. But things are not

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

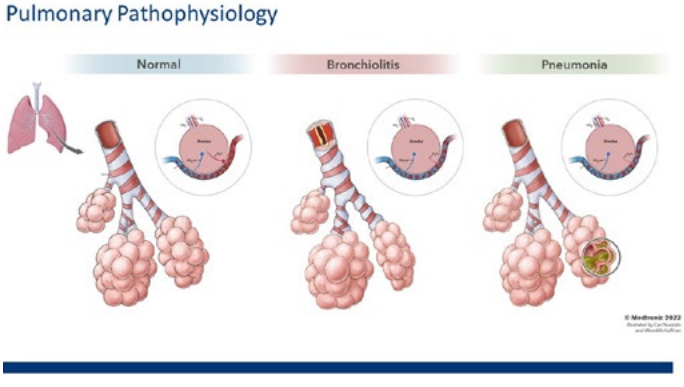
getting really worse as far as gasses go, but they're not really improving. Typically, you deal with this till the early hours of the morning, so typically around 4:00 AM, you think, "Okay, I'm going to try to lay down a little bit because I've been up on my feet all night and just to give my back a break, and my feet a break," when you get a call from the bedside nurse saying, "Hey, I think my patient's respiratory rate is beginning to decline."

You tell her to stop the Precedex and call you back in 30 minutes to see how things are going. You get a call saying, "Hey, can you please come to the bedside because respiratory rate isn't getting any better?" You do a gas, and the gas is, as you see, 7.15 and CO_2 is 90. This is where I'm going to stop this scenario. What we're going to do is we're going to pick it apart and use this as the foundation to walk through the different modes of non-invasive support that we clinically use.

Whenever we decide to support our patients, there are a few things we're trying to do. The rationale behind respiratory support can be broken down into these four key objectives. We are either trying to modify the alveola gas composition. By that, I mean we're trying to increase the fraction of inspired oxygen. As our patient's lung pathology worsens, we get to a place where because of increase in atelectasis or increase in size of infiltrates, you start to lose your FRC.

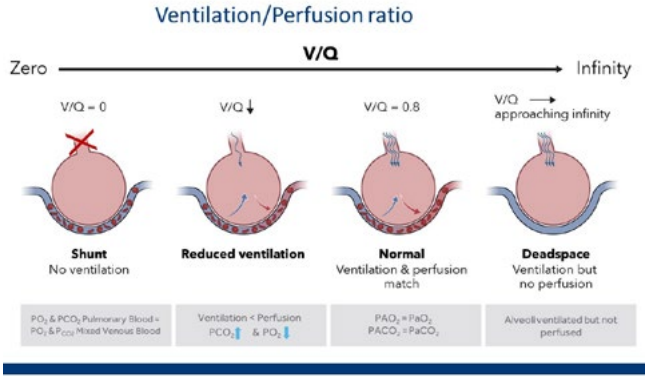
At this point, we need to use a modality that will help us maintain end-expiratory lung volumes. This is where the high-flow nasal cannula, CPAP, BiPAP and intubations come into play. If the patient continues to worsen and the lung compliance continues to worsen, now the lungs's become much stiffer, much heavier to move. As a result of that, we need to start using modalities that help with the work of breathing as far as the respiratory muscle function goes. This can be achieved either with a non-invasive modality or an invasive modality. But since this session is primarily focused on the non-invasive modes of support, that's what I'm going to limit myself to. If things don't get any better and you have near complete or near total wide out, then you have to consider ECMO or some other form of heart-lung bypass to support your patient.

Now, before I go into the specific modes, I want to just spend the next couple of slides quickly reviewing some basic lung pathophysiology just to make sure that we are all on the same page because I recognize that I'm talking to an audience with different levels of expertise.



Going into the winter, the two most common pathophysiology that we'll be dealing with in our world as pediatricians is either we're dealing with bronchiolitis, which is an inflammation of the smaller airways that results in airway edema, increased secretions, and slopping off of the epithelial cells as they're killed by the virus, which leads to obstruction of the airway. There is a subset of patients who have reactive airway disease or bronchospasm because of their strong family history of asthma. These patients will truly benefit from some bronchodilator therapy. But for the most part, most of these patients don't really respond to bronchodilators because the underlying pathophysiology is not bronchospasm, but airway occlusion from all the inflammatory debris. The other common diagnosis that we are going to be dealing with as we walk into the winter is pneumonia, which is basically an inflammation of the alveola with a deposition of cellular debris that results in the alveola being filled with inflammatory debris making it difficult for gas exchange to take place.

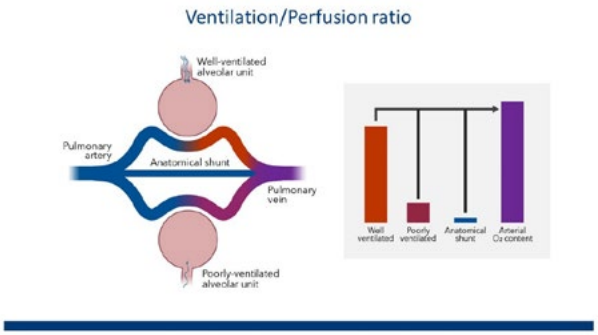
I want to quickly go over V/Q matching because the saturation of oxygen that leaves the lung is influenced by these different pathophysiologies that we're going to quickly review. Normally, when everything is working well, your V/Q ratio is about 0.8. This is where you have a normal PaO2 and normal PaCO2 on your blood gasses. Now, if for whatever reason, my lung pathophysiology is such that my ventilation is reduced, then my V/Q ratio drops to less than 0.8.



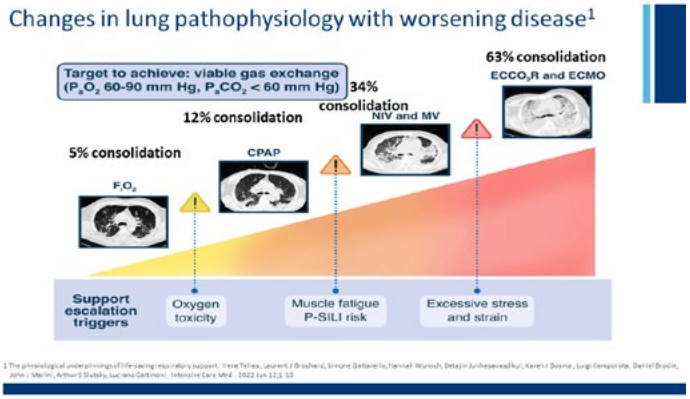
What is reflected in my blood gas is that I see that my PCO2 levels start to rise and my PAO2 levels start to drop. The extreme of this is when my alveola completely gets filled up with cellular debris or with fluid to the degree that I don't have much being able to basically diffuse across to my capillaries. In these situations, you have what is known as a shunt, or an intrapulmonary shunt. The classic hallmark of a shunt is that you crank up your FiO2, and clinically, you don't really see your oxygen saturation getting any better because there's nothing making its way through here to your capillaries to have gas exchange. The other extreme is a dead space, and that's when the degree of ventilation is greatly larger than the rate of perfusion for that given alveola unit. That is seen when your lungs are extremely hyperinflated or for whatever reason, your blood flow to the matching alveola is compromised.

The net oxygen saturation that leaves your lung is the combination of the blood coming from well aerated lung units with great V/Q components combined with those with poorly ventilated or poor V/Q components. Now, normally, about 3% of the cardiac output goes through the lungs without seeing any gas exchange. But as our lung pathophysiology worsens, this fraction starts to increase. What you begin to see is that your net arterial oxygen content leaving the lungs diminishes. As we go through our patient, we're going to see what happens to our patient from

the time they hit the door on the floor through their calls in the ICU as far as these different segments of the lung go.



I'm going to borrow this slide from Gattinoni's paper to highlight what are the changes that take place as our patient's conditions worsens.

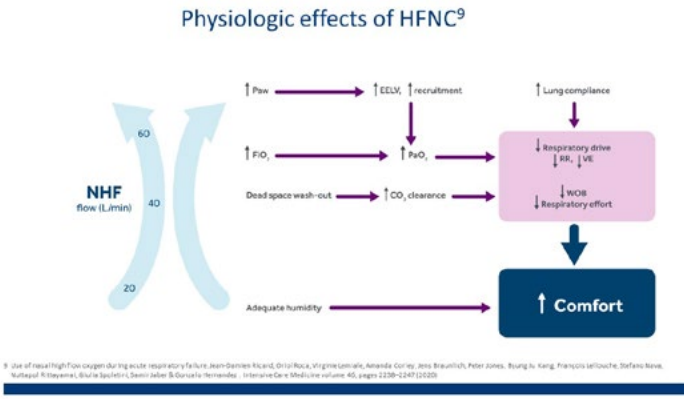


From left to right, we're going to see what happens when our lung consolidation increases from 5% on the left side all the way to 60% or more on the right side. We're going to see what steps we need to take to try to get our arterial blood gasses to stay between 60 and 90 as far as the PaO2 goes and to try to keep our PaCO2 less than 60. Generally, with patients with less than 5% consolidation, your FRC is fairly okay. Your work of breathing is not too terrible. You can get away with nasal cannula oxygen support up to a point beyond which if you keep them at 100% FiO2 for a long time, you run the risk of oxygen toxicity and also absorption atelectasis, because the 100% FiO2 washes out the nitrogen in the alveoli, and over time, you make them more prone to atelectasis. Once you start to cross the 10% mark, you have to start thinking of modalities that can actually help you maintain end-expiratory volumes in your patient. This is where high-fluid nasal cannula, CPAP comes into play because these are great modalities for you to help keep things open to facilitate gas exchange. Now, if your patient continues to worsen as far as the lung pathophysiology goes and you start to see more opacities, your FRC continues to drop, your lung compliance continues to worsen, your lungs becomes stiffer and heavier and harder to move, resulting in increased work of breathing. Now you start to engage more of your accessory muscles or your patient starts to engage more of their accessory muscles, and now they run the risk of running to respiratory muscle fatigue. You may also see wild swings intrathoracic pressure as they worsen push them at risk for the spontaneous breathing-induced lung injury. This is where you have to think of stepping up to a BiPAP modality where they get help not just with maintaining end-expiratory lung volumes, but also help to reduce the work of breathing when they try to inhale. Beyond 30%, you're usually at a place where now you have to think of intubating these patients because non-invasive is not going to cut it anymore. We all have had this experience where the patient comes in, they go into ARD as you intubate them, and you run PAP too, depending on your institution, pressure control, you go to bi-level or the oscillator. If things don't get any better, you find yourself in a realm where now your only hope for your patient is putting them on ECMO.

Whenever we are called to the bedside to help a patient in respiratory distress, the key things that we need to keep in mind as we try to select the different modalities is what am I dealing with here? Am I dealing with increased dead space? Am I dealing with a long pathophysiology that results in a lot of the deoxygenated blood making its way to the systemic circulation without any gas exchange. What is my patient's work of breathing like? What is the status of the lung? Am I dealing with lung volumes that are decreased and that need to be recruited, or do I need to intubate them? Then also what we do is not without harm.

We'll talk about the limitations for the different modes of non-invasive support. The simplest form is nasal cannula. They come through the door, we put them on nasal cannula. This works best for patients with normal pulmonary mechanics and whose work of breathing is not too terrible. The key point here is we try not to use high FiO2s for a long time because of the risk of oxygen toxicity. High-fluid nasal cannula has made a world of difference in my world in pediatrics because it affords us the ability to independently adjust how much FiO2 I'm giving the patient, the flow, and also it gives me the ability to humidify the oxygen, which makes it much more comfortable for my patient. Now, the key principle here is to make sure that the flow that you said is higher than your patient's inspiratory flow demand. The reason why this is important is because that enables us to wash out CO_2 from the airways. The higher flow enables us to stent the patient's airways as well, making it a little bit easier for them to maintain an expiratory volumes. Also the net result of all this is that the work or breathing gets less, the patient gets more comfortable, and their respiratory rate actually starts to decrease.

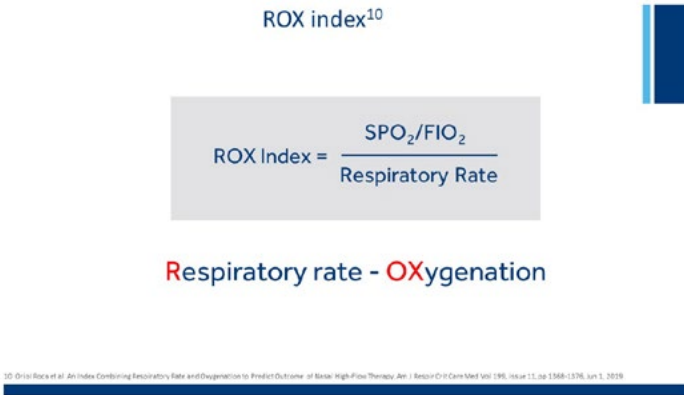
In my world in pediatrics, for patients less than 10 kilos, we usually start with flows anywhere from 1-2 liters per kilogram per minute. Anything higher than that is a little bit uncomfortable because of the rate of flow. For patients who are larger than 10 kilos, we typically will increase by 0.5 liters per kilogram per minute.



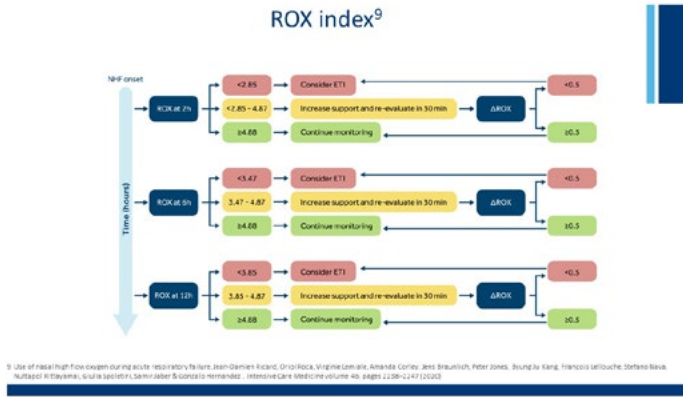
The net effect or the net benefit of high flow is that on this side, you can see I can independently adjust the flow rate that my patient needs to decrease their work of breathing. I can increase how much FiO2 they need to meet the hypoxic needs. The net result of that is that by increasing the FiO2, I can increase my arterial PaO2 by increasing the mean airway pressure.

By stenting the airways and the alveoli, I increase my end-expiratory lung volume, improve my lung recruitment, thereby improving my lung compliance. The net result is I have a patient whose respiratory rate goes down, work of breathing goes down, and they're generally more comfortable if this works well for them. Typically within an hour, an hour and a half, if high-flow is working, you should see your patient's work of breathing get better, saturations get better. If you don't see this happen after an hour, we'll talk about what to do for that patient in just a minute.

How do I know if my high-flow is working? In the adult world, there's this index known as the ROX index that is used. It's basically the ratio of your patient's oxygen saturation on your pulse ox divided by how much FiO2 they are on as a fraction of 100. If let's say your patient is on 40% FiO2, you will use 0.4, and you divide all this by the respiratory rate. The key point here is the higher the ROX index, the better my patient is doing.



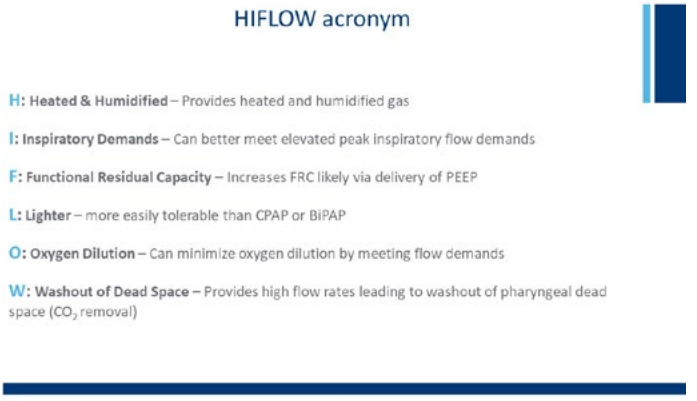
In pediatrics, this is hard to apply because the respiratory rate for the different age groups varies. If I take a neonate, for example, who breathes 40-60 times a minute, the ROX index I get even for a healthy neonate, is going to be really low compared to the strapping teenage boy who breathes 12-14 times a minute. That makes it challenging for us to adopt this. But in the adult world, they have an algorithm that is used to guide them as far as who is going to do well or who is going to fail.



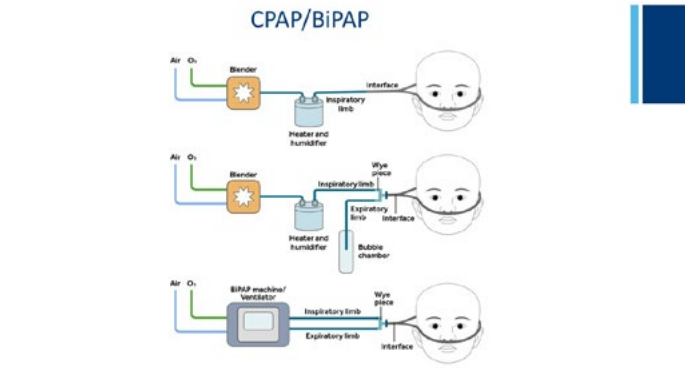
To not belabor the point, I'm just going to use the two-hour mark. Let's say you are an adult RT, you put your patient on high-flow, on the two-hour mark, you do the ROX calculation. If your ROX index is less than 2.85, it is recommended to just consider intubating this patient. If you are between 2.85 and 4.87, the recommendation is to crank up your high-flow support to the maximum that is suitable for that given patient and reevaluate in 30 minutes. If in 30 minutes your ROX increases by 0.5, you can continue high-flow. If you're not seeing any significant improvement, then you may want to consider intubating your patient. Now, high-flow nasal cannula is not without its potential complications. Because it's designed to deliver more flow than the patient's inspiratory demand, there's always a risk for air-trapping, pneumothorax, and pneumomediastinum in patients who are bronchospastic or have severe reactive airway disease. In those patient populations, you have to use it with care.

One of the questions that we entertain from time to time clinically is, is there a difference between putting my patient in high-flow versus using CPAP? The studies don't seem to demonstrate significant differences in length of stay as far as somebody who is on 2 liters per kilo per minute high-flow nasal cannula support versus somebody who is just on a CPAP of seven.

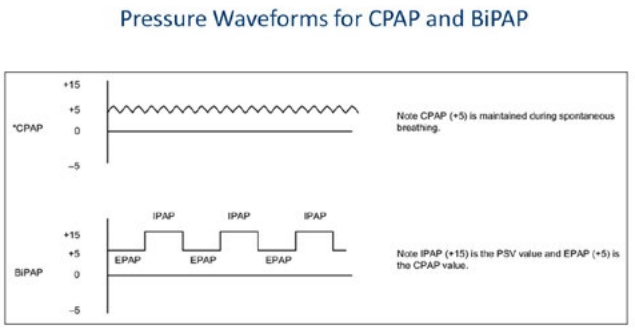
You can use both modalities if, for whatever reason, you don't have access to high-flow. Contraindications to high-flow use. Now, anybody with very severe hypoxemia, I would recommend intubating. Kid comes in, your SATs are barely in the 40s, I'd rather intubate this kid than try to play around with high-flow. If you have any patient in severe shock with all hemodynamic instability, you're better off intubating them. If there are any facial injuries, skull-based trauma, or pneumothorax, I would recommend that you rather intubate them than use high-flow. This is just an acronym, again, that just quickly reviews everything we just talked about, so I'm not going to deliver the point.



The next modality is the CPAP and BiPAP modalities. I put the slides here because for those RTs who are from the NICU, you guys are used to the bubble CPAP, those of you in the pediatric intensive care unit will be using the CPAP/BiPAP interface with a ventilator.

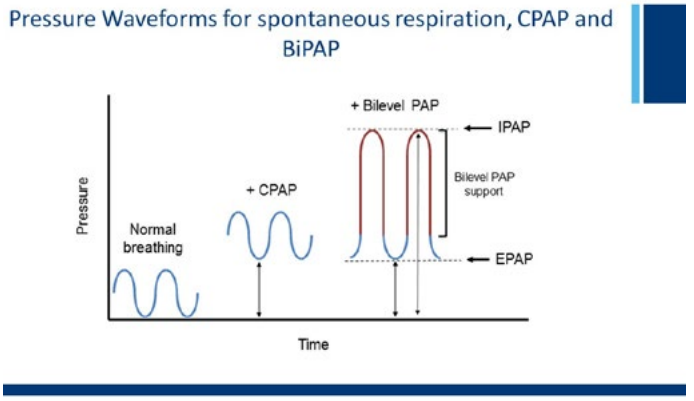


The difference between these two looking at the waveforms is that with the CPAP modality, you pick a level of support and that stays throughout.



In this diagram on the graph at the top, we see a patient at a CPAP of five and the patient just breathes consistently around that same level of support. With BiPAP, there are two levels of support that are provided. We provide an EPAP or the expiratory positive airway pressure that is used to stent the alveoli and to maintain end-expiratory lung volumes. But on top of that, we provide the inspiratory positive airway pressure that helps with the inspiratory work of breathing, making it a little bit easier for our patient to get air into their lungs.

Putting it all together side by side, on the left side is what a normal breathing waveform looks like.

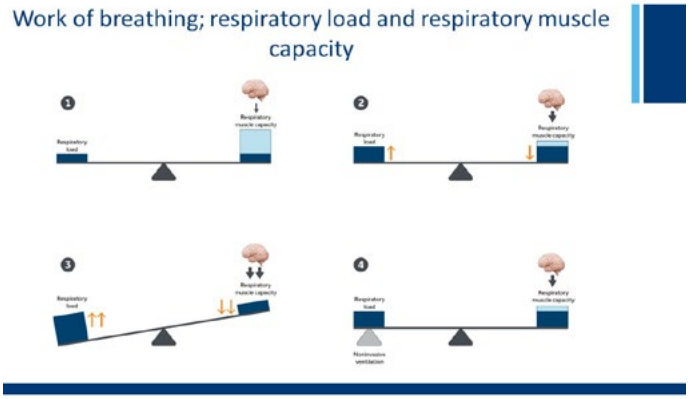


While we give them a little bit support with CPAP, this is what it looks like. They breathe at a slightly higher pressure through both the inspiratory and expiratory cycles. Then you move to the bi-level or the BiPAP where you have the EPAP and the IPAP. The difference between these two, the EPAP and the IPAP, is what drives the tidal volume into your patient. The amount of tidal volume that you get is going to be reflective of your patient's airway resistance and lung compliance at that given time.

This is a screenshot of what the BiPAP screen looks like. If you have the different modalities out there, but the screens are all similar. Here we have a patient on an IPAP of 12/8, so the inspiratory positive pressure is 12, the expiratory positive pressure is eight.

We give them a little bit of a rate, in this case, 10, 30% FiO2. The rise time, it tells you how quickly it takes the event to reach the set inspiratory pressure. One is the fastest, five is the slowest. You will also see your leak percentage, which tells you how much of the volume is leaking from your patient. The patient trigger tells you what percentage of the patient's efforts are supported. Here you have a ti/tot. This tells you what percentage of the total respiratory cycle is being used for inspiration. Usually, you want this number to be less than 40. Anything less than 40 tells you that your level of BiPAP support is not enough and you need to crank up.

I want to spend a couple of minutes on a unique population that we also see at this time of the year.



These are the kids with neuromuscular diseases. Your SMAS, your Duchenne kids, nemaline rod myopathies who come in with respiratory illness. I want to spend some time with them because these are a population...

This is a population that can fool you into thinking they're okay,

when they're actually not doing that well. The first schematic is a diagram that basically sets up the stage for what is required for normal respiratory effort. We need a normal central drive from the brain for us to breathe normally. The normal respiratory load when all things are going well is really small.

You and I don't even realize we're breathing. We don't pay attention to it every day. However, if I were to run four flights of steps from the ICU to the floor to a code, being out of shape, I would be acutely aware of the fact that I'm breathing because now my respiratory load is up. I'm going to be using a higher percentage of my respiratory muscle capacity to breathe.

With our neuromuscular kids, the issue with them is that at baseline, their respiratory muscle capacity is much lower than yours and mine because of their generalized hypotonia. There are some of them who may also have issues with central drive if they've had any strokes in the past or any traumatic brain injuries in the past.

For these patients, when there's even a slight increase in their respiratory load, they end up using a very high proportion of their respiratory muscle capacity just to stay alive. When they come in with RSV or adenovirus, what ends up happening is that the respiratory load significantly exceeds what their respiratory muscle capacity is able to do.

Because of the underlying hypotonia, you're not going to see the level of flaring and retraction that we see in healthy kids that signals to us that this is a kid that is in severe distress.

I want you to bear in mind that you will not always see the retractions to the degree that you would see in a healthy kid. You'll see the see-saw breathing, but just keep in mind that these are kids that you have to be very vigilant with. To help these patients, the non-invasive modality like a BiPAP mode, while it doesn't really impact the respiratory muscle capacity, will help offset the load that these respiratory muscles have to move.

By ramping up the level of non-invasive support, we find ourselves in a place where these patients do a little better with the non-invasive modality.

How do you know who is going to do well and who is not going to do well? Generally, as you ramp up your non-invasive modality, if your patient still remains hypoxemic, if hemodynamically things are not looking well, you're getting more hypotensive, or even your mental status is beginning to change, you're getting more lethargic, your CO_2 levels are beginning to rise, or you have a lot of secretions.

That's the challenge because to keep the BiPAP mask on a patient who has a lot of secretions makes it very challenging to get in there and suction them, especially because any time you take off the mask, they lose the positive pressure and they de-recruit. Those are patients in a room you may want to entertain intubating them.

Of course, if they are unable to tolerate the interface, it's always a challenge, especially in my world in pediatrics. It's hard to keep the mask on in certain age groups because it's just you combine stranger danger with trying to stick something on their face that blows air really fast into their face is not the most comfortable feeling for these toddlers.

When should you consider intubating your patient? If their level of mentation is decreasing, as we saw in our patient in the scenario where your nurse calls you to the bedside to say, "Hey, your respiratory rate is now dropping down to 15, even though we've stopped your Precedex." If your CO_2 is rising despite being on increased levels of non-invasive support, if your patient can no longer safely protect their airway or they're having challenges handling their secretions, you may want to consider intubating them.

Generally, looking at their respiratory effort, if the breathing is now becoming more shallow or your tidal volumes are beginning to decrease on your BiPAP support. If you're beginning to see paradoxical abdominal breathing pattern, these are all signs that your patient's respiratory reserve is beginning to diminish and you should consider intubating the patient.

Let's go back to our patient. By the time you come on in the morning to take over from your colleague who was on at night, what is signed out to you is that they're on full-phase BiPAP, 10/5, your FiO2 is 80%. Your stats are barely in the low 90s. You get a gas, and your gas is 7.15, your CO_2 is 90. Your PaO2 on ABG is 40, BiPAP is 16, and your base deficit is minus 8. What would you guys do for this patient? Then this is clearly a patient that needs to be intubated because they are clearly failing non-invasive support.

With this, I thank you for your time, and I'll entertain any questions that you have for me.

The recording of this presentation can be found at https://www.medtronic.com/covidien/en-us/clinical-education/catalog/webinar-wednesdays.html on October 24, 2023.

Early Intervention in Critical Care: The Road to Recovery

Robin Helms, RRT

Patients admitted to the intensive care unit (ICU) are often placed on bedrest to restore physiological and hemodynamic stability. According to Adler and Malone (2012), bedrest has been attributed to the development of severe muscle weakness, functional impairments, and loss of quality of life.[1] Other consequences of bedrest include adverse effects on the cardiovascular system, the respiratory system, and the neuromuscular system.[2] Patients in the ICU are often intubated for prolonged periods of time and suffer long-term impairments. After only one week of bedrest, a patient's muscle strength may decrease as much as 20%, with an additional decrease of 20% each week that follows.[3] These patients benefit most when treated with earlier interventions. These interventions may include early mobility, early tracheostomy, and early communication.

Early Mobility

Early mobility is associated with many positive outcomes. Mobilization is defined as "physical activity that is performed at a suitable intensity, providing physical benefits for the body, and helping the circulation, central and peripheral perfusion, ventilation, and the level of consciousness."[4] It involves improving muscle strength and mobility. Procedures like chair sitting, edge-of-bed sitting, sit-to-stand, and even walking in the ICU are attributed to positive outcomes. Zhang et al. (2019) found that early mobility not only decreases the incidence of intensive care unit-acquired weakness but also reduces the number of ventilator days and increases the discharge-to-home rate.[5] Early mobility may also optimize cardiopulmonary and neuromuscular status as well as maximize independent function.[3]

Early mobility is often seen as a complex task to achieve in the ICU, hence why patients are treated with bedrest.[3] However, early mobility can be achieved by selecting the appropriate patients at the appropriate times. LDS Hospital in Salt Lake City created an Early activity protocol. Their protocol was initiated once the patient achieved initial physiological stability and would continue throughout the ICU stay.[6]

Robin Helms is a registered respiratory therapist who has over 5 years of clinical experience working with acute care patients at a Level 1 trauma center. She completed her Bachelor's degree in Respiratory Care in 2018. Robin has experience working with patients in many different critical care areas, such as medical, cardiac, trauma, emergency, and more. Robin has recently joined our Passy Muir clinical team to explore a new role in education. She is currently a full-time clinical specialist for Passy Muir.

The criteria they followed for initiation is based on neurologic, respiratory, and circulatory criteria. Neurologically the patient is required to respond to verbal stimuli. Respiratory considerations were that the FiO2 should be less than 60%, and the PEEP should be less than 10 cm H2O. Circulatory criterion is based on the absence of orthostatic hypotension and catecholamine drips.[6]

Patients are assessed to determine if they meet this criterion 24 hours after admission. Once the patient meets this criteria, early mobilization begins and occurs daily. LDS hospital has found that implementation of this early activity protocol has shown a decrease in hospital length of stay, a decrease in mechanical ventilation weaning failure, and an increase in extubations.[6]

Early Tracheotomy

Patients admitted to the ICU with unstable respiratory conditions are often intubated with an endotracheal tube. Intubation periods can last from up to three weeks depending on medical stability.[7] Endotracheal intubation has risks of airway trauma, tachycardia, malposition, laryngospasm, airway stenosis, increased airway resistance, negative impacts on swallowing, and negative pulmonary pressure.[8] When patients need prolonged intubation (greater than 7 days), they often require a tracheostomy. Early tracheotomy should be considered when patients are stable, and it is safe to do so. Early tracheotomy can be defined as less than 7 days after endotracheal intubation. Although tracheotomy procedures have risk factors involved, there are many benefits that come from placing a tracheostomy tube. Not only is a tracheostomy tube more comfortable for our patients, but with a tracheostomy tube our patients are able to restore a more natural physiology to their upper airway. Mubashir et al (2021) found that earlier tracheotomy was associated with reduced ICU length of stay by 13 days, and reduced duration of mechanical ventilation by 18.30 days.[9] Another study, found that early tracheotomy is also analogous with the reduction of hospital-acquired pneumonia, and reduction of mortality rates especially when the tracheostomy is performed within the first seven days of intubation.[10] Earlier tracheotomy is also associated with shorter duration of mechanical ventilation days and ICU days, which may contribute to reducing unnecessary resources.[11]

Once a patient has a tracheostomy tube, this opens them up to even more possibilities for early interventions. With a tracheostomy tube in place, there is less need for deeper sedation.[12] A lower level of sedation provides a patient with the ability to participate in mobilization and communication.

Early Communication

Communication is vital to caring for patients. The ADA requires hospitals to provide the necessary services to allow patients effective communication.[13] Earlier communication is associated with improving quality of life.[14] Patients have improved self-esteem, improved mood, improved ability to be understood by others, and improved reported cheerfulness when they have access to communication.[14] Communication can be provided to patients in many ways depending on their medical status. Some patients may be able to communicate through writing or hand gestures, but the most effective means of communication is through voice. Patients with tracheostomies can be subject to earlier communication with the use of the Passy Muir speaking valve (PMV). Use of the PMV helps to restore more natural physiology for our patients by restoring flow to the upper airway. With a restoration of airflow to the upper airway, our patients will be able to generate speech.

Further Benefits of the PMV

Although we primarily think about early communication when it comes to use of the PMV, there are a plethora of additional physiologic benefits. The PMV helps to restore normal subglottic pressures, which may improve swallow function and reduce the risk of aspiration.[15] It may also expedite the weaning process by restoring physiological positive end-expiratory pressure which allows the patient to restore a more normal expiratory airflow pattern.[15] The PMV has also been shown to improve secretion management by enabling a stronger and more effective cough.[15]

Financial Implications of Early Intervention

When thinking about earlier interventions, it is the patient who benefits most. However, hospitals may see a benefit as well. A study was performed by Falkenstein et al. to assess the economic impact of early mobility, they found that initiating an early mobility program resulted in an average direct cost savings of $8,239 per patient with an annual cost saving projection of $2,352,744.[16] These cost savings are a direct result of reducing ventilator days, reducing hospital length of stays, and reducing the need for additional resources.

Conclusion

Helping our patients to recover requires earlier interventions. As the research shows, implementing earlier interventions in all aspects of care provides improved patient outcomes and impacts economic considerations. Patients deserve due diligence in advocating for their early recovery. Early mobility, early tracheostomy, and early communication can be put into practice as a start on the road to recovery.

References

1 Adler, J., & Malone, D. (2012). Early mobilization in the Intensive Care Unit: A systematic review. *Cardiopulmonary Physical Therapy Journal*, *23*(1), 5–13. https://doi.org/10.1097/01823246-201223010-00002

2 Doiron, K. A., Hoffmann, T. C., & Beller, E. M. (2018). Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. *Cochrane Database of Systematic Reviews*, *2018*(12). https://doi.org/10.1002/14651858.cd010754.pub2

3 Perme, C., & Chandrashekar, R. (2009). Early mobility and walking program for patients in intensive care units: Creating a standard of care. *American Journal of Critical Care*, *18*(3), 212–221. https://doi.org/10.4037/ajcc2009598

4 Castro-Avila, A. C., Serón, P., Fan, E., Gaete, M., & Mickan, S. (2015). Effect of early rehabilitation during Intensive Care Unit stay on functional status: Systematic review and meta-analysis. *PLOS ONE*, *10*(7). https://doi.org/10.1371/journal.pone.0130722

5 Zhang, L., Hu, W., Cai, Z., Liu, J., Wu, J., Deng, Y., Yu, K., Chen, X., Zhu, L., Ma, J., & Qin, Y. (2019a). Early mobilization of critically ill patients in the intensive care unit: A systematic review and meta-analysis. *PLOS ONE*, *14*(10). https://doi.org/10.1371/journal.pone.0223185

6 Hopkins, R. O., Spuhler, V. J., & Thomsen, G. E. (2007a). Transforming ICU culture to facilitate early mobility. *Critical Care Clinics*, *23*(1), 81–96. https://doi.org/10.1016/j.ccc.2006.11.004

7 Astrachan, D. I., Kirchner, J. C., & Goodwin, W. J. (1988). Prolonged intubation *vs.* tracheotomy: Complications, practical and psychological considerations. *The Laryngoscope*, *98*(11), 1165–1169. https://doi.org/10.1288/00005537-198811000-00003

8 Rahimi, M., Kareem, H., Shamsi, A., Majedi, H., & abdulkareem, H. (2022). Comparison of the Complications of Endotracheal Intubation with Laryngeal Mask Airway in Patients Under General Anesthesia. *HIV Nursing 2023*, *23*(2), 840–845. https://doi.org/10.31838

9 Mubashir, T., Arif, A. A., Ernest, P., Maroufy, V., Chaudhry, R., Balogh, J., Suen, C., Reskallah, A., & Williams, G. W. (2021). Early versus late tracheostomy in patients with acute traumatic spinal cord injury: A systematic review and meta-analysis. *Anesthesia & Analgesia*, *132*(2), 384–394. https://doi.org/10.1213/ane.0000000000005212

10 Adly, A., Youssef, T. A., El-Begermy, M. M., & Younis, H. M. (2017). Timing of tracheostomy in patients with prolonged endotracheal intubation: A systematic review. *European*

Archives of Oto-Rhino-Laryngology, *275*(3), 679–690. https://doi.org/10.1007/s00405-017-4838-7
11 Arabi, Y., Haddad, S., Shirawi, N., & Shimemeri, A. A. (2004). Early tracheostomy in intensive care trauma patients improves resource utilization: a cohort study and literature review. *Critical Care*, *2004*(8), R347–R352. https://doi.org/DOI 10.1186/cc2924
12 Durbin, C. G. (2010). Tracheostomy: Why, When, and How? *Respiratory Care*, *55*(8).
13 *ADA Requirements: Effective Communication*. ADA.gov. (2023). https://www.ada.gov/resources/effective-communication/
14 Freeman-Sanderson, A. L., Togher, L., Elkins, M. R., & Phipps, P. R. (2016). Quality of life improves with return of voice in tracheostomy patients in intensive care: An observational study. *Journal of Critical Care*, *33*, 186–191. https://doi.org/10.1016/j.jcrc.2016.01.012
15 O'Connor, L. R., Morris, N., & Paratz, J. (2021). The safety and efficacy of prolonged use of one-way speaking valves. *Australian Critical Care*, *34*(4), 319–326. https://doi.org/10.1016/j.aucc.2020.09.003
16 Falkenstein, B. A., Skalkowski, C. K., Lodise, K. D., Moore, M., Olkowski, B. F., & Rojavin, Y. (2020). The economic and clinical impact of an early mobility program in the Trauma Intensive Care Unit: A Quality Improvement Project. *Journal of Trauma Nursing*, *27*(1), 29–36. https://doi.org/10.1097/jtn.0000000000000479

Chronic Cough, Empowering People Through Education

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Kathy Przywara, Vice-President of Community at Asthma and Allergy Foundation of America (AAFA).

Host: Welcome to The Exhale Podcast, a candid conversation about current matters relating to respiratory diagnostic and lung health. Your host today is Mark Russell, marketing communications manager for Vitalograph in North America, a global leader in respiratory diagnostics. Today we had a conversation with Kathy Przywara. She's the vice-president of community at the Asthma and Allergy Foundation of America. We had a discussion about chronic cough and her own experiences with it.

Mark Russell: Kathy, welcome to our podcast.

Kathy Przywara: Thank you, Mark, for inviting me, and I'm excited to be here.

Mark Russell: Great. Well, hey, why don't you please give us a little background on yourself? Education, experience, and your current responsibilities.

Kathy Przywara: Yeah, so I'm currently the vice-president community at the Asthma and Allergy Foundation of America. I manage AAFA's online communities, our social media, and how we share all of our resources that support patients and families managing asthma and allergies. And this includes our kids with food allergies division.

So I came into this space as a community member. So I have asthma, allergies, eczema and food allergies, and I've also dealt with a chronic cough. So my now adult children have had various combinations of these atopic conditions through the years as well. So I also get the caregiver perspective. I came in as a volunteer on the community forums early in the journey with my children and discovered a lot about my own conditions. And so I wanted to give back to help other families that need this critical information to help them manage their conditions, their children's conditions, and advocate for that care.

Mark Russell: Great. So what are the criteria of a chronic cough and what types of chronic coughs are there?

Kathy Przywara: So chronic cough is defined as a cough that lasts eight weeks or longer in adults or four weeks in children. And coughs can be either acute or chronic. So an acute cough usually starts suddenly and is caused by something like allergies or respiratory infection, like a cold or the flu or sinus infection. And those usually go away after three weeks, but sometimes you get that lingering or what they call a subacute cough that lasts three to eight weeks. And then chronic coughs last longer than eight weeks. So if you have a cough that's hanging on for eight weeks or more, then that's considered a chronic cough. And then some coughs are dry and others are productive. So a productive cough is one that brings up mucus. And that dry cough is just that, it's kind of that hacking dry cough that you sometimes get.

Mark Russell: So what are the chronic cough symptoms and risks? I mean, if somebody has a lingering cough, what are the risks for people with this terrible disease?

Kathy Przywara: A cough usually starts with something that's irritating your airways. So you feel that tickle in your throat or that kind of twitch in your chest and you just need to cough. So sometimes you cough once or twice and you can clear that feeling, but sometimes it sends you into a coughing fit, and that can be really stressful for the person coughing and for people around you too. So a chronic cough is more than just an annoyance. It can interrupt your sleep. Mine often acts up as I'm trying to fall asleep. So I get half asleep and I wake up, I'm coughing and I have to sit up and I have to get some water, and then we repeat the whole situation again. That disrupted sleep can lead to fatigue, difficulty concentrating, headaches and so forth. And severe cases of chronic cough, especially with those coughing fits, can actually cause vomiting, lightheadedness, and even rib fractures.

Mark Russell: Thanks. Gosh, that's pretty tough. So what are the most common causes of a chronic cough?

Kathy Przywara: So some common causes of chronic cough are tobacco use or exposure to secondhand smoke. Post nasal drip, this can be from allergies, sinusitis. Asthma and COPD can cause a cough that can be chronic. Acid reflux can also cause a cough because you have that reflux that irritates and causes a cough. Some medications like ACE inhibitors used to treat high blood pressure, heart failure, and kidney disease, those have a side effect of a common cough. So if you develop a cough and you've been put on a new medicine, check with your doctor to make sure that it's not a known side effect.

Then there's sort of some other kind of scarier things like lung cancer and other lung diseases like bronchiectasis or interstitial lung disease that can cause the chronic cough. Sometimes

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

no specific cause can be found, and sometimes that's called a neurogenic cough. And this is when they've ruled out all the common and even the scary stuff and you still have a cough and they've tried treating the underlying conditions like allergies and asthma and reflux and just nothing is making the cough better. So fortunately, chronic cough typically disappears once the underlying problem is treated though.

Mark Russell: So what chronic cough treatments have been developed to help?

Kathy Przywara: Treatment for chronic cough will depend on what's triggering the cough, right? If it's irritants that are triggering it, then we try and avoid the irritants. So don't smoke, avoid secondhand smoke. Poor air quality can trigger a cough in some people. So check your air quality before going outside. Keep your windows closed when the air quality index is high. Avoid or reduce your exposure to things like allergens that you're allergic to.

AAFA has a great resource to help you find ways to improve your indoor air quality as well. If you have an underlying infection like a sinus infection or bronchitis, the doctor can treat the infection, and then the cough should clear up. And likewise, if you have reflux, doctor can help you come up with a reflux treatment, which may be avoiding spicy foods, avoiding eating too late before you lay down to go to sleep.

And there are some medicines that can help as well. As far as symptomatic treatments, things like cough drops or hard candy, you have to be careful with these with smaller children, obviously. Cough suppressants. Stay well hydrated. Make sure that you're drinking enough fluids to keep those mucous membranes moist and not irritated. Steamy showers or moist air can help. And for kids, check with their doctor about what's appropriate to give them.

Mark Russell: I'm sure even a humidifier would definitely help with people with cough.

Kathy Przywara: Yeah, there are some things you want to take into consideration if you decide to get a humidifier. Make sure that you're cleaning it correctly because humidifiers, because it's wet, those can breed mold. So just make sure that it's getting clean so that you're not putting a different irritant or allergen into your air and breathing in those mold spores.

Mark Russell: And I'm sure, speaking of mold, mold is probably another factor that can bring on chronic cough also, wouldn't you say?

Kathy Przywara: That would be falling under those allergens. So things like molds or dust mites that can live year-round indoors/ as I mentioned, AAFA has a great resource that you can download that gives you kind of a room-by-room checklist to go through your home to look for ways to improve your indoor air quality. And you can find that at aafa.org/healthyhome.

Mark Russell: So, what are the challenges do you see with people with chronic cough experience and what can be done to help reduce these challenges?

Kathy Przywara: So I think first one is getting a diagnosis. Cough is a pretty common thing. So people sometimes will just dismiss a cough and not really realize how long they've had it. Once you do realize, "Hey, I've been coughing for a long time, maybe it's time to go get this looked at." It can take a while to run different tests, try different treatment options and interventions to see what's going to work. This is especially true if the trigger isn't clear, or if the cough only partially gets better with one type of treatment. This can be really frustrating, but don't give up. Keep working with your doctor because a cough can be more than just an irritation.

And then another thing is people feel isolated. A cough, especially like a chronic cough or if you go into coughing fits, coughs are very obvious and people can feel really embarrassed or self-conscious. It can make you shy away from social situations. Nobody wants to be the person constantly coughing in a restaurant or a movie theater or on an airplane. So our experience with COVID has made it even more awkward to have a cough. People around you automatically think you have something contagious, and it may just not be true.

Mark Russell: I agree with that. Boy, I tell you, during COVID, or even just soon after, anytime I coughed, you could watch the reactions of people all the time. It is like such an alert of what's going on. "Is this person infected with something? Is it still COVID?" It really has changed society's outlook.

Kathy Przywara: It definitely has. And I tend to wear a mask. Even before COVID, I would wear a mask to reduce my exposure to allergens, to viruses and stuff like that. So particularly if you're wearing a mask and you start coughing, people automatically assume that you're sick.

Mark Russell: Yeah, exactly. And then like you said, indoor or outdoor air quality, you just don't really have a chance. With outdoor air quality around here, we get a cold front come in from the north of Canada. If there's any fires, you can see the quality of air change radically, and the smell and it's more smokier. And it's amazing that that can be affected from here in the middle of the country from all the way up to Canada.

Kathy Przywara: Right. And where I lived in California, we had wildfires all the time, and that was a constant source of irritation and our air quality would be really bad. If you are dealing with poor air quality like that, there are ways that you can stay indoors and help improve your indoor air quality. Things like an air purifier can help like a portable one. Or if you are running your air conditioning, make sure that you're not drawing air in from outside. Check windows and doors in your garage and stuff for leaks to see where the bad outdoor air is coming in.

Mark Russell: Absolutely. And I remember growing up as a kid, we used to have a attic fan and you'd open up the windows and it would suck all that air into the house. You can't really do that anymore. It kind of brings in a lot of more allergens and air quality out there.

Kathy Przywara: Yeah. And more modern houses also are built to be more sealed up, right? Because of weather efficiency and stuff like that. They're more sealed. And so your outdoor air and that poor air quality can get indoors and then it gets trapped in there. So opening the windows will bring more outdoor air in, but it doesn't necessarily take the indoor air out.

Mark Russell: Out. So why is it important to raise awareness

about chronic cough and where can patients find more information out there to help them better diagnose this terrible disease?

Kathy Przywara: So it's more than just a cough. It impacts your life in ways that others may not see or appreciate. Like I said, it can be a cause of sleep disturbance. It's just exhausting to be coughing all the time. So having more awareness allows people to advocate for themselves both for diagnosis and treatment, but also with other people in their lives that their cough may impact, family, friends, coworkers that hear them coughing and are just irritated or frustrated by it. And then patients and caregivers can find more information and get support on AAFA's online community. We have a free online community. You can be somewhat anonymous and pick a username. And we have staff and volunteers who help answer questions, they share their experiences. We can provide more information to people as they're going through this journey. And that can be found at aafa.org/join.

Mark Russell: Well, Kathy, what's the best advice you can give somebody when they feel they might have chronic cough since you're a person that has had it in the past?

Kathy Przywara: I think the best advice for somebody who thinks they have chronic cough is go see your doctor. They're the one that can help do that workup, that investigation of what might be the triggers. They'll take a good history, find out what's happening, when it started, what things seem to maybe relate to when the cough is worse. Is it allergy season that brings it on? Maybe we need to treat your allergies better. Is it an asthma cough? Are your asthma symptoms acting up? Maybe your asthma's not under control and we need to adjust that. I think the best advice is just see your doctor and don't give up.

Mark Russell: I agree. If you try to self-treat something like that, it may get worse.

Kathy Przywara: Yep.

Mark Russell: Well, Kathy, thank you so much. This is great information. I appreciate the time and the background of how you've experienced your own chronic cough symptoms and how you were able to treat it, and this is really good information.

Kathy Przywara: Well, thank you again for inviting me and I hope this information is helpful to people out there.

Host: You've reached the end of another episode of The Exhale Podcast. Don't forget to follow us for upcoming new episodes. And please take our survey to help us provide good content for the future. Thank you for your listening, and we look forward to you joining us again on The Exhale Podcast, brought to you by Vitalograph.

BiWaze Clear System – Effects of Oxygen Bleed-in on FiO_2 Delivery In Vitro

Niko Kontoudios RRT and Robert DiBlasi RRT-NPS, FAARC

Introduction

In the field of respiratory therapy, oxygen (O_2) therapy plays a critical role in the management of patients with compromised respiratory function. One essential parameter in O_2 therapy is the fraction of inspired oxygen (FiO_2), which refers to the concentration of O_2 in the inspired gas mixture. Accurate control and maintenance of FiO_2 levels are crucial in providing optimal oxygenation while minimizing the risk of O_2 toxicity or hypoxia. O_2 bleed-in is a technique that uses an auxillary gas flow to supplement the delivered FiO_2 during oscillating lung expansion (OLE) therapy.

This bench study aimed to investigate the effects of O_2 bleed-in on FiO_2 levels during OLE therapy with BiWaze Clear (ABM Respiratory Care, USA) under various therapeutic parameters.

Study Method

We utlized the ASL 5000 spontaneously breathing lung simulator (Ingmar Medical, USA) to simulate two patient models: an adult patient weighing 70 kg and a pediatric patient weighing 20 kg. The BiWaze Clear system was configured to deliver two therapy phases: positive expiratory pressure (PEP) and high-frequency oscillation (OSC). Each phase involved the evaluation of two pressure settings, representing a range commonly used during OLE therapy.

FiO_2 measurements were obtained for each O_2 bleed-in flow setting, starting from 1 liter/minute and incrementally increasing up to 15 liters/minute. O_2 bleed-in was achieved by introducing supplemental O_2 flow into the inspiratory path of the coaxial bacterial/viral filter. A paramagnetic O_2 sensor integrated into the ASL lung model was used to continuously analyze the FiO_2 level.

Results

Adult with PEP of 5 cm H_2O	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	24.00
2	29.00
3	35.00
4	41.60
5	48.60
6	54.60
7	61.60
8	67.10
9	76.10
10	81.70
11	86.40
12	89.50
13	91.80
14	93.30
15	94.10

Adult with PEP of 15 cm H_2O	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	24.50
2	27.50
3	31.50
4	35.00
5	38.50
6	42.00
7	45.50
8	49.00
9	52.50
10	56.00
11	59.50
12	63.00
13	66.50
14	70.00
15	73.50

Adult with OSC of 10 cm H_2O at 4 Hz	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	24.50
2	27.50
3	31.50
4	35.00
5	40.00
6	44.00
7	48.00
8	51.50
9	55.00
10	58.50
11	62.50
12	66.00
13	69.50
14	73.00
15	76.50

Adult with OSC of 30 cm H_2O at 4 Hz	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	23.30
2	25.50
3	28.30
4	31.40
5	34.60
6	37.80
7	40.70
8	43.80
9	46.20
10	49.10
11	51.50
12	54.70
13	57.20
14	59.30
15	62.20

Pediatric with PEP of 5 cm H_2O	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	26.70
2	34.30
3	43.00
4	49.60
5	55.40
6	63.00
7	69.80
8	74.80
9	80.00
10	84.30
11	88.00
12	91.60
13	93.30
14	94.50
15	94.90

Pediatric with PEP of 15 cm H_2O	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	26.00
2	32.50
3	38.00
4	44.00
5	50.00
6	56.00
7	60.00
8	66.00
9	71.00
10	76.00
11	80.00
12	84.00
13	87.50
14	90.00
15	92.50

Niko Kontoudios and Robert DiBlasi are with Seattle Children's Hospital, Seattle, Washington, USA.

Pediatric with OSC of 10 cm H_2O at 4 Hz	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	26.00
2	32.50
3	40.00
4	46.00
5	53.00
6	58.00
7	64.00
8	70.00
9	75.00
10	79.00
11	84.00
12	88.00
13	91.00
14	93.50
15	95.00

Pediatric with OSC of 30 cm H_2O at 4 Hz	
Bleed O_2 (L/min)	Delivered FiO_2 (%)
1	24.50
2	26.80
3	29.90
4	33.80
5	37.80
6	41.60
7	45.10
8	48.60
9	52.30
10	57.80
11	58.10
12	60.80
13	63.90
14	66.60
15	68.70

Conclusion

This bench study aimed to evaluate the effects of O_2 bleed-in on FiO_2 levels with a variety of therapeutic parameters during OLE therapy with BiWaze Clear. Through a comprehensive evaluation of different therapy parameters, our analysis showed a linear correlation between O_2 bleed-in flow and delivered Fio_2 for all therapy phases and pressures. We created guidance tables with the measured values of FiO_2 for the analyzed bleed-in flow rates for both patient models during the different therapy phases and settings. The findings of this study can aid clinicians in selecting the appropriate flow to bleed-in to optimize FiO_2 delivery with BiWaze Clear.

BiWaze® Clear
SYSTEM

Latest in airway clearance innovation

- Oscilating Lung Expansion (OLE) therapy
- 10 minute airway clearance treatment
- Closed circuit includes Aeorgen® Solo nebulizer
- Superior aerosol efficiency and deposition in the lungs[1]

Learn more at abmrc.com

abm RESPIRATORY CARE

1. DiBlasi, R, et al. (2023). BiWaze Clear Aerosol Comparison White Paper. Seattle Childrens Hospital and Research Institute. https://abmrc.com/wp-content/uploads/2023/07/BiWaze-Clear-Aerosol-Comparison-White-Paper.pdf

BiWaze® and ABM Respiratory Care® are registered trademarks of ABMRC, LLC.

©2023 ABMRC, LLC. ALL RIGHTS RESERVED. PRTN-1585539264-330 Rev 1.0 AUG-2023 ENG US

Study Finds Many Benefits of Neurally Adjusted Ventilatory Assist (NAVA) for Newborns

Chris Campbell

Helping newborns be healthy and get stronger is a goal for every neonatal intensive care unit.

Technology is helping clinicians achieve this goal in bigger and better ways, but one study sought to quantify exactly how much for something called Neurally adjusted ventilatory assist — otherwise known as NAVA.

NAVA is a support technology for the respiratory system that is triggered by the electrical activity of the diaphragm (EAdi).

But just how effective is NAVA for newborns in respiratory distress, and is it a reliable index to guide medical staff during weaning and extubation?

That's what the study "Weaning in neurally adjusted ventilatory assist: a prospective interventional study in neonates" sought to find out.

In the study, the authors describe NAVA: "Pressure assistance is provided in proportion to and synchronous with the electrical activity of the diaphragm (EAdi), and its amount is adjustable by the operator via an amplification factor called NAVAlevel.[1]"

The study was produced by Cosi G, Monzani A, Genoni G, De Franco S, Parlamento S, Bona G, et al. through the Neonatal and Pediatric Intensive Care Unit, Maggiore della Carità Hospital, Novara, Italy; Division of Pediatrics, Department of Health Sciences, University of Eastern Piedmont, Novara, Italy.

In the study, 34 newborns with respiratory failure were ventilated with synchronized intermittent mandatory ventilation plus pressure-regulated volume control plus pressure support (SIMV(PRVC)+PS) for 12 hours and switched to NAVAuntil extubation. Ventilator and vital parameters, oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2) ratio (S/F), arterialized capillary blood gases (aCBG), and sedatives dose were recorded. The occurrence of reintubation within the first 72 hours, pneumothorax and mortality were evaluated.

What the study found was that NAVA is very safe to use in neonates and the EAdi peak "could be a reliable index to guide the physicians during weaning and extubation."

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

Struggles with pediatric patients

The study authors say that while NAVA has been shown to be effective for newborns, there isn't a lot of data on the subject found through study.

"In pediatric patients, NAVAhas been shown to enhance patient-ventilator interaction and synchrony, improving the outcome of mechanical ventilation by reducing its duration and avoiding ventilator-induced lung injury.[2-7] To synchronize ventilation is a challenge for the neonatologist because of rapid respiratory rates, small tidal volumes, periodic breathing patterns, short inspiratory times, and variable airleaks around the endotracheal tube.[8] Up to now, only few studies about NAVAefficacy and safety in newborns exist, and most of them enrolled a small number of subjects and used NAVAonly for short-term.[9-11] Only three studies evaluated NAVAin a cohort of preterm neonates for longer time (12, 24 and 26 hours, respectively)[12-14] and only one of them was a randomized-controlled trial of NAVAversus conventional mechanical ventilation.[14] In all of these papers, NAVAimproved patient-ventilator synchrony and reduced ventilator assistance with an improvement of ventilation parameters. Furthermore, Longhini et al. reported a decrease in the need of sedation during NAVA[12] and Stein et al. showed no differences in short-term complications like intraventricular hemorrhage (IVH), pneumothorax (PNX) or necrotizing enterocolitis (NEC), compared to conventional mechanical ventilation.[13] Kallio et al. evaluated the length of hospital stay, the need of mechanical ventilation and sedation with no differences between conventional ventilation and NAVA.[14] Aim of our study was to assess in a cohort of newborns the efficacy and safety of NAVA used for a longer period, until extubation. Moreover, we aimed to analyze ventilation parameters during NAVAhelpful to guide the operator during the weaning process."

The Study

The study authors conducted prospective uncontrolled interventional study from January 2015 to June 2016 in the Neonatal Intensive Care Unit (NICU) of the Maggiore della Carità University Hospital (Novara, Italy). "The institutional ethics committee approved the study, written informed consent was obtained from the patient's parents/ guardians," the authors wrote. "The study was in line with principles of the Declaration of Helsinki. All patients requiring mechanical ventilation admitted to the NICU were considered eligible if matching the following inclusion criteria: 1) age <28 days of life; 2) presence of spontaneous breathing effort able to trigger the ventilator;

3) availability of the only NAVAventilator in our NICU (Servo-N ventilator, Maquet Critical Care, Solna, Sweden)."

The patients, once selected, received ventilation using NAVA until the point of extubation, "unless matching the following discontinuation criteria: 1) FiO_2 >0.6 to maintain SpO_2≥90%; 2) persistent hypercapnia, defined as $PcCO_2$>60 mmHg and/or pH<7.25 in spite of a progressive increase of ventilatory support; 3) heart rate (HR) >180 beats/min and/or respiratory rate (RR) >80 breaths/min for more than 15 consecutive minutes."

Out of the 34 newborns included in the study, the media GA was listed by the authors was 33 weeks.

Results

The study authors wrote about the overwhelming success of the NAVA in the study subjects.

"After 6 hours of NAVA, a significant reduction of FiO_2 (0.25 versus 0.32), and peak inspiratory pressure (13 versus 18 mmHg), and a significant increase of S/F (383 versus 316) were found, compared to SIMV(PRVC)+PS," the study said. "Other ventilation, vital and aCBG parameters were similar in both ventilation modes. During NAVA a significant reduction of sedation was shown. All subjects were successfully extubated guided by EAdi peak during weaning. No reintubation, pneumothorax, or death were recorded."

The authors added that: "Notably in our study NAVA delivered an effective ventilation in neonates with different clinical and pathophysiological features."

The authors noted that their study appears to be the first where a "standardized protocol of weaning using NAVA is proposed." The authors write that more studies of newborns are needed to see the effectiveness of NAVA at various points of ventilation.

References

1 Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure.
2 Piastra M, D Luca D, Costa R, Pizza A, De Sanctis R, Marzano L, et al. Neurlly adjusted ventilatory assist vs pressure support ventilation in infants
3 De la Oliva P, Schuffelmann C, Gomez-Zamora A, Villar J, Kacmarek RM. Asynchrony, neural drive, ventilatory variability and comfort: NAVA versus pressure support
4 Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in pediatric units
5 Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children
6 Bordessoule A, Emeriaud G, Morneau S, Jouvet P, Beck J. Neurally adjusted ventilatory assist improves patient-ventilatory interaction in infants
7 Kallio M, Peltoniemi O, Antilla E, Pokka T, Kontiokari T. Neurally adjusted ventilatory assist in pediatric intensive care
8 Keszler M. State of the art in conventional mechanical ventilation
9 Beck J et al Patient-ventilator interaction during Neurally adjusted ventilatory assist
10 Lee J Kim et al. Randomized crossover study of Neurally adjusted ventilatory assist
11 Stein H et al. Prospective crossover comparison of Neurally adjusted ventilatory assist
12 Longhini R et al. Neurally adjusted ventilatory assist in preterm neonates
13 Stein H, Howard D. Neurally adjusted ventilatory assist in neonates weighing <1500 grams: a retrospective analysis
14 Kallio M et al. Neurally adjusted ventilatory assist in preterm neonates with respiratory distress

Life After Mechanical Ventilation: An Expert Interview on a New Accreditation to Improve Outcomes

Nathaniel A Miller, PhD

Executive Summary
When patients are unable to breathe sufficiently on their own, mechanical ventilation may be required. Mechanical ventilation is the most common intervention used in patients admitted to ICUs (Intensive Care Units). Mechanical intervention saves lives in acute cases, but numerous studies document how prolonged mechanical ventilation can lead to a host of negative physical, financial, and mental outcomes for patients. Over the past twenty years, Gene Gantt, RRT, FAARC has worked with TennCare, Tennessee's state Medicaid program, to develop best practices for safely and successfully weaning patients off of long-term mechanical ventilation. In this interview, he discusses his successes, which have recently been standardized as a widely-recognized accreditation available nationally through the non-profit Physician-Patient Alliance for Health & Safety.

Consequences of Prolonged Mechanical Ventilation
The need for mechanical ventilation may occur as a result of a range of breathing and respiratory illnesses, including acute asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, lung cancer, and trauma. During the COVID pandemic, there was a surge in patients requiring mechanical ventilation. In the US, one study found that almost 90% of COVID patients required mechanical ventilation. An audit of patients from England, Wales, and Northern Ireland found that two-thirds of COVID patients who required critical care in the UK had mechanical ventilation within 24 hours of admission. Most COVID patients who experienced respiratory failure often required prolonged mechanical ventilation for two weeks or longer.

More than a million patients who are admitted to US intensive care units (ICUs) receive mechanical ventilation each year. Nearly 10% of all critically ill patients and up to 34% of those ventilated for more than two days require extended periods of ventilatory support. Prolonged mechanical ventilation (PMV) has been defined as ventilation for more than 21 days or for more than four days following a tracheostomy. Currently, over 100,000 patients per year require prolonged mechanical ventilation. With advances in skill and technology, the rate of PMV cases is increasing rapidly from year to year.

Nathaniel Miller is a freelance writer who lives in Denver. He is a recovering academic who previously held a visiting professorship and research fellowships at the University of Cambridge and New York University Abu Dhabi. His writing has appeared in The New York Times, The Marginalia Review, Reading Religion, and elsewhere.

When prolonged, mechanical ventilation, especially in alternate care settings where most patients are elderly, becomes a major safety issue. In the vast majority of states in the US, there are little to no quality requirements for mechanical ventilation in long-term care facilities (such as Skilled Nursing Facilities) that establish adequate staffing ratios of qualified respiratory therapists, advanced monitoring of pulse oximetry/end-tidal CO2, outcomes tracking, use of advanced technologies, or quality oversight. Additionally, there is no accreditation program focused on this specialty service. As a result, there are ventilator-dependent/tracheostomized patients who receive substandard long-term care where no outcomes are achieved or expected.

Researchers have found that the care of patients who have prolonged mechanical ventilation is expensive and their overall outcomes are often poor. As Dr Mario Fadila and his colleagues at the SIU School of Medicine and the University of Missouri write:

"Prolonged mechanical ventilation increases the risk of pneumonia, barotrauma, tracheal injuries and musculoskeletal deconditioning. At the same time, delayed weaning is associated with increased morbidity, mortality, hospital stay and risk of long-term care facility discharge."

The seemingly simple example of device alarm failure illustrates the dangers patients undergoing prolonged mechanical ventilation face. In 2002, the Joint Commission on Accreditation of Health Care Organizations (JCAHO) reviewed 23 reports of death or injury that were related to mechanical ventilation. Nineteen of those events resulted in death, four in a coma, and the vast majority — 65% — were related to alarms. There was often no response, or a delayed response, to mechanical ventilation alarms. In some cases, the alarm was set incorrectly. Some ventilator disconnections did not trigger an alarm. When an alarm was triggered, it was not always audible in all areas of patient care. This review prompted JCAHO to include alarm safety in the National Patient Safety Goals for 2003.

Until very recently, there have been no standardized protocols for safely weaning patients off of long-term mechanical ventilation.

New accreditation is now available from the Physician-Patient Alliance for Health & Safety (PPAHS), a national non-profit (501(c)(3)) advocating for patient health and safety priorities. The PPAHS Accreditation in Enhanced Respiratory Care builds

on a program developed by Gene Gantt, Registered Respiratory Therapist, for TennCare. Gantt's program has achieved a 65% liberation rate from long-term mechanical ventilation and the American College of Chest Physicians awarded it a national recognition of excellence. The newly available Accreditation in Enhanced Respiratory Care is based on standards published by the American Association for Respiratory Care (AARC), where Gantt was also the former chair of the long-term care section and AARC representative to the Respiratory Compromise Institute.

I sat down to chat with Gene about TennCare's successes and the role of the new Accreditation in Enhanced Respiratory Care in translating these successes to the national level.

An Interview with Gene Gantt, RRT, FAARC

What are the main issues and challenges healthcare providers face when it comes to patients on mechanical ventilation?

The main issue is finding the most appropriate quality resource for long-term ventilation. These vary from state to state. There are three discharge options:

- Long-term acute care hospitals, where available. These are still considered acute care and have a length of stay of 28-30 days, but then they too need discharge options for long-term care if liberation from ventilation isn't achieved in that time frame.
- Skilled nursing facilities. These vary in scope, quality, and payment availability. Depending on state Medicaid options a state may or may not cover these higher-acuity services.
- Direct discharge to home, where continued efforts to wean from ventilation are much less likely.

On the national level, what mechanisms are in place to ensure high standards of respiratory care for patients on long-term mechanical ventilation?

There are no national standards from the Centers for Medicare & Medicaid Services or any other governing bodies that provide target standards for long-term ventilator care. In terms of costs, which affect provision, each state sets its own payment rate and requirements.

Tell me about your role in starting the Enhanced Respiratory Care program in Tennessee.

We originally established Tennessee's very first long-term ventilator program in a Skilled Nursing Facility, which is to say, a state-regulated nursing home, in 2001, as a means of preparing families for ventilator care at home. Our idea was that we could do a better job preparing caregivers if we could do so at a slower pace than traditionally done in a busy hospital ICU. At that time we were the hands-on providers of respiratory care and as clinicians, we wanted to make our facility as safe and clinically sound as possible. Although there were no standard requirements at the time we opted to staff our unit 24 hours a day with respiratory therapists and to provide redundant monitoring in case of ventilator failure or accidental disconnect.

Once we admitted our first patients, our respiratory therapists recognized that the majority had weaning potential so they began the process of weaning them from the ventilator. In our first year, we were successful in liberating 65% of those admitted to the unit.

Realizing that model was successful, we developed the initial ten standards we felt to be key to our success and presented them to the Tennessee Board of Respiratory Care, who adopted them as an official position statement. In 2007 we presented the Tennessee position statement to the AARC where it was adopted as a formal position statement there as well.

We continued our work as providers until 2013, and then joined the TennCare Bureau to develop the current pay-for-performance model we use today. We now oversee the quality of that program statewide.

Tell me about the relationship between national standards of respiratory care for patients on mechanical ventilation and Tennessee's efforts.

The standards of care were first developed and used in Tennessee beginning in 2001 and were first codified as a Medicaid requirement there in 2014. The successful outcomes achieved from following the standards stimulated the idea of national accreditation of facilities that met or exceeded the standards.

Could you describe the best practice for weaning a patient off mechanical ventilation?

The best practice will depend on the patient. Weaning from long-term ventilation is made more difficult due to patient stress and often deep depression. One of the very first steps we recommend is to humanize the patient so that they feel more optimistic. For example, the placement of a speaking valve so they can communicate does wonders for the weaning process. Not only does it allow them to speak but it's also beneficial in alveolar/lung recruitment resulting in more stable oxygen saturation. All of the patients in long-term care have failed standard protocols so respiratory therapists must be creative in their methods.

Where does PPAHS's Accreditation and Certification in Enhanced Respiratory Care fit into the national landscape of respiratory care provision?

There are two parts here to talk about, certification of the clinician, and then accreditation of facilities.

Certification entails clinicians taking continuing medical education courses on Enhanced Respiratory Care. These courses educate clinicians through online and hands-on learning in:

- Culture of a Weaning Program
- Resident Selection
- Quality of Life
- Weaning Approaches
- Ventilator Unit Technology/Equipment
- Discharge Processes
- Process Improvement

There are relatively few training courses that are specific to long-term care. Respiratory therapists who specialize in this arena rely on manufacturers and clinical experience to learn the ropes. The PPAHS offers specialized programs targeted toward long-term care.

Accreditation of facilities is recognition that the facility has met or exceeded the national standard of care. Previously, there were no regulatory or Medicare/Medicaid standards from state to state. Enhanced Respiratory Accreditation offers facilities an opportunity to practice at a high level and to be recognized once they meet or exceed the standards. These standards create a safe environment for those receiving care in non-acute facilities. Additionally, it provides families with the assurance that the facilities are operating at a high clinical level and that their loved

West Meade Place (Nashville, TN) was the first facility to receive Enhanced Respiratory Care Accreditation. Pictured with Gene Gantt (far right) are Michael Wong (PPAHS) and James Wright and Clyde Heflin.

ones are being cared for according to a recognized standard of care.

What role does data collection/metrics tracking play in improving and maintaining high standards of respiratory care? What are some of the issues and challenges in data collection and management on state and national levels?
Collecting data is extremely important, if nothing is measured there is no benchmark for improvement. By collecting data and participating in accreditation a facility can benchmark their success to that of other institutions practicing in the same manner. This gives a facility a way to measure improvement.

The challenge to collecting accurate data is to make sure that each facility is using the same formulas for calculation. For example, if a facility only counts patients they "think" they can wean versus "all qualified admissions," the data wouldn't match up to those who use the "all qualified admissions" category.

How about equipment, what needs to change in terms of availability and training to improve and maintain high standards of respiratory care?
Many long-term care respiratory therapists don't get the opportunity to attend live state or national seminars and as a result, they are not aware of the latest technological advances. That's one of the main benefits of the new PPAHS certification. As new products become available, we will host periodic equipment showcase sessions where manufacturers will come to the respiratory therapists to showcase new products.

There will often need to be investments made to improve outcomes and many times these costs pose a challenge. However, improved outcomes should equal increased reimbursement from a payer like managed care or TennCare in order to offset the costs of investment in new equipment. Structuring reimbursement properly provides the best outcome for clinicians and their patients.

How can we continue to improve outcomes for weaning patients from mechanical ventilation?
By expecting success instead of settling for providing custodial care for long-term ventilation patients.

Where can clinicians and patients get more information on Enhanced Respiratory Care?
More information on certification and accreditation in Enhanced Respiratory Care can be obtained by going to https://ppahs.org/enhanced-respiratory-care/.

About Gene Gantt, RRT, FAARC
Gene Gantt is the co-founder and CEO of Eventa, LLC, and a well-respected registered respiratory therapist who has practiced in the post-acute care arena since 1984 and is widely recognized for his excellent work on critical patient safety issues. He has represented the American Association for Respiratory Care (AARC) at various conferences addressing the need for patient monitoring and promoting clinician awareness of early recognition of respiratory compromise. He is the AARC representative to the Respiratory Compromise Institute, a coalition of leading medical organizations, and the Physician-Patient Alliance for Health & Safety.

About Physician-Patient Alliance for Health & Safety
The Physician-Patient Alliance for Health & Safety is ranked internationally as a top-100 patient safety organization (Agilience Authority Index, July 2023) and is a national advocacy force for addressing patient health and safety priorities shared by patients, physicians, regulators, and industry. PPAHS seeks to ensure that the best medications, medical inventions, and technology that can improve care and reduce costs are employed. PPAHS works to advance patient health and safety by developing and highlighting best practices and recommendations through better use and application of clinical practices and experiences, information technologies and checklists, and healthcare information. As a voice in support of ideas and innovation that can improve care, we encourage a health ecosystem that fosters a culture of patient safety. For more about PPAHS, please visit www.ppahs.org.

Characterization and Inhibition of Inflammasome Responses in Severe and Non-severe Asthma

Jay C Horvat[1], Richard Y Kim[1,2], Natasha Weaver[1], Christopher Augood[1,3], Alexandra C Brown[1], Chantal Donovan[1,2], Pierrick Dupre[1,4], Lakshitha Gunawardhana[1], Jemma R Mayall[1], Nicole G Hansbro[3], Avril A B Robertson[5], Luke A J O'Neill[6], Matthew A Cooper[7], Elizabeth G Holliday[1], Philip M Hansbro[1,3] and Peter G Gibson

Abstract

Background. Increased airway NLRP3 inflammasome-mediated IL-1β responses may underpin severe neutrophilic asthma. However, whether increased inflammasome activation is unique to severe asthma, is a common feature of immune cells in all inflammatory types of severe asthma, and whether inflammasome activation can be therapeutically targeted in patients, remains unknown.

Objective. To investigate the activation and inhibition of inflammasome-mediated IL-1β responses in immune cells from patients with asthma.

Methods. Peripheral blood mononuclear cells (PBMCs) were isolated from patients with non-severe (n = 59) and severe (n = 36 stable, n = 17 exacerbating) asthma and healthy subjects (n = 39). PBMCs were stimulated with nigericin or lipopolysaccharide (LPS) alone, or in combination (LPS + nigericin), with or without the NLRP3 inhibitor MCC950, and the effects on IL-1β release were assessed.

Results. PBMCs from patients with non-severe or severe asthma produced more IL-1β in response to nigericin than those from healthy subjects. PBMCs from patients with severe asthma released more IL-1β in response to LPS + nigericin than those from non-severe asthma. Inflammasome-induced IL-1β release from PBMCs from patients with severe asthma was not increased during exacerbation compared to when stable. Inflammasome-induced IL-1β release was not different between male and female, or obese and non-obese patients and correlated with eosinophil and neutrophil numbers in the airways. MCC950 effectively suppressed LPS-, nigericin-, and LPS + nigericin-induced IL-1β release from PBMCs from all groups.

Conclusion. An increased ability for inflammasome priming and/or activation is a common feature of systemic immune cells in both severe and non-severe asthma, highlighting inflammasome inhibition as a universal therapy for different subtypes of disease.

1University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia. 2University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, Australia. 3Centenary Institute, Centre for Inflammation, and University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, Australia. 4University of Montpellier, Montpellier Cancer Research Institute (IRCM), Montpellier, France. 5The University of Queensland, School of Chemistry and Molecular Biosciences, Brisbane, Australia. 6Trinity College Dublin, Trinity Biomedical Sciences Institute, School of Biochemistry and Immunology, Dublin, Ireland. 7Sitala Bio Ltd., Cambridge, UK. Open Access – This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

Introduction

Severe asthma is characterized by persistent disease activity despite therapy.[1,2] This results in increased morbidity, decreased quality-of-life, and absenteeism from school/work, with > 50% of people with severe asthma unable to maintain full-time employment.[3] In addition, patients with severe asthma account for > 50% of all asthma-associated health care costs, despite only 5-25% of patients having severe asthma (reviewed in[4-11]). Improved understanding of the immunopathological and pathophysiological processes that underpin severe asthma may provide effective therapeutic targets and/or management strategies to reduce the burden of this severe, debilitating disease.

Much clinical and experimental evidence shows that severe asthma is a heterogeneous disease, which complicates the development and application of effective therapies. Approximately 50% of patients with severe asthma have eosinophil-dominated airway inflammation and elevated type 2 (T2) responses (e.g. IL-4, IL-5, IL-13, immunoglobulin [Ig]E levels). However, T2-low subtypes of severe asthma also occur where patients have lower FeNO and airway and systemic eosinophils, and present with increased T1 and/or T17 responses associated with neutrophil-dominant airway inflammatory responses.[6,9,10,12] Additionally, severe asthma in obese women is a distinct severe immunological clinical phenotype.[6,13-16] Recently, T2-directed biologics were introduced as effective therapies for severe T2 asthma.[17,18] However, alternative approaches and immunological targets are still urgently needed for severe T2-low disease.[17,18]

Accumulating clinical and experimental evidence strongly implicate excessive NLRP3 inflammasome activation and IL-1β production in severe asthma pathogenesis, particularly, neutrophil-high, T2-low subtypes.[19-26] We showed that NLRP3 inflammasome and IL-1β responses are increased in experimental models of severe, neutrophilic asthma.[27] Increased NLRP3 and IL-1β responses correlate with increased neutrophil numbers, severity of airflow obstruction, and reduced asthma control in patients, the majority of which were on ICS maintenance therapy. Most importantly, we showed that therapeutically targeting NLRP3 inflammasome responses with the highly NLRP3-specific inhibitor, MCC950, reduces IL-1β production, steroid-insensitive neutrophilic inflammation, and AHR in experimental disease. These findings demonstrate roles for inflammasome-dependent, IL-1β responses in the pathogenesis of severe, neutrophilic asthma and that increased NLRP3 activation in severe asthma may be therapeutically targeted to treat severe, T2-low disease. Whilst we showed that NLRP3 expression in sputum is associated with features of severe neutrophilic asthma, whether increased ability for NLRP3 inflammasome priming and activation and IL-1β release are key features of immune cells in other phenotypes of severe or non-severe asthma, and whether inflammasome responses in immune cells from patients with asthma can be inhibited with MCC950, is unknown.

We hypothesized that the ability for NLRP3 inflammasome priming and/or activation and IL-1β release are increased, and can be therapeutically inhibited, in immune cells from patients with severe asthma. In this study, we characterized the ability for inflammasome priming, activation, and IL-1β release from immune cells from patients with severe and non-severe asthma, and healthy controls, and examined the effects of therapeutic suppression with MCC950.

Materials and methods

Full details are provided in the Online Repository.

Study approvals

All procedures were performed with approval from the Hunter Area Health Service (2019/ETH01030) and University of Newcastle Human Research Ethics Committee (H-2017-0088). All participants gave written informed consent before their inclusion.

Study population

The study sample comprised 151 adult participants (≥ 18 years) divided into 4 diagnostic subgroups: 39 healthy controls, 59 patients with non-severe (mild-moderate, stable) asthma, 36 patients with severe stable and 17 with severe exacerbating asthma (Table 1). Details on participant recruitment, asthma diagnosis, stratification into severe and non-severe (stable or exacerbating), and eosinophilic and non-eosinophilic, asthma and obese and non-obese participants and exclusion criteria are outlined in the Supplementary Materials. Sputum samples were induced and processed as previously described.[28]

Isolation of peripheral blood mononuclear cells (PBMCs), NLRP3 inflammasome priming and activation and assessment of IL-1β release

PBMCs were isolated from whole blood and seeded at 2×10^5 cells/well as outlined in the Supplementary Materials. They were then centrifuged prior to incubation in media and/or pre-treatment with lipopolysaccharide for 2 or 4 h (Additional file 1: Fig. S1A, B). LPS pre-treatment primes immune cells for NLRP3 inflammasome-induced IL-1β by inducing the intracellular production of NLRP3, pro-caspase-1 and pro-IL-1β.[29-31] PBMCs were then exposed to the NLRP3 inflammasome-activating compound, nigericin in the absence or presence of MCC950, for + 1 h (Additional file 1: Fig. S1A, B). Sham treatments for nigericin and MCC950 received PBS. Stimulated PBMCs were then centrifuged and culture supernatants collected for quantification of IL-1β by ELISA as outlined in the Supplementary Materials.

Statistics

Group comparisons were between patients with asthma (classified as non-severe [stable], severe [stable], severe [exacerbating]) and healthy controls. The primary outcome IL-1β was measured 1 h following nigericin or sham treatment, which occurred 2 or 4 h after LPS or sham treatment. Experimental variables included 4 pre-treatments (Media, LPS, Nigericin, LPS + Nigericin) and 2 drug treatments with MCC950 (negative, positive). This was a 'split plot' design where a sample from each patient was analyzed under each combination of experimental variables (4×2 repeated measures per patient). The continuous outcome of IL-1β were analyzed with a Linear Mixed Model that included covariates for sex and obesity and a four-way interaction term for asthma group by the experimental design variables (pre-treatment*drug*asthma*time point) as well as all the lower order terms. The model was adjusted for within-person correlation of outcomes due to repeated measures and the optimal correlation structure (compound symmetry) was selected by comparing Akaike information criterion (AIC) values for different models. Linear mixed models were used to allow for the complex nature of the data and analysis, which included repeated measures on individual samples, different group sizes, some missing data values, and the need to adjust for covariates. Mixed models use all available data and produce robust estimates under a missing at random assumption.

Model effects and comparisons of interest were estimated via the restricted maximum likelihood method and presented as mean differences with 95% Confidence Intervals and associated p-values. Model validity was assessed via plots including studentized residuals versus fitted plots. Heteroscedasticity (non-constant variance) was present due to the extreme range of outcome values, so the robust variance estimator was used. Model *p*-values for selected comparisons were compared against those from non-parametric tests (Wilcoxon-Mann–Whitney) for model validation, producing broadly similar results.

Results

Nigericin-induced NLRP3 inflammasome-mediated IL-1β release is commonly increased in PBMCs from patients with severe and non-severe asthma

The NLRP3 inflammasome is a multimeric protein signaling complex of the innate immune response that, upon activation, recruits, and proteolytically cleaves inactive pro-caspase-1 in active caspase-1.[27,30-37] Active caspase-1, in turn, cleaves inactive pro-IL-1β, to produce and release biologically active IL-1β.[27,30-37] We first assessed the response of PBMCs from healthy subjects and patients with severe and non-severe asthma (Table 1) to NLRP3 inflammasome-induced IL-1β release. To do this we challenged PBMCs with the canonical NLRP3 activator, nigericin, which activates the NLRP3 inflammasome by inducing cellular potassium efflux.[38] Without nigericin treatment, there was no difference between IL-1β release from PBMCs from

Table 1 Subject characteristics

Characteristic	Class or Statistic	Asthma status				Overall *P* value	Pairwise comparisons			
		Healthy (*N* = 39)	Non severe (NSA; *N* = 59)	Severe (SA[S]; *N* = 36)	Severe exacerbating (SA[E]; *N* = 17)		NSA vs Healthy	SA(S) vs Healthy	SA(S) vs NSA	SA(E) vs SA(S)
Age (years)	Mean (SD)	45.0 (17.6)	52.1 (17.2)	62.9 (14.1)	58.0 (18.5)	< 0.001	0.042	< 0.001	0.003	0.318
Sex	Female	28 (72%)	42 (71%)	17 (47%)	11 (65%)	0.079	0.948	0.030	0.020	0.234
	Male	11 (28%)	17 (28%)	19 (53%)	6 (35%)					
Race	White	38 (97%)	50 (85%)	34 (94%)	17 (100%)	0.089	0.048	0.470	0.197	1.000
	Other	1 (2.6%)	9 (15%)	2 (5.6%)						
BMI, kg/m2	Mean (SD)	28.5 (5.8)	29.9 (6.3)	29.7 (7.8)	30.6 (8.4)	0.668	0.257	0.444	0.877	0.696
Obesity status	Non-obese	16 (41%)	13 (22%)	10 (28%)	6 (35%)	0.079	0.044	0.228	0.526	0.578
	Obese	23 (59%)	46 (78%)	26 (72%)	11 (65%)					
Asthma characteristics										
Age of symptom onset, years	Median (Q1, Q3)	N/A	12.0 (4.0, 27.5)	7.0 (3.5, 35.0)	11.0 (5.0, 28.5)	0.789	N/A	N/A	0.657	0.454
	Mean (SD)	N/A	17.1 (16.5)	18.9 (22.0)	20.4 (20.9)	0.792	N/A	N/A	0.655	0.804
Mean ACQ-6	Median (Q1, Q3)	N/A	0.67 (0.33, 1.17)	1.17 (0.42, 1.84)	2.50 (1.17, 3.50)	0.001	N/A	N/A	0.036	0.007
	Mean (SD)	N/A	0.89 (0.81)	1.30 (1.02)	2.28 (1.48)	< 0.001	N/A	N/A	0.054	0.023
Asthma control (*N*, %) (ACQ-6 classification)	> 1.50 0.75–1.50 < 0.75	N/A	10 (17%) 18 (31%) 30 (52%)	12 (33%) 10 (28%) 14 (39%)	11 (65%) 2 (12%) 4 (24%)	0.005	N/A	N/A	0.179	0.094
Exacerbations, past 12 months										
Number of ED visits (*N*, %)	0 1 ≥2	N/A	53 (93%) 3 (5.3%) 1 (1.8%)	33 (94%) 1 (2.9%) 1 (2.9%)	13 (76%) 2 (12%) 2 (12%)	0.117	N/A	N/A	1.000	0.103
Number of hospitalizations (*N*, %)	0 1 ≥2	N/A	53 (93%) 3 (5.3%) 1 (1.8%)	33 (94%) 2 (5.7%)	14 (82%) 1 (5.9%) 2 (12%)	0.248	N/A	N/A	1.000	0.131
Number of unscheduled Dr visits (*N*, %)	0 1 ≥ 2	N/A	39 (68%) 10 (18%) 8 (14%)	24 (69%) 4 (11%) 7 (20%)	4 (24%) 3 (18%) 10 (59%)	0.002	N/A	N/A	0.650	0.004
Number of OCS courses (*N*, %)	0 1 ≥2	N/A	37 (65%) 12 (21%) 8 (14%)	14 (40%) 4 (11%) 17 (49%)	2 (12%) 3 (18%) 12 (71%)	< 0.001	N/A	N/A	0.002	0.117
Lung function										
FEV_1preb2pp	Mean (SD)	98.95 (12.04)	82.90 (14.79)	66.76 (19.03)	67.57 (17.75)	< 0.001	< 0.001	< 0.001	< 0.001	0.886
FVCpreb2pp	Mean (SD)	100.95 (12.55)	91.89 (14.47)	81.45 (16.27)	78.84 (15.14)	< 0.001	0.002	< 0.001	0.002	0.591
FEV_1/FVC, %	Mean (SD)	77.51 (14.90)	72.32 (9.85)	63.54 (12.72)	67.55 (10.29)	< 0.001	0.042	< 0.001	< 0.001	0.274
Sputum inflammatory markers										
Sputum eosinophils, %	Mean (SD)	0.28 (0.38)	4.76 (9.92)	6.14 (12.35)	5.50 (6.61)	0.459	0.007	0.001	0.254	0.954
Total eosinophils (×10^6/mL)	Mean (SD)	0.01 (0.02)	0.39 (1.17)	0.42 (0.66)	0.22 (0.22)	0.688	0.012	0.004	0.204	0.534
Sputum neutrophils, %	Mean (SD)	32.30 (24.35)	35.61 (25.92)	44.52 (27.99)	41.23 (25.64)	0.506	0.714	0.244	0.204	0.746
Total neutrophils (×10^6/mL)	Mean (SD)	2.02 (2.41)	3.59 (5.40)	4.59 (7.07)	3.31 (4.84)	0.712	0.902	0.423	0.345	0.885
Total cell count (×10^6/mL)	Mean (SD)	5.04 (3.48)	6.47 (6.23)	9.17 (8.54)	6.34 (4.73)	0.025	0.552	0.117	0.125	0.248
Asthma inflammatory phenotype (*N*, %)	Eosinophilic Non-eosinophilic	9 (100%)	14 (33%) 29 (67%)	10 (45%) 12 (55%)	6 (55%) 5 (45%)	0.037	0.092	0.030	0.226	0.451

Overall *P* values are from ANOVA or Kruskal–Wallis for numeric variables and Chi-squared test or Fisher's exact test for categorical variables. *P* values for pairwise comparisons of numeric variables are from *T* tests or Wilcoxon-Mann–Whitney tests and are unadjusted for multiple testing. *ACQ-6* Asthma Control Questionnaire-6, *BMI* Body Mass Index, *FEV_1preb2pp* Pre-Bronchodilator % Predicted FEV_1, *FVCpreb2pp* Pre-Bronchodilator % Predicted FVC

asthma patient groups compared to healthy subjects (Fig. 1A, B). However, following treatment with nigericin, PBMCs from patients with severe or non-severe asthma had increased IL-1β release compared to PBMCs from healthy subjects (Fig. 1C, D). Interestingly, there was no statistical difference between the amount of IL-1β released from PBMCs from severe and non-severe patients, and no difference between PBMCs from stable, compared to exacerbating, asthma patients. These findings suggest that increased sensitivity to nigerin-induced NLRP3 inflammasome activation-mediated IL-1β release is a common feature of systemic immune cells in patients with asthma.

Overall *P* values are from ANOVA or Kruskal–Wallis for numeric variables and Chi-squared test or Fisher's exact test for categorical variables. *P* values for pairwise comparisons of numeric variables are from *T* tests or Wilcoxon-Mann–Whitney tests and are unadjusted for multiple testing. *ACQ-6* Asthma Control Questionnaire-6, *BMI* Body Mass Index, *FEV_1preb2pp* Pre-Bronchodilator % Predicted FEV_1, *FVCpreb2pp* Pre-Bronchodilator % Predicted FVC

Nigericin-induced NLRP3 inflammasome-activation-mediated IL-1β release in PBMCs from patients with

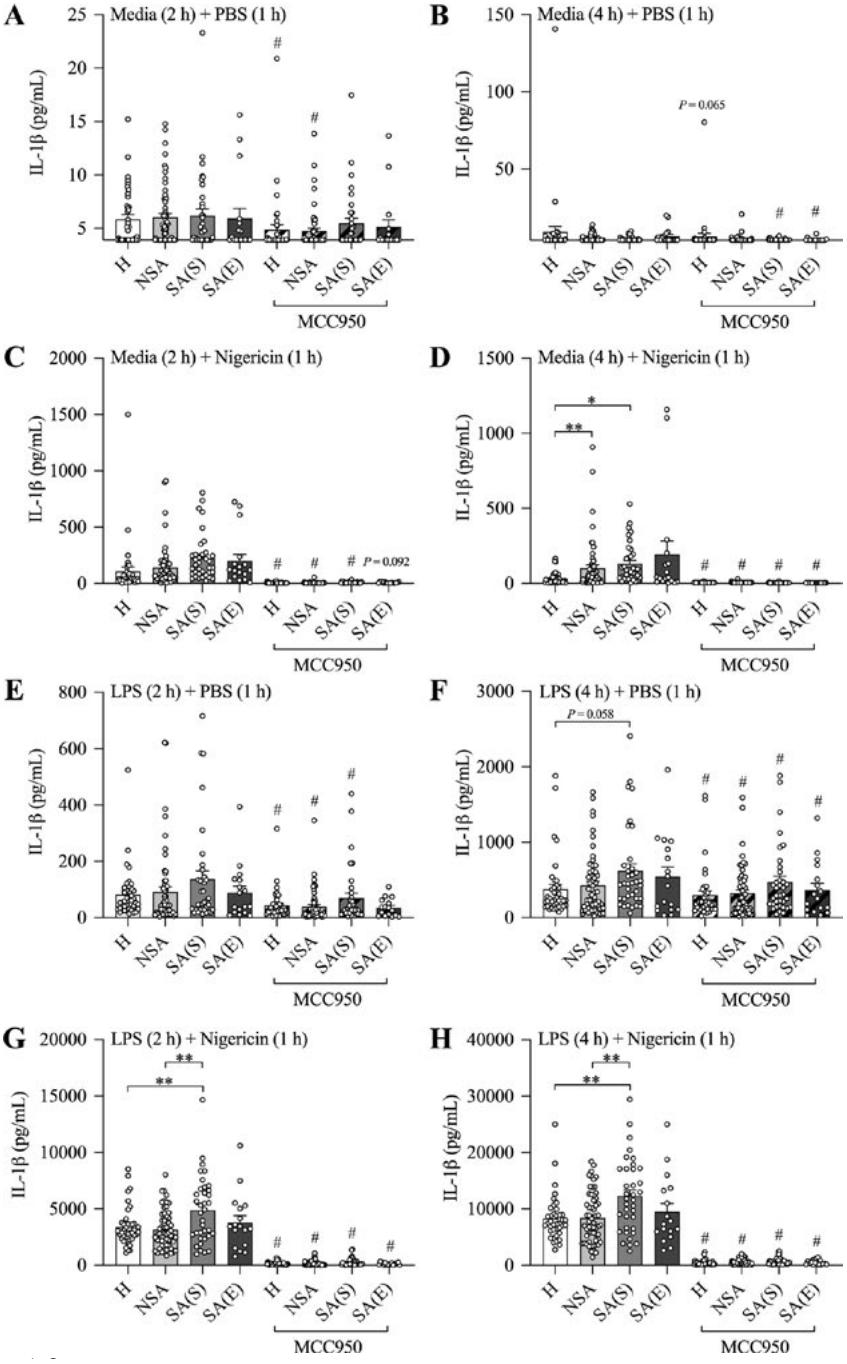


Fig. 1 Peripheral blood mononuclear cells (PBMCs) from healthy subjects and patients with asthma differ in LPS- and nigericin-induced NLRP3 inflammasome–mediated IL-1β release. PBMCs from patients with non-severe asthma (NSA), severe asthma (stable SA(S); exacerbating SA(E)), and healthy (H) subjects were pre-treated with media (**A**–**D**) or LPS (**E**–**H**) for 2 (**A**, **C**, **E**, **G**) or 4 (**B**, **D**, **F**, **H**) hours before being treated with PBS (**A**, **B**, **E**, **F**) or Nigericin (**C**, **D**, **G**, **H**) for 1 h, and the effects of LPS and/or nigericin stimulation on IL-1β release was assessed in culture supernatants. Some cells were treated with MCC950 at the same time as PBS or nigericin stimulation to assess the effects of NLRP3 inflammasome inhibition on IL-1β release. Data are presented as means ± SEM ($N = 17$–59). $^{*}P < 0.05$, $^{**}P < 0.01$. $^{\#}P < 0.05$ compared to control not treated with MCC950

asthma is not affected by sex or obesity status and correlates with neutrophilic inflammation

We next performed analyses to determine whether increased nigericin-induced NLRP3 inflammasome-mediated IL-1β release in asthma patients is different in males compared to females, or in obese compared to non-obese subjects. Nigericin-induced IL-1β release from PBMCs from all patients with asthma (severe and non-severe combined, as there was no difference in nigericin-induced IL-1β between these) was significantly increased compared to healthy subjects (Additional file 1: Tables S1 and S2, Fig. 2A, B). Stratification by sex and obesity status showed no effects on nigericin-induced responses. These findings show that increased nigericin-induced NLRP3 inflammasome-mediated IL-1β release occurs in both males and females as well as obese and non-obese subjects with asthma.

We next assessed correlations between on IL-1β release by nigericin-challenged PBMCs from all asthmatic subjects and BMI, asthma control (ACQ-6), sputum eosinophils and neutrophils (total, %) and pre-bronchodilator lung function (FEV_1, FVC, FEV_1/FVC) to determine whether increased NLRP3 inflammasome activation in PBMCs is associated with specific features of disease. Interestingly, nigericin-induced IL-1β release from PBMCs from asthma subjects positively correlated with

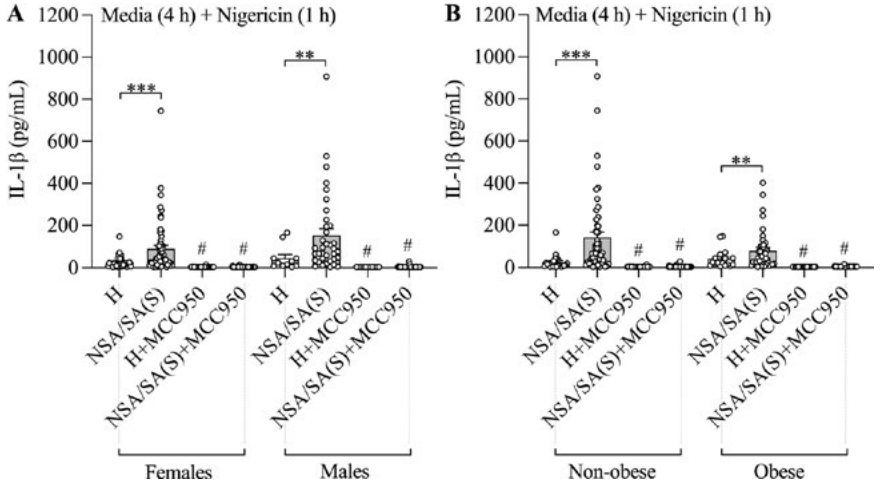


Fig. 2 Nigericin-induced NLRP3 inflammasome-mediated IL-1β release in peripheral blood mononuclear cells (PBMCs) from patients with asthma is not affected by sex or obesity. PBMCs from patients non-severe (NSA) and severe stable (SA(S)) asthma and healthy (H) subjects were pre-cultured with media for 4 h before being stimulated with nigericin for 1 h, and the effects on IL-1β release assessed in culture supernatants. Some cells were treated with MCC950 at the same time as nigericin stimulation. The effects of nigericin stimulation and NLRP3 inflammasome inhibition on IL-1β release were assessed following stratification of subjects by sex **A** and obesity) status. Data are presented as means ± SEM ($N = 11–59$). $^{**}P < 0.01$, $^{***}P < 0.001$. $^{\#}P < 0.05$ compared to control not treated with MCC950

neutrophil, but not eosinophil number or percentage in patient sputum, and negatively correlated with FEV_1 and FVC, but not FEV_1/FVC (Table 2). These findings suggest that increased pre-priming to NLRP3 inflammasome-mediated IL-1β release by systemic immune cells is associated with increased neutrophilic airway inflammation and lower lung function in asthma in our cohort comprised of patients with neutrophilic and eosinophilic disease phenotypes.

PBMCs from severe asthmatics have further increases in IL-1β production following LPS-induced priming and nigericin-induced NLRP3 inflammasome activation

NLRP3 inflammasome-mediated IL-1β responses involve two distinct signals. Signal one is the priming signal, which initiates the expression and translation of inflammasome components, such as NLRP3 and pro-caspase-1, along with pro-IL-1β and their assembly into a complex.[29-31] Signal two is the activating signal which initiates NLRP3 inflammasome-mediated cleavage and release of active IL-1β.[29-31] In order to further characterize NLRP3 inflammasome responses in immune cells from patients with asthma, we next assessed the release of IL-1β from PBMCs from healthy subjects, and patients with severe and non-severe asthma, following 2 and 4 h of pre-treatment with LPS (signal one),[29-31] prior to nigericin (signal two)-induced activation. LPS alone increased IL-1β release from PBMCs from all subject groups, however, there were no significant differences between any groups (Fig. 1E, F). However, following treatment with LPS + nigericin, PBMCs from patients with severe asthma released increased IL-1β levels compared to PBMCs from patients with nonsevere asthma and healthy subjects (Fig. 1G, H). Interestingly, there were no differences between the amount of IL-1β released from PBMCs from non-severe patients and healthy subjects or stable compared to exacerbating severe asthma patients. Together, these findings demonstrate that, whilst systemic immune cells from asthma patients are more sensitive to nigericin-induced inflammasome activation (signal two), an increased response to both LPS-induced priming (signal one) and nigericin-induced activation (signal two) of the NLRP3 inflammasome is a unique feature of systemic immune cells in patients with severe asthma. This increased response to LPS-induced priming and nigericin-induced activation is not affected during exacerbations of severe asthma.

Table 2 Nigericin stimulation of peripheral blood mononuclear cells from patients with severe and non-severe asthma, Spearman correlation coefficients between IL-1β release and key clinical characteristics

	Media (2 h) + Nigericin (1 h)		Media (4 h) + Nigericin (1 h)	
BMI	$r = -0.14$	$P = 0.190$	$r = -0.11$	$P = 0.299$
ACQ-6, mean	$r = 0.12$	$P = 0.258$	$r = 0.01$	$P = 0.892$
Sputum eosinophils, %	$r = -0.11$	$P = 0.398$	$r = 0.05$	$P = 0.681$
Sputum eosinophils total	$r = 0.12$	$P = 0.352$	$r = 0.15$	$P = 0.253$
Sputum neutrophils, %	$r = 0.27$	$P = 0.030$	$r = 0.39$	$P = 0.001$
Sputum neutrophils, total	$r = 0.35$	$P = 0.006$	$r = 0.39$	$P = 0.002$
FEV_1preb2pp	$r = -0.24$	$P = 0.022$	$r = -0.18$	$P = 0.088$
FVCpreb2pp	$r = -0.21$	$P = 0.041$	$r = -0.17$	$P = 0.095$
FEV_1/FVC, %	$r = -0.11$	$P = 0.303$	$r = -0.16$	$P = 0.130$

ACQ-6 Asthma Control Questionnaire-6, *BMI* Body Mass Index, *FEV_1preb2pp* Pre-Bronchodilator % Predicted FEV_1, *FVCpreb2pp* Pre-Bronchodilator % Predicted FVC; *r* Spearman rho

Increased LPS-induced NLRP3 inflammasome priming and nigericin-induced activation in PBMCs from patients with severe asthma compared to other subjects is not affected by sex or obesity status and correlates with both neutrophilic and eosinophilic inflammation

We next performed analyses to determine whether increased IL-1β release induced by LPS + nigericin treatment severe asthma is different in males compared to females, or in obese compared to non-obese subjects. LPS + nigericin-induced IL-1β release from PBMCs from patients with severe asthma was significantly increased compared to other participant groups (non-severe asthma and healthy subjects combined, as there was no difference in LPS + nigericin-induced IL-1β between these groups) and stratification by sex (Additional file 1: Tables S3 and S4, Fig. 3A) or obesity status (Additional file 1: **Tables S3 and S4,** Fig. 3B**) had no effects**. These findings suggest that increased LPS-induced NLRP3 inflammasome priming and nigericin-induced activation occurs in both males and females as well as in obese and non-obese subjects with severe asthma.

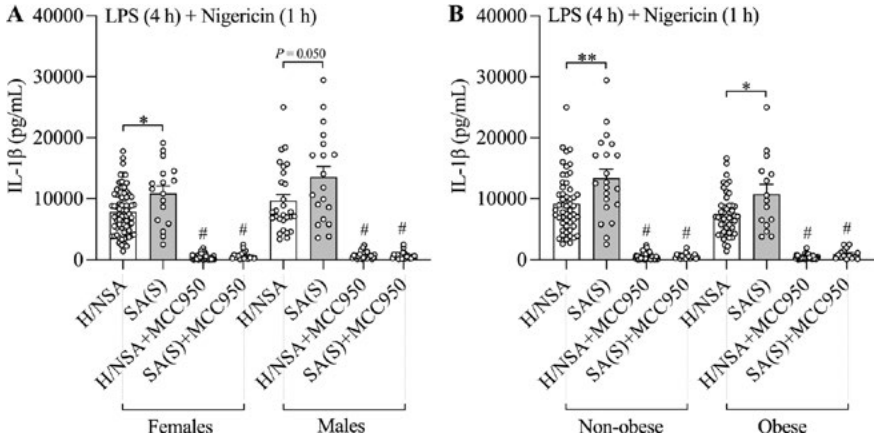


Fig. 3 Increased LPS-induced NLRP3 inflammasome priming and nigericin-induced activation in peripheral blood mononuclear cells (PBMCs) from patients with severe asthma compared to other subjects is not affected by sex or obesity. PBMCs from patients with non-severe (NSA) and severe stable (SA(S)) asthma, and healthy (H) subjects were pre-stimulated with LPS for 4 h before stimulation with nigericin for 1 h, and the effects of LPS + Nigericin on IL-1β release was assessed in culture supernatants. Some cells were treated with MCC950 at the same time as nigericin stimulation. The effects of LPS + Nigericin stimulation and NLRP3 inflammasome inhibition on IL-1β release were assessed in patients with SA(S) compared to other subjects (H and NSA together) following stratification of subjects by sex **A** and obesity **B** status. Data are presented as means ± SEM ($N = 15–70$). $^{*}P < 0.05$, $^{**}P < 0.01$. $^{\#}P < 0.05$ compared to control not treated with MCC950

We next assessed correlations between on IL-1β release by LPS + nigericin-treated PBMCs from patients with severe asthma and BMI, control, eosinophilic and neutrophilic inflammation in sputm and lung function, LPS + nigericin-induced IL-1β release from PBMCs from patients with severe asthma positively correlated with both total eosinophilic and neutrophilic inflammatory cell numbers in sputum (Table 3). These findings suggest that increased LPS-induced NLRP3 inflammasome priming and nigericin-induced activation in systemic immune cells is associated with both eosinophilic and neutrophilic inflammatory responses in the airways of patients with severe asthma.

MCC950 reduces LPS- and NLRP3 inflammasome-induced IL-1β release from PBMCs with the greatest effects in those with severe asthma

Finally, we determined the effectiveness of MCC950 treatment in reducing NLRP3 inflammasome-mediated IL-1β release from PBMCs from patients with asthma. MCC950, potently suppressed IL-1β release from PBMCs from patients with severe (stable and exacerbating) and non-severe asthma and healthy subjects that are stimulated with nigericin alone, LPS alone, or LPS + nigericin (Fig. 1A–H). We show that the greatest effects of MCC950 suppression on NLRP3 inflammasome-mediated IL-1β release occurs in PBMCs from severe asthmatics (Table 4). Furthermore, we show that MCC950 effectively suppressed IL-1β release following stimulation with nigericin alone and LPS + nigericin in males and females as well as obese and non-obese subjects (Additional file 1: Tables S5 and S6). Together these findings indicate that MCC950 potently suppresses NP3 inflammasome-mediated IL-1β responses in systemic immune cells from all patients with asthma irrespective of disease severity and sex or obesity status.

Table 3 LPS + Nigericin stimulation of peripheral blood mononuclear cells from patients with severe asthma, Spearman correlation coefficients between IL-1β release and key clinical characteristics

	LPS (2 h) + Nigericin (1 h)		LPS (4 h) + Nigericin (1 h)	
BMI	$r = -0.13$	$P = 0.436$	$r = -0.27$	$P = 0.113$
ACQ-6, mean	$r = 0.12$	$P = 0.489$	$r = -0.00$	$P = 0.980$
Sputum eosinophils, %	$r = -0.17$	$P = 0.456$	$r = 0.26$	$P = 0.247$
Sputum eosinophils, total	$r = 0.46$	$P = 0.043$	$r = 0.55$	$P = 0.012$
Sputum neutrophils, %	$r = 0.40$	$P = 0.067$	$r = 0.18$	$P = 0.415$
Sputum neutrophils, total	$r = 0.48$	$P = 0.032$	$r = 0.33$	$P = 0.158$
FEV_1preb2pp	$r = 0.17$	$P = 0.339$	$r = 0.12$	$P = 0.478$
FVCpreb2pp	$r = 0.13$	$P = 0.473$	$r = 0.14$	$P = 0.435$
FEV_1/FVC, %	$r = 1.00$	$P = 0.568$	$r = 0.06$	$P = 0.741$

ACQ-6 Asthma Control Questionnaire-6, *BMI* Body Mass Index, *FEV_1preb2pp* Pre-Bronchodilator % Predicted FEV_1, *FVCpreb2pp* Pre-Bronchodilator % Predicted FVC, *LPS* Lipopolysaccharide, *r* Spearman rho

Discussion

We, and others, previously showed that NLRP3 inflammasome and IL-1β responses are increased in the airways of patients with severe and neutrophilic asthma.[19-26] Here, we show that systemic immune cells from all patients with asthma, both severe and nonsevere asthmatics that contain both eosinophilic and non-eosinophilic populations, have an increased ability for nigericin-induced NLRP3 inflammasome activation compared to those from non-asthma subjects (Fig. 1D). NLRP3 inflammasome activation has been shown to play a critical role in breaking tolerance to antigens and the induction of experimental asthma.[39,40] Our findings provide clinical evidence that an increased ability for inflammasome activation in systemic immune cells may play a crucial role in the pathogenesis of inflammatory processes that underpin both severe and nonsevere asthma. After puberty, females are more likely to have asthma than males (60% versus 40% of non-severe asthma)[41] and up to 82% of patients with severe asthma are female.[42] Furthermore, we, and others, have identified severe asthma in obese women as a distinct clinical phenotype that is associated with increased NLRP3 inflammasome responses in the airways.[6,13-16] Here, we show that inflammasome responses are not increased in systemic immune cells from female versus male, or obese versus non-obese, people with asthma. Interestingly, we did see a small increase in inflammasome responses in systemic immune cells from obese non-asthmatic subjects compared to non-obese controls, but this did not reach statistical significance. We also show that there are no differences between nigericinor

Table 4 Effect size of MCC950 on IL-1β secretion from peripheral blood mononuclear cells

	Non-severe vs Healthy	Severe vs Healthy	Severe vs Non-severe	Severe vs Severe (exacerbating)
Media (2 h)				
Mean diff. (95% CI)	– 0.3 (– 1.1 to 0.5)	0.3 (– 1.0 to 1.6)	0.5 (– 0.7 to 1.8)	0.1 (– 1.5 to 1.7)
P value	0.5016	0.6882	0.3812	0.9070
LPS (2 h)				
Mean diff. (95% CI)	– 13.5 (– 40.2 to 13.3)	– 28.2 (– 59.2 to 2.8)	– 14.7 (– 51.8 to 22.3)	– 68.8 (– 178.6 to 41.0)
P value	0.3244	0.0755	0.4355	0.2202
Nigericin (1 h)				
Mean diff. (95% CI)	– 32.2 (– 120.9 to 56.5)	– 113.9 (– 213.6 to – 14.2)	– 81.7 (– 162.7 to – 0.8)	– 76.0 (– 251.7 to 99.7)
P value	0.4773	0.0256	0.0484	0.3970
LPS (2 h) + Nigericin (1 h)				
Mean diff. (95% CI)	240.2 (– 412.3 to 892.7)	– 1380.9 (– 2399.2 to – 362.5)	– 1621.0 (– 2589.7 to – 652.4)	– 937.6 (– 2363.3 to 488.1)
P value	0.4710	0.0082	0.0011	0.1981
Media (4 h)				
Mean diff. (95% CI)	– 2.4 (– 11.6 to 6.8)	2.2 (– 0.9 to 5.4)	4.6 (– 4.0 to 13.3)	1.5 (– 0.4 to 3.5)
P value	0.6096	0.1600	0.2948	0.1293
LPS (4 h)				
Mean diff. (95% CI)	– 30.3 (– 74.4 to 13.8)	– 66.8 (– 128.9 to – 4.7)	– 36.5 (– 99.4 to 26.4)	29.5 (– 87.9 to 146.8)
P value	0.1783	0.0357	0.2560	0.6229
Nigericin (1 h)				
Mean diff. (95% CI)	– 73.6 (– 118.2 to – 29.1)	– 99.7 (– 143.4 to – 56.1)	– 26.1 (– 86.0 to 33.8)	62.0 (– 109.8 to 233.8)
P value	0.0013	< 0.0001	0.3933	0.4799
LPS (4 h) + Nigericin (1 h)				
Mean diff. (95% CI)	– 79.3 (– 1646.5 to 1487.9)	– 3735.3 (– 6046.7 to – 1423.8)	– 3655.9 (– 5915.2 to – 1396.7)	103.4 (38.1 to 168.8)
P value	0.9210	0.0016	0.0016	0.0020

LPS Lipopolysaccharide

Descriptive statistics are shown as mean difference (95% confidence interval)

LPS + nigericin-induced IL-1β release in PBMCs from asthmatic subjects (severe and non-severe subjects combined) with eosinophilic versus non-eosinophilic asthma (Additional file 1: Table S7 and Fig. 4). This suggests that the increased ability for activation of inflammasome responses that we have identified may be universal features of systemic immune cells in patients with severe and non-severe asthma (i.e. all asthma) and are not dependent upon sex or obesity status, or sputum granulocyte composition. Together, these findings highlight that an increased ability for activation of inflammasome responses in systemic immune cells may play a fundamental underlying role in asthma.

We also show that systemic immune cells from patients with severe asthma release more IL-1β following a combination of pathogen (LPS)-induced priming and NLRP3 inflammasome activation compared to cells from patients with non-severe asthma (Fig. 1G, H). These findings indicate a potential fundamental difference between severe and non-severe asthma. They demonstrate that systemic immune cells from patients with severe asthma have an increased ability to respond to pathogen component-induced priming step required to produce inflammasome components and pro-IL-1β, in addition to increased ability to respond to inflammasome activation required to cleave and release active IL-1β. Microbial infections are an important stimulus for NLRP3 inflammasome priming and activation in the lung.[27,38-45] We previously showed that respiratory infections have important roles in initiating immune responses, including NLRP3 inflammasome-mediated IL-1β responses, in the asthmatic lung that promote severe, steroid-insensitive asthma.[6,27,44,45] Our current findings demonstrate that systemic immune cells in severe asthmatics may also be more responsive to infection-induced priming and subsequent NLRP3 inflammasome-mediated, steroid-insensitive inflammatory responses. Our clinical findings highlight a potential mechanism to explain the link between infection and the induction of heightened inflammatory processes that underpin severe asthma.

Furthermore, we show that increased LPS + nigericin-induced NLRP3 inflammasome-mediated IL-1β release from PBMCs from patients with severe asthma correlate with increased total eosinophil and neutrophil numbers in the airways (Table 3). This suggests that the responses we have identified are associated with both eosinophilic, and neutrophilic, inflammatory responses in severe asthma. We previously showed that respiratory infections influence the nature of inflammatory responses in experimental severe asthma with bacterial infections promoting neutrophilic, and viral infections promoting eosinophilic, inflammation.[45] Based upon these findings, we propose that systemic immune cells in patients with severe asthma may have increased sensitivity to inflammasome priming and activation to different triggers and that the nature of the inflammasome-activating stimuli in the airways upon recruitment, plays the

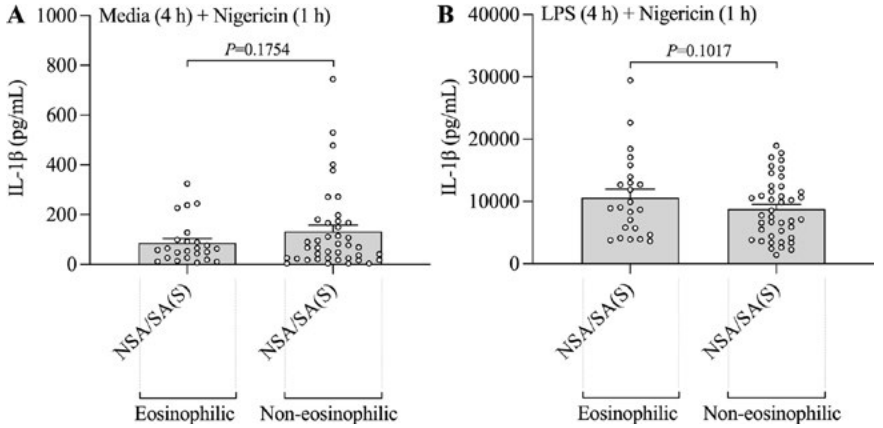


Fig. 4 Increased LPS-induced and/or nigercin-induced NLRP3 inflammasome-mediatedIL-1β release in peripheral blood mononuclear cells (PBMCs) from patients with asthma is not affected by sputum inflammatory phenotype. PBMCs from patients non-severe (NSA) and severe stable (SA(S)) asthma were **A** pre-cultured with media for 4 h before being stimulated with nigericin for 1 h, or **B** pre-stimulated with LPS for 4 h before stimulation with nigericin for 1 h, and the effects on IL-1β release were assessed in culture supernatants. The effects of nigericin or LPS + Nigericin stimulation on IL-1β release were assessed following stratification of subjects by sputum inflammatory phenotype. Data are presented as means ± SEM (*N* = 24–41)

crucial role in determining the nature of the inflammatory phenotype in severe asthma. Interestingly, we show that immune cells have similar responses in stable and exacerbating severe asthmatics. This suggests that the heightened responsiveness to infection-induced priming of inflammasome-mediated responses in severe asthmatics when stable may underpin the increased risk of viral and/ or bacterial infection-induced exacerbations in patients with severe asthma.[43,46,47]

We previously showed that increased IL-1β responses drive steroid-insensitive, inflammation and AHR, and that inhibiting NLRP3 activation with MCC950 reduced IL-1β production and ablated these features in murine models of severe asthma.[27] We now show that increased NLRP3 inflammasome-mediated IL-1β release from immune cells from humans with severe asthma can be pharmacologically inhibited with MCC950, demonstrating therapeutic potential for inflammasome inhibition in clinical settings. We show that increased ability for inflammasome activation is common to severe and non-severe asthma, in male and female, and obese and non-obese, individuals and is associated with neutrophilic and eosinophilic inflammation in severe asthma. Thus, therapeutic strategies that target inflammasome priming and/or activation may represent a new, broadly applicable approach to asthma management, particularly in severe, T2-low subtypes of disease.

It should be noted that there is a significant difference between the ages of the SA, NSA and healthy control groups. These data agree with previous findings that show that older asthmatics are more likely to have increased disease severity. Whilst our data clearly show increases in inflammasome-mediated IL-1β release from PBMCs from asthmatics, a link between increased IL-1β release from PBMCs and age cannot be ruled out and requires investigation in future studies. A limitation of the current study is that we performed all assessments in systemic immune cells. Whilst we were not able to conduct our NLRP3 inflammasome stimulation studies on cells isolated from the airways of participants, it is also likely that inflammasome responses would have already been activated to varying degrees in these cells and this would convolute the interpretation of the outcomes and compromise the relevance of the findings. We have previously shown that airways NLRP3 inflammasome responses are associated with increased neutrophilic and eosinophilic inflammation in the airways in both experimental and clinical asthma,[16,27] and there are subjects with asthma and IL-5-, IL-17A-/F- and IL-25-high sputum cytokine profiles that have increased sputum eosinophil and neutrophil numbers.[48,49] These findings highlight the co-existence of T2 and non-T2 cytokine responses in the airways with both eosinophilic and non-eosinophilic airways inflammation. Our data in the current study, that have been generated from PBMCs, extend upon these findings to support a fundamental underlying role for an increased ability of NLRP3 inflammasome responses in systemic immune cells in being associated with both eosinophilic and neutrophilic inflammatory cell numbers in the airways. Indeed, our data highlight that, as opposed to inflammatory cells and responses in the airways, systemic cells may be more homogenous in their behavior with a critical role for inflammasome responses underpinning both eosinophilic and non-eosinophilic asthma.

Another limitation of the study was that the cellular source and intracellular mechanisms of inflammasome signaling and IL-1β release from different cells were not fully characterized. We also did not perform a more detailed characterization of immune responses beyond eosinophilic and neutrophilic inflammation to provide a more thorough delineation between T2 and non-T2 asthma. Unfortunately, such analyses were not feasible in the current study, which was designed to assess the differences of NLRP3 inflammasome priming and activation, and effectiveness of inflammasome inhibition, in systemic immune cells in asthma. Nevertheless, our study, which investigated responses in a large number of subjects, clearly shows increased inflammasome responses, and highlights the potential for therapeutic targeting, in systemic immune cells in all subtypes of asthma. Our findings are novel and will spur future studies that identify the cellular source(s) of altered inflammasome responses and fully characterize which components of the inflammasome signaling network are altered in these cells as well as further interrogate these responses in T2 and non-T2 asthma. Importantly, our study shows strong relationships between IL-1β release from PBMCs and asthma status. These studies highlight the utility of investigating cytokine responses from PBMCs and other systemic immune cells for better understanding the immunobiology of asthma. Of note, through minor alterations to the assay system employed in the current study IL-17, which is an example of a cytokine known to be related to neutrophilic endotypes of asthma, release from PBMCs of subjects with eosinophilic and non-eosinophilic asthma could be explored.

We have previously shown that NLRP3 inflammasome-mediated IL-1β responses in the airways play a key role in the pathogenesis of severe neutrophilic asthma. The current study extends upon these findings by demonstrating, for the first time, that systemic immune cells in clinical asthma have an increased ability for inflammasome-mediated IL-1β release, regardless of asthma subtype. Importantly, we highlight that NLRP3 inflammasome-mediated IL-1β responses can be therapeutically suppressed in systemic immune cells from patients across all subtypes of both severe and non-severe asthma.

Abbreviations

LPS	Lipopolysaccharide
NLRP3	NLR family, pyrin domain–containing (NLRP) 3 inflammasome
PBMC	Peripheral blood mononuclear cell
T2	Type 2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-023-02603-2.

Acknowledgements

We acknowledge clinical technical support from Dr Erin Harvey and Lorissa Hopkins from the University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia.

Author contributions

JCH, RYK, NW, CA, and PGG wrote the manuscript and prepared the figures. JCH, RYK, MAC, PMH and PGG conceived and designed the studies. JCH, RYK, CA, ACB, CD, PD, JRM and NGH designed, performed, and validated the ex vivo cell stimulation and inhibition studies. PGG and LG collected and analyzed clinical patient samples, generated demographic data, and provided intellectual input on clinical asthma. NW and EGH designed and performed all statistical analyses. LAO, AAB, and MAC synthesized the NLRP3 inhibitor (MCC950) for ex vivo experimental studies and provided intellectual input on the role of NLRP3-associated inflammatory responses, and design of PBMC culture methodology. All authors read, edited, and approved the final manuscript.

Funding

This work was funded by grants from the NHMRC (1120252, 1118973). PMH is supported by an NHMRC Fellowship (1175134).

References

1 Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–73.

2 Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet. 2009;373:1905–17.

3 Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax. 2010;65:787–94.

4 Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. Eur Respir J. 2002;19:61–7.

5 Wang W, Li JJ, Foster PS, Hansbro PM, Yang M. Potential therapeutic targets for steroid-resistant asthma. Curr Drug Targets. 2010;11:957–70.

6 Hansbro PM, Kim RY, Starkey MR, Donovan C, Dua K, Mayall JR, Liu G, Hansbro NG, Simpson JL, Wood LG, et al. Mechanisms and treatments for severe, steroid-resistant allergic airway disease and asthma. Immunol Rev. 2017;278:41–62.

7 Hansbro PM, Scott GV, Essilfie AT, Kim RY, Starkey MR, Nguyen DH, Allen PD, Kaiko GE, Yang M, Horvat JC, Foster PS. Th2 cytokine antagonists: potential treatments for severe asthma. Expert Opin Investig Drugs. 2013;22:49–69.

8 Shaw DE, Berry MA, Hargadon B, McKenna S, Shelley MJ, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. Association between neutrophilic airway inflammation and airflow limitation in adults with asthma. Chest. 2007;132:1871–5.

9 Wadhwa R, Dua K, Adcock IM, Horvat JC, Kim RY, Hansbro PM. Cellular mechanisms underlying steroid-resistant asthma. Eur Respir Rev. 2019;28:190096.

10 Galvao I, Kim RY, Shen S, Budden KF, Vieira AT, Hansbro PM. Emerging therapeutic targets and preclinical models for severe asthma. Expert Opin Ther Targets. 2020;24:845–57.

11 Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract. 2017;3:1.

12 Buhl R, Humbert M, Bjermer L, Chanez P, Heaney Liam G, Pavord I, Quirce S, Virchow JC, Holgate S. Severe eosinophilic asthma: a roadmap to consensus. Eur Respir J. 2017;49:1700634.

13 Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178:218–24.

14 Lefaudeux D, De Meulder B, Loza MJ, Peffer N, Rowe A, Baribaud F, Bansal AT, Lutter R, Sousa AR, Corfield J, et al. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. J Allergy Clin Immunol. 2017;139:1797–807.

15 Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181:315–23.

16 Pinkerton JW, Kim RY, Brown AC, Rae BE, Donovan C, Mayall JR, Carroll OR, Khadem Ali M, Scott HA, Berthon BS, et al. Relationship between type 2 cytokine and inflammasome responses in obesity-associated asthma. J Allergy Clin Immunol. 2021;149:1270–80.

17 Grainge CL, Maltby S, Gibson PG, Wark PA, McDonald VM. Targeted therapeutics for severe refractory asthma: monoclonal antibodies. Expert Rev Clin Pharmacol. 2016;9:927–41.

18 Niessen NM, Fricker M, McDonald VM, Gibson PG. T2-low: what do we know?: Past, present, and future of biologic therapies in noneosinophilic asthma. Ann Allergy Asthma Immunol. 2022;129:150–9.

19 Simpson JL, Phipps S, Baines KJ, Oreo KM, Gunawardhana L, Gibson PG. Elevated expression of the NLRP3 inflammasome in neutrophilic asthma. Eur Respir J. 2014;43:1067–76.

20 Baines KJ, Simpson JL, Wood LG, Scott RJ, Gibson PG. Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples. J Allergy Clin Immunol. 2011;127(153–160):160.e151-159.

21 Besnard AG, Togbe D, Couillin I, Tan Z, Zheng SG, Erard F, Le Bert M, Quesniaux V, Ryffel B. Inflammasome-IL-1-Th17 response in allergic lung inflammation. J Mol Cell Biol. 2012;4:3–10.

22 Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, Bleecker ER. Analyses of asthma severity phenotypes

and inflammatory proteins in subjects stratified by sputum granulocytes. J Allergy Clin Immunol. 2010;125:1028-1036. e1013.
23 Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, Iwakura Y, Israel E, Bolger K, Faul J, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nat Med. 2014;20:54–61.
24 Konno S, Gonokami Y, Kurokawa M, Kawazu K, Asano K, Okamoto K, Adachi M. Cytokine concentrations in sputum of asthmatic patients. Int Arch Allergy Immunol. 1996;109:73–8.
25 Wanderer AA. Corticosteroid resistance in pulmonary neutrophilic inflammatory disorders and rationale for adjunct IL-1beta targeted therapy. Am J Respir Cell Mol Biol. 2009;41:246–7.
26 Rossios C, Pavlidis S, Hoda U, Kuo CH, Wiegman C, Russell K, Sun K, Loza MJ, Baribaud F, Durham AL, et al. Sputum transcriptomics reveal upregulation of IL-1 receptor family members in patients with severe asthma. J Allergy Clin Immunol. 2018;141:560–70.
27 Kim RY, Pinkerton JW, Essilfie AT, Robertson AAB, Baines KJ, Brown AC, Mayall JR, Ali MK, Starkey MR, Hansbro NG, et al. Role for NLRP3 Inflammasome-mediated, IL-1beta-Dependent Responses in Severe, Steroid-Resistant Asthma. Am J Respir Crit Care Med. 2017;196:283–97.
28 Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology. 2006;11:54–61.
29 Groslambert M, Py BF. Spotlight on the NLRP3 inflammasome pathway. J Inflamm Res. 2018;11:359–74.
30 Pinkerton JW, Kim RY, Robertson AAB, Hirota JA, Wood LG, Knight DA, Cooper MA, O'Neill LAJ, Horvat JC, Hansbro PM. Inflammasomes in the lung. Mol Immunol. 2017;86:44–55.
31 Schroder K, Tschopp J. The inflammasomes. Cell. 2010;140:821–32.
32 Kim RY, Pinkerton JW, Gibson PG, Cooper MA, Horvat JC, Hansbro PM. Inflammasomes in COPD and neutrophilic asthma. Thorax. 2015;70:1199–201.
33 Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proILbeta. Mol Cell. 2002;10:417–26.
34 Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. Annu Rev Immunol. 2009;27:229–65.
35 Stutz A, Golenbock DT, Latz E. Inflammasomes: too big to miss. J Clin Invest. 2009;119:3502–11.
36 Franklin BS, Bossaller L, De Nardo D, Ratter JM, Stutz A, Engels G, Brenker C, Nordhoff M, Mirandola SR, Al-Amoudi A, et al. The adaptor ASC has extracellular and "prionoid" activities that propagate inflammation. Nat Immunol. 2014;15:727–37.
37 Kufer TA, Fritz JH, Philpott DJ. NACHT-LRR proteins (NLRs) in bacterial infection and immunity. Trends Microbiol. 2005;13:381–8.
38 Katsnelson MA, Rucker LG, Russo HM, Dubyak GR. K+ efflux agonists induce NLRP3 inflammasome activation independently of Ca2+ signaling. J Immunol. 2015;194:3937–52.
39 Besnard A-G, Guillou N, Tschopp J, Erard F, Couillin I, Iwakura Y, Quesniaux V, Ryffel B, Togbe D. NLRP3 inflammasome is required in murine asthma in the absence of aluminum adjuvant. Allergy. 2011;66:1047–57.
40 Li H, Willingham SB, Ting JP, Re F. Cutting edge: inflammasome activation by alum and alum's adjuvant effect are mediated by NLRP3. J Immunol. 2008;181:17–21.
41 Rhodes L, Moorman JE, Redd SC. Sex differences in asthma prevalence and other disease characteristics in eight states. J Asthma. 2005;42:777–82.
42 Group TES. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J. 2003;22:470–7.
43 Ackland J, Watson A, Wilkinson TMA, Staples KJ. Interrupting the conversation: implications for crosstalk between viral and bacterial infections in the asthmatic airway. Front Allergy. 2021;2: 738987.
44 Essilfie AT, Horvat JC, Kim RY, Mayall JR, Pinkerton JW, Beckett EL, Starkey MR, Simpson JL, Foster PS, Gibson PG, Hansbro PM. Macrolide therapy suppresses key features of experimental steroid-sensitive and steroid- insensitive asthma. Thorax. 2015;70:458–67.
45 Kim RY, Horvat JC, Pinkerton JW, Starkey MR, Essilfie AT, Mayall JR, Nair PM, Hansbro NG, Jones B, Haw TJ, et al. MicroRNA-21 drives severe, steroid-insensitive experimental asthma by amplifying phosphoinositide 3-kinase-mediated suppression of histone deacetylase 2. J Allergy Clin Immunol. 2017;139:519–32.
46 Cookson W, Moffatt M, Rapeport G, Quint J. A pandemic lesson for global lung diseases: exacerbations are preventable. Am J Respir Crit Care Med. 2022;205:1271–80.
47 McDowell PJ, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker S, Hardman TC, Arron JR, Choy DF, Bradding P, et al. Exacerbation profile and risk factors in a type-2-low enriched severe asthma cohort: a clinical trial to assess asthma exacerbation phenotypes. Am J Respir Crit Care Med. 2022;206:545–53.
48 Seys SF, Scheers H, Van den Brande P, Marijsse G, Dilissen E, Van Den Bergh A, Goeminne PC, Hellings PW, Ceuppens JL, Dupont LJ, Bullens DM. Cluster analysis of sputum cytokine-high profiles reveals diversity in T(h)2-high asthma patients. Respir Res. 2017;18:39.
49 Seys SF, Long MB. The quest for biomarkers in asthma: challenging the T2 versus non-T2 paradigm. Eur Respir J. 2022;59:2102669.

Dräger

THIS IS VENTILATION

The new Evita

draeger.com

Dräger. Technology for Life®

Our Aqua…

Your secretion management

PMV® 007
(Aqua Color™)

The only speaking Valve backed by mountains of research, the **Aqua Color**™ Passy Muir® Valve may:

- Facilitate secretion management
- Improve swallowing
- Reduce aspiration
- Facilitate weaning and expedite decannulation
- Improve olfaction
- Improve speech production
- Promote better hygiene, and
- Be used on a ventilator

To find out more, visit **www.passymuir.com**

Passy Muir®

ALL PASSY MUIR VALVES PROUDLY MADE IN USA

© Passy-Muir, Inc.