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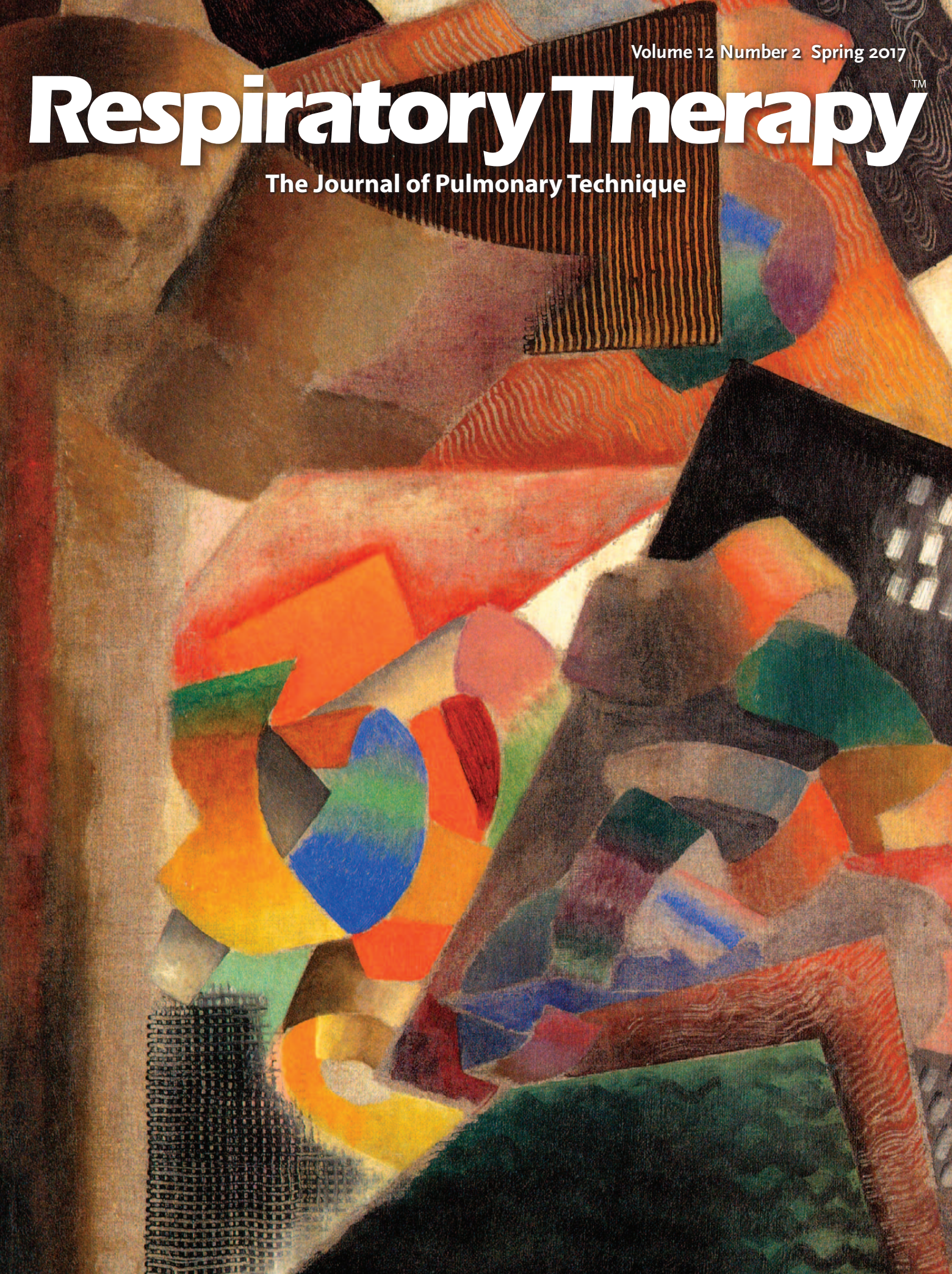
Respiratory Therapy™

The Journal of Pulmonary Technique



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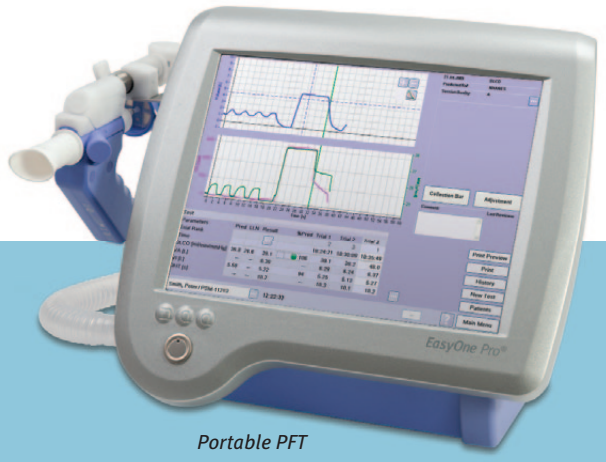

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News

■ Spring 2017

Nasal High-Flow Less Effective Than CPAP as Primary Support for Preemies

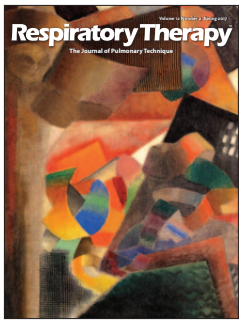
Nasal high-flow therapy is significantly less effective than nasal continuous positive airway pressure (CPAP) when used as primary support for preterm infants with respiratory distress, according to a randomized study reported online in The New England Journal of Medicine. The trial, known as HIPSTER, was halted early because high-flow therapy produced treatment failure 25.5% of the time compared to a failure rate of 13.3% with CPAP (P<0.001). Nasal high-flow therapy, using heated and humidified air, has become increasingly popular as an alternative to CPAP as a primary therapy. Roughly two thirds of intensive care units in the United States, Australia and New Zealand use it for that purpose. It has already been shown to be effective for neonates as postextubation support. "It's a much less bulky mode of support, it's more comfortable for the babies, it's easier to use, and parents seem to prefer it," said chief author Dr. Calum Roberts, a neonatologist at the Royal Women's Hospital in Melbourne, Australia. "But to assess how effective it is takes a number of years." The HIPSTER study began in 2012. He said the new findings will make doctors more selective in how they use it, noting that it worked for a majority of the neonates. In Australia and Norway, the research team enrolled 564 infants with a gestational age of at least 28 weeks, all with early respiratory distress who had not received surfactant therapy. Half received nasal high-flow therapy and the rest received nasal CPAP. If high-flow therapy didn't work, that infant was switched to CPAP. CPAP recipients were switched to intubation and mechanical ventilation if that treatment failed. The overall failure rates were twice as high with nasal high-flow. The pattern was seen "both among infants with a gestational age of less than 32 weeks and among those with a gestational age of 32 weeks or greater at randomization," the researchers said. They also found that the median duration of respiratory support was four days with nasal high-flow versus three days for CPAP (P=0.005). In addition, the high-flow babies were more likely to be given supplemental oxygen (P=0.02). Nasal trauma was more than twice as likely to occur with CPAP. The rates were 18.5% with CPAP compared with 8.3% for high-flow (P<0.001). There was no significant difference in costs. One infant died in each group. High-flow "doesn't seem to be as effective as CPAP overall, but the other thing we learned from the study is that for the majority of babies, high flow was effective," Dr. Roberts said. "It comes down to the fact that for the babies who are a bit less premature and who have slightly less breathing difficulty, it would be appropriate treatment to use high-flow as the first line of support."

Ganshorn SpiroScout Spirometer Cleared by FDA

The FDA has given Ganshorn Medizin Electronic GmbH good news by giving 510(k) clearance for its SpiroScout Spirometer. The SpiroScout is a complete spirometer based on the unique ultrasonic measurement principle of Ganshorn. But the SpiroScout is much more than just a spirometer. The SpiroScout is the first ultrasonic spirometer to simultaneously measure flow and gas density providing all necessary information about the volume and gas exchange from one single measurement. Other unique features of the SpiroScout are: high precision spirometry due to direct to flow measurement, easy to clean, easy to operate, all ATS/ERS repeatability criteria built-in the software, no perceived resistance increasing patient comfort, teal-time BTPS correction, drift free and highly accurate, and no volume calibration and warm-up time necessary. Ganshorn Medizin Electronic GmbH has been creating innovative medical products in the respiratory field for over 30 years and finally decided in 2016 to bring their innovative pulmonary function product line to the United States. If you would like to find out more information about the SpiroScout or would like to learn more about the Ganshorn technology visit www.ganshorn.us.

FDA Clears World's Smallest CPAP

ResMed announced at the 35th annual J.P. Morgan Healthcare Conference that the US Food and Drug Administration has cleared ResMed's AirMini, the world's smallest continuous positive airway pressure (CPAP) device. ResMed's tiny yet fully-featured AirMini, to be launched later this year, is designed as a secondary CPAP, making it easier for people to continue their sleep apnea therapy while traveling. As an addition to ResMed's industry-leading Air Solutions portfolio, the AirMini offers multiple benefits to home medical equipment providers—supporting increased therapy compliance and convenience for their patients, and incremental revenue opportunities. "ResMed



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DEPARTMENTS

ARTICLES

AirMini is the portable travel CPAP patients and home medical equipment providers have been waiting for, and we look forward to bringing it to market later this year," said ResMed CEO, Mick Farrell. "It fits easily in carry-on luggage—even in the seatback pocket on the plane–and delivers all the best-in-class comfort features patients need to get the best sleep." ResMed is a global leader in connected care, with more than 2 million patients remotely monitored every day. Our 5,000-strong team is committed to creating the world's best tech-driven medical device company—improving quality of life, reducing the impact of chronic disease, and saving healthcare costs in more than 100 countries.

Antipsychotics Linked to Respiratory Failure

Antipsychotics have been linked to respiratory failure in a dose-dependent manner among patients with chronic obstructive pulmonary disease (COPD), results of a large observational study show. Multiple cases about acute respiratory distress or acute respiratory failure [ARF] from the use of antipsychotics have been reported during the past decades. Nevertheless, no population-based studies have been conducted to examine this potential drug safety issue, according to the study investigator with the National Defense Medical Center in Taipei, Taiwan. Clinicians should exercise caution when prescribing antipsychotics to patients with COPD and avoid high doses if possible, the investigators write. The researchers analyzed healthcare claims records in the Taiwan National Health Insurance Database and antipsychotic medication history for 5032 patients with COPD who developed incident and idiopathic ARF (excluding cardiogenic, traumatic, and septic causes). Using a case-crossover study design, they compared antipsychotic use during the 2 weeks before the ARF event (case period) and an earlier control period 2 to 3 months before the ARF event. A total of 590 (11.7%) patients with ARF filled at least one antipsychotic prescription during the case period, compared with 443 (8.8%) during the control period. This corresponds to a 1.66-fold (95% confidence interval [CI], 1.34 – 2.05; P < .001) adjusted increased risk for ARF, regardless of antipsychotic class and route of administration. The risk for ARF with antipsychotic use was dose-dependent, increasing from a 1.52-fold risk for a low defined daily dose (DDD) of 0.25 or less to a 3.74-fold risk for a high DDD of 1 or more. The authors urged healthcare professionals to be vigilant about the development of ARF in COPD patients receiving antipsychotic treatment, especially during the initial phase of treatment," he said.

Treatment of Bronchiectasis Shows Promise

Monaghan Medical Corporation (MMC) announced that the findings of a study published in the most recent issue of Academic Radiology shows that patients with non-cystic fibrosis (CF) bronchiectasis responded favorably to airway maintenance therapy using the Aerobika device. This latest study adds to the growing base of evidence that demonstrates Monaghan's drug-free Aerobika device is effective for lung health maintenance. In this latest study, researchers noted significant improvements in ventilation function for a number of bronchiectasis patients after three weeks of using the Aerobika device. There were no adverse events related to the use of the device reported during the study. Bronchiectasis is a condition in which the structure and function of the airways become permanently damaged, usually as the result of infection or other condition. Patients suffering from chronic bronchiectasis typically have trouble clearing mucus from airways and suffer from a repeating pattern of airway damage, mucus buildup, and recurrent infections. The result is typically a vicious cycle of decline, resulting in reduced air exchange in the smaller airways.

There are three primary goals in the successful treatment of bronchiectasis: 1. Treat any underlying conditions and lung infections 2. Remove mucus from the lungs, and 3. Prevent complications. Researchers have observed overlap between bronchiectasis and other chronic airway diseases such as chronic obstructive pulmonary disease (COPD). Studies show that these types of patients tend to have higher rates of exacerbation and worse outcomes. The overlap between bronchiectasis and COPD was highlighted in a recent study presented at the 2016 CHEST annual meeting in October. Investigators found that 92.7 percent of COPD patients who had experienced more than one exacerbation in the previous 12 months also had bronchiectasis. The results of the study published in Academic Radiology showing effectiveness in treating bronchiectasis patients using the Aerobika device are in line with another 2016 real-world

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1. Independent lab testing analyzed and compared average airflows at the mouth generated by high frequency chest wall oscillation (HFCWO) therapy in 10 subjects using home care garments. Airflows measured at commonly prescribed medium pressures (50% of maximum) at multiple therapy frequencies (5, 10, 15, and 20 Hz). Test data and reports on file at Hill-Rom, Inc.
2. Market data and reports on file at Hill-Rom, Inc.
3. Sound testing results based on average noise level at 4 microphone positions at 1 meter. Sound for each device measured at medium pressure at frequencies of 5, 10, 15, and 20 Hz. A comfortable hearing level is typically considered at 60 dB and lower. Reference on file at Hill-Rom, Inc.
4. About the connection between sound level and loudness, there are various theories. Research by Richard M. Warren leads to a level difference of 6 dB.
5. Clinical studies with patients using HFCWO therapy as listed in PubMed search through 2015. Includes HFCWO devices from Hill-Rom, Electromed, International Biophysics Corporation and Respiratory Technologies, Inc. On file at Hill-Rom, Inc.

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Enhancing outcomes for patients and their caregivers: Hill-Rom

study presented at the European Respiratory Society (ERS) International Congress. Investigators found the Aerobika® device demonstrated a clinically significant reduction in exacerbations in as little as 30 days of treatment when used as an add-on to usual COPD medications. In the study, 15 participants with non-CF bronchiectasis and 15 age-matched healthy volunteers underwent spirometry, plethysmography, computed tomography (CT), and hyperpolarized He magnetic resonance imaging (MRI). Bronchiectasis patients also completed a Six-Minute Walk Test, the St. George's Respiratory questionnaire, and Patient Evaluation Questionnaire (PEQ), and returned for a follow-up visit after three weeks of daily oscillatory positive expiratory pressure (Aerobika device) use. The Aerobika device is hand-held, easy-to-use and drug-free. When the patient exhales through the device, intermittent resistance creates positive pressure and oscillations simultaneously, which expands the airways, helps expel the mucus to the upper airways where it can be coughed out, and may also aid in improved drug deposition.

Formulation Capabilities Bring Hope for Patients with Chronic Breathing Problems

Chronic respiratory diseases that affect the airways and different structures of the lungs are on the rise. As per an article in the journal Office of Disease Prevention and Health Promotion prevalence of asthma has been increasing since 1980. Furthermore, COPD is believed to be one of the fourth main causes of death in North America. In 2006, about 120, 000 succumbed to COPD in the United States. This figure was close to the number of patients who lost their battle against lung cancer. Last year, Jackson, Mississippi was declared as the "Allergy Capital" of the United States by experts in "Asthma and Allergy Foundation of America". Researchers at Allied Market Research analyzing the share and size and growth in the COPD and asthma devices market say concerns over air pollution will open new avenues for the industry.

Big Brands Bank on Billion Dollar Inhaler Industry

A major announcement in the inhaler industry arrived when Elder Pharmaceuticals Limited revealed that it is banking on the Rs. 800 Cr nasal inhaler category in India. This pharma company plans on strengthening its rural marketing plans and selling products through a strong distribution channel. Reduced price points as well as attractive packaging are believed to be some of the areas where inhaler manufacturers would be focusing more. A company named Teva made winds in the COPD and asthma devices market, when it announced that the Food and Drug Association has finally accepted to review the manufacturers new drug applications for two new products. The first salmeterol product is Teva's fixed-dose combination ICS and LABA, which are delivered through the company's RespiClick breath-actuated, MDPI. Another fluticasone propionate, which is an ICS monotherapy delivered through the RespiClick device, has also caught quite an attention.

New Prototype Nebulizer Would Soon Replace Injections

Nebulizers are not new. Medical practitioners have been using bulky and big electric nebulizers for the past 25 years to help kids' breath without difficulty during an asthma attack. However, an advanced prototype nebulizer developed in 2015 at the famous RMIT, Melbourne, completely revolutionized the COPD and asthma devices market. Designed to easily fit into a human hand the device can deliver a higher dose of drugs per minute than the current nebulizers available in the market. Product developers behind this advanced device said that the product will soon replace the injections as well as traditional inhalers for patients with conditions such as diabetes, cancer, asthma and cystic fibrosis. The product developers further add that it is too early to say what the price of the product will be, but they hope it to be below US$50. Ideally with the new version that's affordable enough, their demand in developing nations such as India, Africa and others, where diseases are often spread through reuse of non-sterilized needles would increase.

Ultrasonic Nebulizer Set to Revolutionize

Pocket-size or small ultrasonic nebulizer applying a novel nozzle that can enhance inhalers are witnessing higher demand. Industry experts believe that inhalation has opened new routes for the non-invasive, drug delivery techniques, both local as well as systematic applications. Besides this, excessive control over the particle size and with output is playing a critical part in ensuring the efficiency and effectiveness of the expensive drug delivery has caught the attention of various scientists and researchers. A group of innovators from the "Department of Electrical Engineering and Computer Science" at the reputed University of California has invented novel equipment for inhalation drug delivery, which fulfils the requirements unmet by existing commercial devices. This is a clear indication that the future of the COPD and asthma devices market will remain robust in years to come.

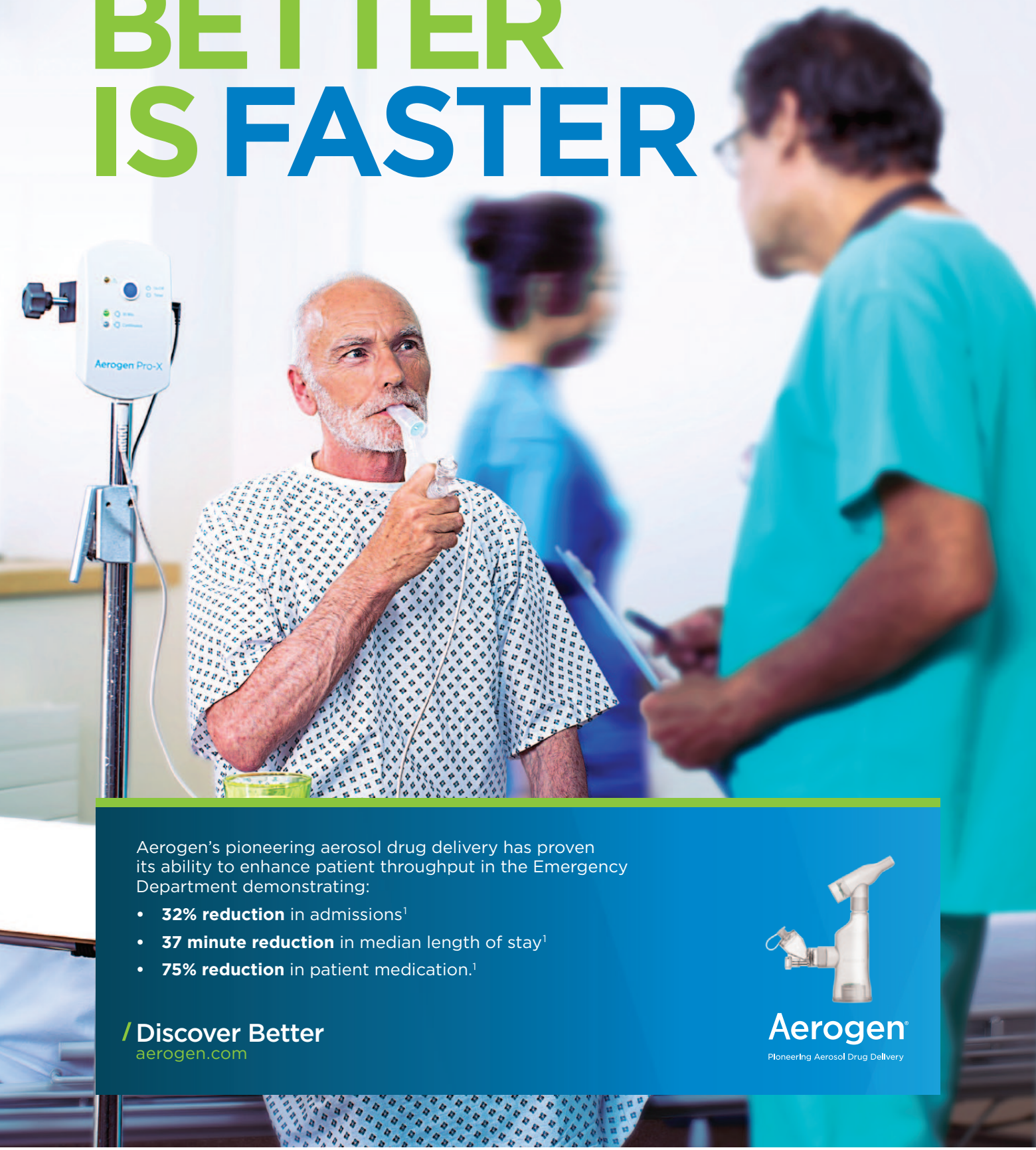
Research and Development in the Drug Powder Inhalers strengthens

Pulmonary as well as nasal delivery is a rapidly growing field. Growth in this segment is particularly driven by the dominance of several, chronic obstructive, particularly in developing countries such as the India, Africa and others. Furthermore, the Dry-powder-inhaler technology that uses engineered particles has also become the most preferred approach, when it comes to inhalation formulation over other aerosols as well as dry-powder technologies. A company named "Capsugel's Dosage Form Solutions" shot to fame when it made a huge investment in two important components required to administer an inhalation dosage forms for its end users. The company's inhalation formulation as well as process design applies a particle-engineering production platform. Another attraction is the manufacturer's full range of engineered dry-powder-inhaler capsule. Capsugel's product is in its Phase 3 clinical manufacturing scales. They are also operating with equipment makers to design finished equipment as well as further optimize the solution. Such products will create new opportunities for many COPD and asthma devices market players.

Metered Dose Inhalers Segment Witnesses B2B Deals

In 2017, the Metered Dose Inhaler segment will observe major business to business deals. Propeller Health has already set the stage by partnering with a drug delivery system brand called Aptar Pharma. The investor took this bold step to become the first to the market connected, integrated metered dose inhaler company. Commenting on the recent development David Van Sickle, the chief executive officer at the Propeller, said "Patients and physicians deserve better designed inhalers that are easier to use and help them successfully treat their chronic respiratory disease." Sickle further explained "We are excited to work with Aptar to bring important digital innovation to respiratory drug delivery. We expect our connected inhaler to become the cornerstone for a platform of digital programs that will support and encourage better management of and quality of life with chronic respiratory disease. Together I believe we have the scale

BETTER IS FASTER



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- **37 minute reduction** in median length of stay[1]
- **75% reduction** in patient medication.[1]

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1 Dunne R et al. Aerosol dose matters in the Emergency Department: A comparison of impact of bronchodilator administration with two nebulizer systems. Poster at the American Association for Respiratory Care. 2016

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and expertise to impact millions of patients with asthma and COPD around the world."

Protection Added Against Gastric Splash-back

Dale, the company that pioneered improvements in enteral access, is again advancing patient care and practitioner protection with the release of its new ACE Connector (485) with ENFit technology. The new ENFit-compatible ACE Connector incorporates the benefits of the legacy ACE (475), along with additional new features. "Clinicians are welcoming the enhanced streamlined design and added safety," says John Brezack, President of Dale. "Dale has just made a great product even better." A new hybrid medication port retains the original ACE auto seal technology and combines it with a new ENFit syringe/plunger activated male port. The seal and the plunger work in unison to provide the practitioner a higher level of protection against gastric splash-back. In addition, an improved handle design helps prevent mis-insertions of ENFit syringes in low light hospital environments, which can occur during sleeping hours on patient floors. The legacy Dale ACE 475 Connector will continue to be available in support of legacy enteral feeding devices. For more information about Dale's new ENFit Compatible ACE Connector, or to request a product sample, visit www.dalemed.com or call 800-343-3980.

Use of 3D Printed Splints for Infants

Three infants with an often-fatal airway disease have been treated by implanting a 3D printed medical device that improves breathing and changes shape as the children grow, the researchers reported. All three custom airway splint devices were designed to fit the anatomy of each child, researchers at the University of Michigan and colleagues reported in the journal Science Translational Medicine.

The splints were hollow, porous tubes that could be stitched over the affected airways, forming a scaffolding that helped support the weakened structures. They were made with a "bioabsorbable" material known as polycaprolactone that dissolves in the body over time. Researchers at the University of Michigan made the devices using 3D printing, in which materials are added in layers to create custom products. Such printers are already used in medicine to create a number of custom implants, creating new jaws, hips and hearing devices, for example.

Accriva Acquired

Werfen and its subsidiary Instrumentation Laboratory (IL) have announced the acquisition of Accriva Diagnostics, a global leader in in vitro diagnostic (IVD) blood testing at the Point-of-Care (POC), including its flagship product portfolio spanning coagulation, platelet aggregation, CO-Oximetry and incision devices. This acquisition will allow IL to establish a market-leading position in hospital-based POC Hemostasis testing, expand its position in POC Critical Care testing, and complement its leadership of the Hemostasis laboratory segment. "Over the course of our 50-year history, we have demonstrated our strong commitment to expanding our IVD business through organic growth, complemented with highly strategic acquisitions," said Carlos Pascual, CEO at Werfen. "Like our recent acquisition of CA Casyso AG and its Tem subsidiaries, the acquisition of Accriva is exemplary of this commitment, as well as the confidence we have in our future together." An integral part of Werfen, IL develops and manufactures Hemostasis, Critical Care and Patient Blood Management (PBM) products. Key Accriva product additions to the Company's portfolio include Hemochron, the gold standard for Activated Clotting Time (ACT) testing, and VerifyNow, the leading system for platelet function analysis, among other leading brands. These products are primarily used at the POC during interventional cardiac and vascular procedures, and in hospital laboratories. "By acquiring Accriva, we are expanding our product offering, expertise, and know-how in Point-of-Care testing, particularly for Hemostasis," said Ramon Benet, CEO at IL. "The addition of Accriva products to our strong Critical Care, Hemostasis and Patient Blood Management portfolios creates an even more comprehensive and integrated testing solution for hospital acute care settings and laboratories, further impacting positive clinical outcomes and reducing healthcare costs." Accriva, based in San Diego, California, arose from the merger in 2013 of International Technidyne Corporation (ITC) and Accumetrics. The Accriva product portfolio represents over 40 years of POC leadership and expertise, including product development, manufacturing, marketing and sales. Key brands include Hemochron, VerifyNow, Avoximeter CO-Oximetry systems, and Tenderfoot, Tenderlett and Surgicutt incision devices.

Looking at GERD

Gastroesophageal reflux disease (GERD), being female, and certain scores on the St. George's Respiratory Questionnaire (SGRQ) were associated with exacerbations of chronic obstructive pulmonary disease (COPD) in subjects using long-acting controller medication, according to a study presented at the American Thoracic Society International Conference. "Knowing these factors can help clinicians identify subjects at risk for acute exacerbations of their COPD," said Robert Busch, MD, Brigham and Women's Hospital, Boston. Although inhaled medications can decrease the risk for exacerbations, some COPD patients still experience them, Dr. Busch said. Researchers aimed to determine the prospective risk factors for acute exacerbations (AE) of COPD among subjects in the COPDGene study, which focuses on genetic factors relating to COPD. A total of 2489 adults with COPD on tiotropium (TIO), long-acting beta-agonist inhaled corticosteroids (LABA/ICS), and/or short-acting bronchodilators (SAB) alone or in combination were studied using retrospective data from the COPDGene study and prospective data from the telephone and web-based biannual Longitudinal Follow-Up program. Researchers divided subjects according to medication use groups (TIO/LABA/ICS, TIO, LABA/ICS, and SAB); exacerbators and nonexacerbators were identified by the frequency of AECOPD (one or more AECOPD a year compared with zero AECOPD for nonexacerbators). In multiple medication groups, the presence of GERD, female gender, and higher total SGRQ scores were significant predictors of exacerbator status, according to the researchers. Subjects in the LABA/ICS or TIO groups had similar characteristics, such as forced expiratory volume in one second, 6-minute walk distance, percent emphysema by CT scan, and pack-years of smoking. There was a trend toward significantly lower rates of exacerbations in subjects taking TIO compared with those taking the LABA/ICS combination. This was especially true in subjects who did not have a doctor's diagnosis of asthma.

The Benefits of Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) treatment could be a valuable addition to comprehensive therapy in patients with obstructive sleep apnea (OSA) syndrome, according to a new study. The study was presented at the American Thoracic Society International Conference. "In our study with 40 newly diagnosed OSA patients and a control group, pulmonary rehabilitation

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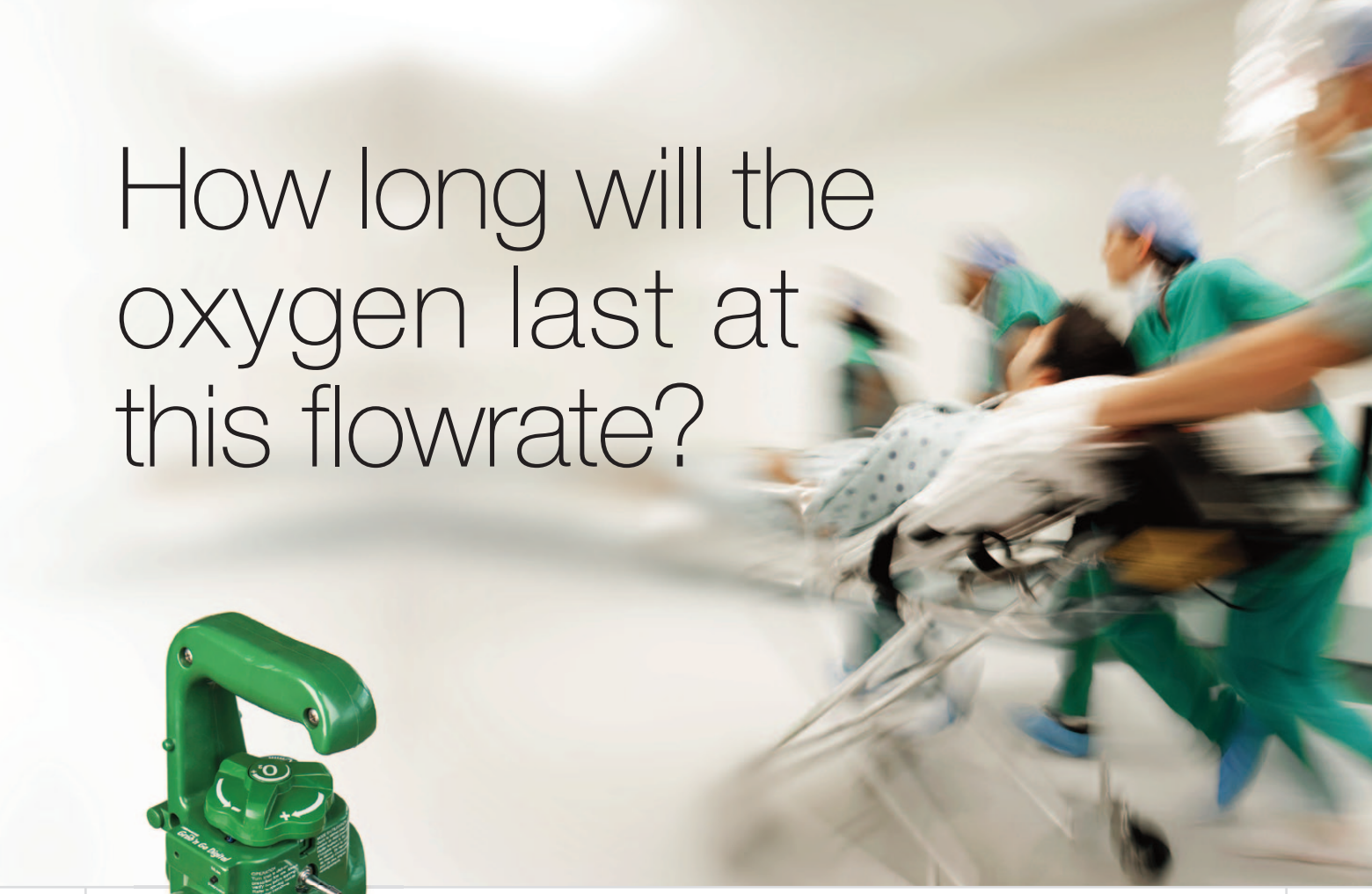

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helped reduce body mass index, certain body circumferences, and improve pulmonary function," said researcher Katerina Neumannova, MSc, PhD, Palacky University, Faculty of Physical Culture, Olomouc, Czech Republic. The classic treatment for patients with OSA is continuous positive airway pressure, often called CPAP or CPAP therapy. Treatment via PR, which is used for conditions such as chronic obstructive pulmonary disease (COPD), has not been thoroughly studied in OSA, even though patients with OSA often have respiratory symptoms associated with a decreased health-related quality of life and a diminished functional capacity. The study included 40 patients with OSA who were randomly assigned to either the PR group (n=20) or the control group (n=20). All patients involved in the study received CPAP therapy as their apnea/hypopnea index (AHI) was higher than 15. The PR group had 6 weeks of 60-minute individual rehabilitation sessions twice a week. The sessions consisted of education, exercise training, breathing retraining, respiratory muscle training, and oropharyngeal exercises. At baseline and then after 6 weeks of CPAP-only use or CPAP with the PR, researchers tracked a number of parameters, including pulmonary function, AHI, body mass index (BMI), percentage of body fat; and neck, waist, and hip circumferences. The final study included 15 patients in the PR group and 20 in the control group, as 5 patients did not complete PR. Although OSA severity was significantly decreased in both groups after the treatment, significant reduction of BMI, neck, waist and hip circumferences was confirmed only in the PR group. That same group also had an improvement in pulmonary function. Patients in both groups had decreased body fat, although body fat loss was higher in the PR group.

"Patients with OSA can benefit from pulmonary rehabilitation treatment," Dr. Neumannova said. "We can determine on a patient-by-patient basis which patients would benefit most from pulmonary rehabilitation based on their individual disease and clinical judgment."

Length of Mechanical Ventilation Poses Risks

Critically ill patients who have been mechanically ventilated for more than seven days are at greatly increased risk for functional impairment and mortality at one year following discharge from the intensive care unit (ICU), according to a new study presented at the American Thoracic Society International Conference. "Prolonged mechanical ventilation has a significant impact on the long-term well-being of patients," said lead author Margaret Herridge. MD, MPH. of the University of Toronto. "In our study of nearly 400 ICU patients, we were able to identify a number of characteristics that predicted subsequent disability. Knowing these risk factors can help guide their rehabilitation needs." The study involved 391 patients who had undergone at least one week of mechanical ventilation. Median ventilation time was 16 days, mean length of stay in the ICU was 22 days, and mean length of stay in the hospital was 29 days. Assessment included the Functional Independence Measure (FIM), an indicator of disability level, along with measures of physical capacity, neuropsychological status, quality of life, healthcare utilization, and mortality. FIM score at seven days post post-ICU discharge was associated with patient age and length of stay in the ICU. The oldest patients with the longest ICU stays had the worst outcomes, with 40% of those patients aged 46-66 years with an ICU length of stay of 14 days or more dying within the first year of follow-up, 29% being readmitted to ICU, and most exhibiting severe impairments in daily activities, including bathing, dressing and climbing stairs. In contrast, patients younger than 42 years of age with an ICU length of stay of less than two weeks had the best functional outcomes. The rate of hospital readmission was high for all patients, ranging from 36% to 43% for different age and length of stay patient groups. FIM score, Charlson score (a measure of comorbidities), and age independently predicted mortality at one year.

"A combination of FIM score at 7 days after ICU discharge, length of stay in the ICU, and patient age can be used to predict subsequent impairment in mechanically ventilated patients," said Dr. Herridge. "Earlier intervention based on these predictions may improve outcomes for these high-risk patients."

COPD Worse in Rural, Poor Areas

Living in a rural area and being poor are risk factors for chronic obstructive pulmonary disease (COPD), said Sarath Raju, MD, MPH, Johns Hopkins School of Medicine, Baltimore, Maryland, lead author of a study presented at the 2015 American Thoracic Society International Conference. The researchers used a nationally representative sample to pinpoint COPD risk factors. "We wanted to identify the prevalence of COPD in urban and rural areas in the U.S. and determine how residence, region, poverty, race and ethnicity, and other factors influence COPD rates," Dr. Raju said. Using data from the National Health Interview Survey, the U.S. Census, and the National Center for Health Statistics Urban-Rural Classification Scheme, the 87,701 participants included a population-based sample of adults older than age 40. The study's main outcome was the prevalence of COPD, defined as self-reported emphysema or chronic bronchitis. The researchers looked at both community-based and individual-based factors that are potential predictors of COPD, such as region, census level poverty, urban/rural residence, fuel sources, age, sex, race/ethnicity, smoking years, household income, home ownership, and education status. The prevalence of COPD in the study was 7.2%. However, in small metro/rural-poor communities, the prevalence was 11.9%. Rural residence, southern residence, and community poverty were all associated with a greater prevalence of COPD. When the researchers added individual income to the model, community poverty was no longer significant. Researchers found an association between biomass fuels and COPD in the South, but there was no association in an overall multivariate model.

"Findings suggest regional differences and the need for future disparities research to understand the potential contribution of occupational exposures, fuel sources, and indoor air pollutants to COPD prevalence in poor, rural areas," the researchers concluded.

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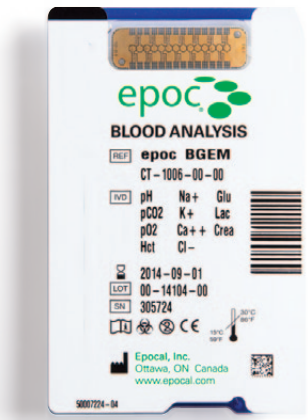

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Case Series: Use of Continuous High Frequency Oscillation (CHFO) in Respiratory Failure and Post-Operative Patients

David Grooms MSHS, RRT, Susan Swedish, BA, RRT, Shawn Price MS, RRT

Introduction

Continuous High Frequency Oscillation (CHFO) is becoming a popular intervention aimed at unsticking and mobilizing airway secretions to prevent atelectasis. In some forms, this therapy is delivered with a mouth-piece or mask, and in conjunction with mechanical ventilation for those who require an artificial airway. The MetaNeb System delivers continuous high-frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP) to facilitate clearance of mucous from the lungs. We present a series of 3 patient cases illustrating improved lung aeration and secretion clearance resultant of CHFO from The MetaNeb System (Hill-Rom).

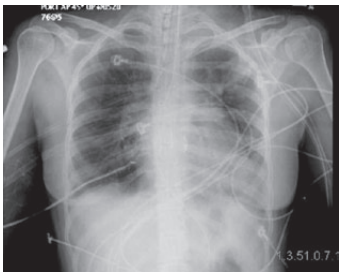
Case 1: The Use of MetaNeb to Improve Lung Aeration During Respiratory Failure

A twenty-one-year-old white female with prior lung transplant (approximately one year prior to admission) presented to our emergency room with acute respiratory failure requiring invasive mechanical ventilation. She had developed failure to thrive and acute chronic hypercarbic respiratory failure. Her past medical history included having bronchopulmonary dysplasia, asthma, deep venous thrombosis, and immunosuppressant therapy.

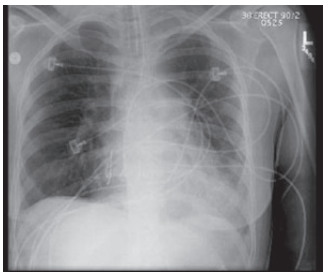
We initiated a lung protective ventilation strategy using the Pressure Control Continuous Mandatory Ventilation (PC-CMV) mode with inspiratory pressures being adjusted to target a tidal volume of 4-6 ml/kg/Ideal Body Weight (IBW) coupled with a respiratory system plateau pressure ≤30 cm H2O. Respiratory rate was increased to 26 breaths per minute to increase alveolar minute ventilation without inducing auto-peep as observed by the expiratory flow waveform returning to baseline. PEEP was increased and limited to 8 cm H2O due to elevated plateau pressures. Fractional inspired oxygen (FiO2) was titrated to a minimum level of .75 (75%). Following the initial ventilator assessment, we suspected the hypercarbia (PCO2 >130) was resultant of profound alveolar de-recruitment and increased physiologic deadspace. Therefore, we utilized a quasi-static pressure volume curve to assess lung recruitment potential to optimize the mechanical ventilation settings incorporating elevated PEEP and alveolar recruitment maneuvers. However, this curve indicated very low potential for lung recruitability therefore open lung ventilation adjuncts were avoided. Subsequently, tracheal gas insufflation, and heliox failed to significantly improve her hypercarbia. At this time, we concluded that we had maximized the mechanical ventilator settings and that atelectasis resultant of mucous plugging was the most likely cause of increased physiologic deadspace.

Therefore, CHFO treatment via the MetaNeb System was initiated in attempt to mobilize suspected mucous plugs that may be present. CHFO had not been previously used as we did not suspect this to be a secretion retention issue. Treatment was initiated with 10cc's Normal Saline Q4 around the clock in-line with mechanical ventilation. The next day, a follow-up chest X-ray revealed improvement in aeration and minimization in secretions was noted by the Respiratory Therapist. A reduction in FiO2 to 0.5 was achieved as well as a reduction in minute volume. An improvement in breath sounds was also documented by the attending MD, RRT, and RN.

CHFO treatment was continued until patient was extubated 5 days later. She was discharged from the ICU 2 days post-extubation and was discharged from the hospital 9 days thereafter. MetaNeb was utilized throughout her hospital stay and was considered an essential therapy in minimizing recurrent secretion problems.



Pre-MetaNeb Treatment



18 Hours Post-MetaNeb Treatment

Conclusions

The strength of this case is that we were able to demonstrate a radiologic improvement in lung aeration with MetaNeb Therapy when other therapies had failed. Although difficult to associate the overall impact on her discontinuance of mechanical ventilation, ICU and hospital discharge, this case may highlight the need to provide specific therapies on an individualized basis.

The previous interventions we employed above where aimed at minimizing suspected atelectasis due to fluid filled alveoli resultant from inflamed lungs, when all the while her ventilation failure was most likely due to mucous accumulation and possible plugging.

The authors are with Sentara Norfolk General Hospital, Norfolk, VA.

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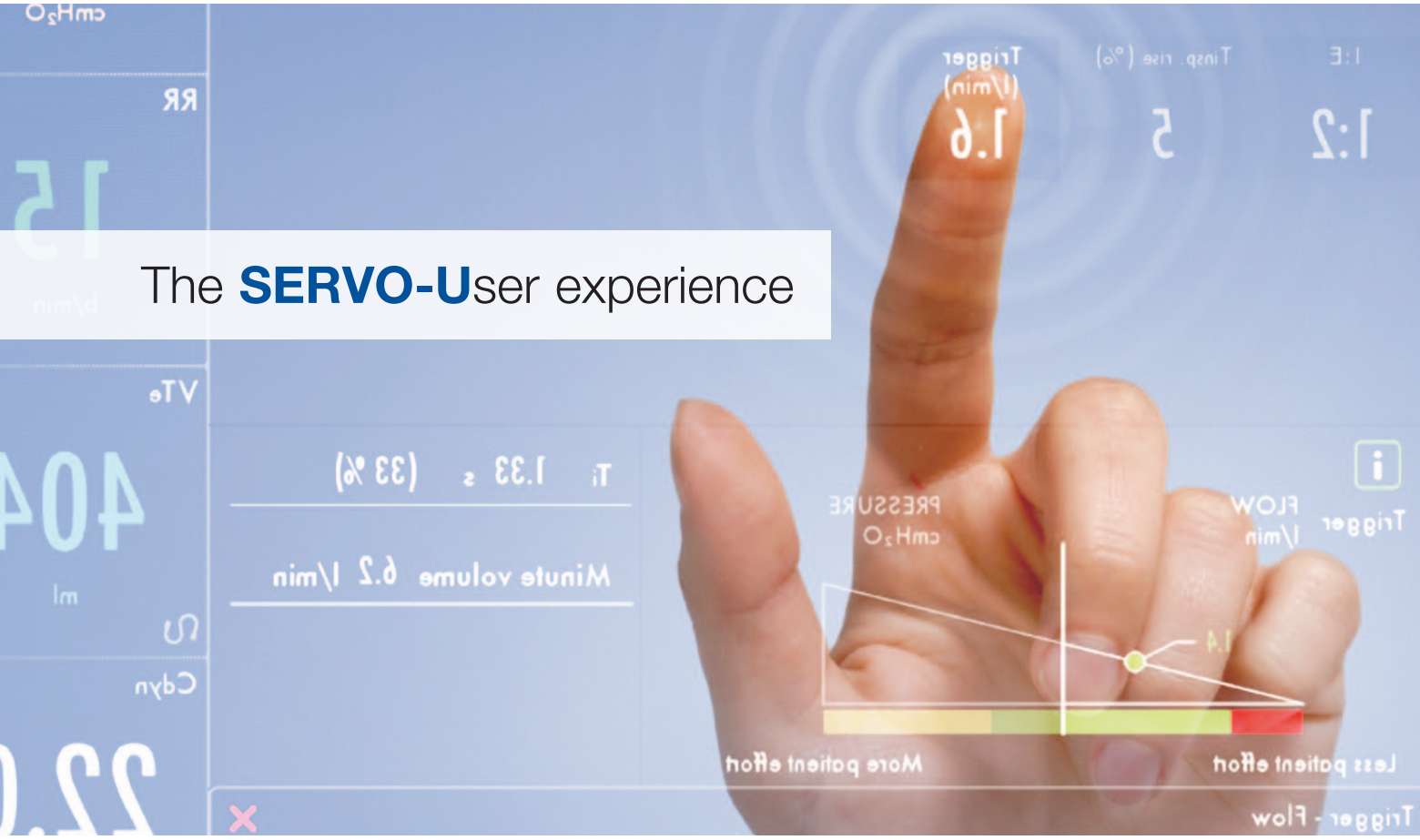

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Case 2: The Use of MetaNeb to Improve Lung Aeration During Respiratory Failure

A 57-year-old Caucasian male patient presented to our Emergency Department on Day 0 with Cardiac Arrest and Respiratory Failure. He had the following co-morbidities: Cardiac arrest s/p successful resuscitation (22 min CPR, immediate bystander resuscitation); respiratory failure; Coronary Artery Disease (CAD), history of prior Coronary Artery Bypass Graft (CABG); hypertension; hyperlipidemia; BPH. He underwent cardiac catheterization after being stabilized with return of spontaneous circulation.

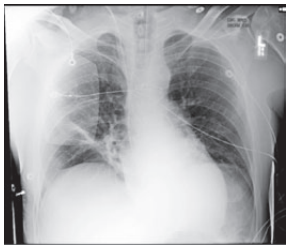
Mechanical ventilation was initiated due to respiratory failure utilizing the Pressure Control Continuous Mandatory Ventilation (PC_CMV) Mode, PEEP 10 cm H2O, FiO2 0.5, respiratory rate of 18 bpm, and inspiratory pressure adjusted to target and exhaled tidal volume of 600mL. No additional respiratory treatments or interventions were being provided.

Chest X-ray on Day 1 at 0352 revealed subsegmental atelectasis in the right middle lobe. To facilitate airway clearance of suspected retained secretions, we initiated in-line MetaNeb therapy on Day 1 at 0919. Four additional treatments administered with bronchodilators and minimum 10 minute durations on the highest percussive frequency setting were given at 1123, 1615, 2028 and 2351 that day.

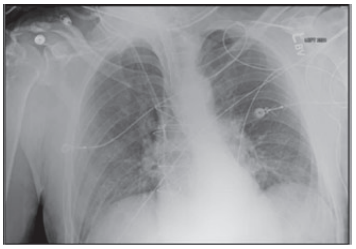
The follow-up chest X-ray was obtained on Day 2 at 0259, after a total of 5 MetaNeb treatments. The CXR showed resolution of the right middle lobe atelectasis.

Within 24 hours of initiating MetaNeb treatment, FiO2 was decreased to 0.35, the P/F ratio increased from 248 to 385, and Static respiratory system compliance improved from 48 to 92 ml/cmH2O (Day 1 compared to Day 2). The patient continued on MetaNeb therapy after extubation on Day 2 at 1025. Chest X-ray at discharge on Day 6 continued to be clear of atelectasis.

This case report is based upon the clinical course of one individual patient and should not be generalized across a subset of patients with similar conditions without a larger clinical trial.



Pre-MetaNeb Day 1 at 0352



Post-MetaNeb Day 2 at 0259 (5 treatments)

Conclusions

In this case, the variable was the introduction of MetaNeb Therapy in-line with the ventilator and this one variable resulted in positive results in the pulmonary system with an increase in P/F Ratio, decrease in FiO2, and improvement in CXR and atelectasis resolution in the right, middle lobe.

Case 3: The Use of MetaNeb to Improve Lung Aeration During Post-Operative Recovery

A 46-year-old male patient presented to our Emergency Department with chest pain and shortness of breath x 3 months. He had elevated troponins of 0.38 and a history of hypertension and hypercholesterolemia, but no other applicable past medical history.

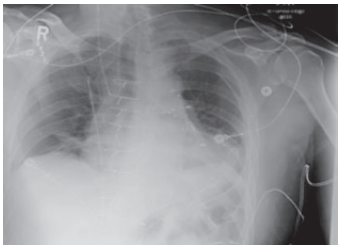
Admitted for a Non-ST elevation Myocardial Infarction (NSTEMI) -Cardiac catheterization revealed the need for a CABG –grafts to the left anterior descending artery, Ramus, OM and PDA. CABG performed 3 days later at 1609 (Day 0). Patient returned from OR intubated and on ventilator. Patient liberated from ventilator four hours later.

An assessment of lung capacity was conducted by performing incentive spirometry which revealed 500 cc with inability to perform breath hold, followed by a weak cough effort. We initiated MetaNeb therapy at 1125 on Day 1 post-operatively to help resolve post-operative atelectasis. Initial settings were low CHFO mode, CPEP 10, and resistance dial set at 1 for 10 min duration.

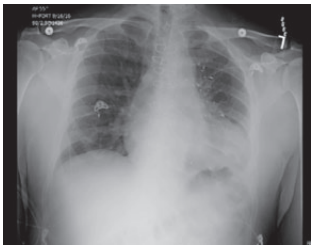
Patient returned to OR at 1530 on Day 1 due to a re-bleed for an exploration and washout, and he was liberated from mechanical ventilation for a second time at 2024 on Day 1.

Post extubation chest X-ray on Day 2 at 0323 revealed bibasilar atelectasis with low lung volumes.

Post extubation on Day 2, MetaNeb therapy was re-initiated, the resistance dial was turned to 2 and IS values noted to be 600 ml. From Day 2 to Day 3, we were able to decrease the level of supplemental FiO2 that was required. By Day 3, the CPEP was increased to 15 cm H2O, and patient was placed on room air, which he remained on until discharge. MetaNeb settings remained the same for the remainder of stay and included 10-15 cc's of normal saline only. Day 4 chest X-ray revealed improvement in atelectasis and IS values noted at 800, after 5 MetaNeb treatments. Day 5 IS values noted to be 1000, and patient was discharged on Day 6.



Post-extubation atelectasis on Day 2 at 0323



Post-MetaNeb Treatment Day 4 at 1418 (5 MetaNeb Treatments)

Conclusions

This patient underwent extensive chest/heart surgery and had to be re-opened due to a leak in one of the grafts. Pt came in with a clear chest X-ray. Following the initial surgery, the patient was unable to take effective deep breaths and chest X-ray following subsequent surgery demonstrated significant atelectasis. The low lung volumes were effectively treated with the adjunct of CHFO, as demonstrated by significant clearing of the chest X-ray on Day 4.

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Speaking Valve Use During Mechanical Ventilation: More than Just for Communication and Swallowing

A Respiratory Therapist's Perspective

Gail M Sudderth, RRT

The inability to communicate during periods of mechanical ventilation (MV) can increase psycho-emotional distress (Egbers, Bultsma, Middlekamp, & Beoerma, 2014) and has been associated with depression and post-traumatic stress disorder (Freeman -Sanderson, Togher, Elkins & Phipps, 2016). One way speaking valves can be used to restore verbal communication for patients who require MV. The Passy Muir® Valve is the only bias-closed position valve that can be used during MV. The Passy Muir Valve opens during inspiration and closes at the end of inspiration, re-directing exhalation through the vocal cords and out through the mouth and nose, which allows for verbal communication. The restoration of airflow, sensation, and positive airway pressure to the aerodigestive tract returns the upper airway to a more normal physiologic condition and may also have other clinical benefits for the patient who requires tracheostomy and MV.

It is common to delay intervention by healthcare practitioners and the use of speaking valves in the ICU on patients who require mechanical ventilation, based on the rationale that patients are "too sick." The literature suggests that this hands-off approach may cause more harm than good and early intervention can minimize or potentially reverse the impact (Burkhead, 2011). The Speech-Language Pathologist (SLP)-Respiratory Care Practitioner (RCP) team is presented with a unique opportunity to co-treat patients who require tracheostomy and MV to provide not only a way to communicate, but also a way to restore airflow and engage the glottis and restore positive pressure to the aero digestive tract. This therapy may enhance weaning and rehabilitation including safer swallowing to reduce aspiration (Amathieu et al., 2012; Rodrigues et al., 2015), improve swallow and cough (Pitts, et al., 2009), reduce respiratory infections (Carmona, Díaz, Alonso, Guarasa, Martínez, & López, 2015), promote alveolar recruitment (Sutt, Cornwell, Mullany, Kinneally & Fraser, 2015) and enhance early mobilization efforts (Massery, 2014).

With few exceptions, patients who require tracheotomy were previously intubated. The presence of an endotracheal tube, along with infection, medications, immobility, disuse atrophy, and co-morbidities often lead to ICU acquired muscle weakness. Muscle weakness is a factor in dysphagia and is associated with increased symptomatic aspiration risk leading to significant morbidity and mortality in ICU patients (Mirzakhani et al., 2013). Lack of airflow to the upper airway during endotracheal intubation continues after a tracheostomy tube is placed with inflated cuff and can lead to sensory changes in the mucosa of the oropharynx and larynx contributing to dysphagia (Burkhead, 2011). A significant number of these patients also develop diaphragmatic weakness as well, resulting in significantly longer duration of MV (Supinski & Callahan, 2012). Diaphragmatic force generating capacity may be reduced as much as 32% after just 5 or 6 days of MV (Schellekens et al., 2016). Respiratory weakness is often associated with difficult weaning and increased mortality. Therefore, it would be reasonable to consider Respiratory Muscle Training (RMT) as part of the weaning and rehab process, along with consideration for preventative strategies to reduce or slow disuse atrophy of the respiratory muscles (Schellekens et al., 2016). RMT has also been linked to improved swallow and cough (Pitts et al., 2009). RMT is generally defined as a technique for improving respiratory muscle function and includes performing inspiratory and/or expiratory maneuvers against a resistance. However, further research is needed to establish efficacy in certain patient groups and specific training protocols should be implemented for Respiratory Muscle Training specific to various patient populations. Inspiratory Muscle Training (IMT) has been reported to increase exercise endurance, muscle strength, and perceived dyspnea in patients with COPD (Geddes, O'Brien, Reid, Brooks & Crowe, 2008), and Expiratory Muscle Training (EMT) has been linked to reduced perception of dyspnea in COPD patients during exercise and improved cough and swallow safety (Laciuga, Rosenbek, Davenport, & Sapienza, 2014).

While patients with tracheostomy and MV participate in a weaning and rehabilitation process, they also must have their communication needs met. Clinicians would agree that patients may be able to employ different methods of verbal communication at varying times during their illness, and any and all methods of providing voicing should be explored. However, while some methods of ventilator assisted speech do assist the patient with voicing and the ability to communicate (McGrath, Lynch, Wilson, Nicholson & Wallace, 2016; Hoit, Banzett, Lohmeier, Hixon, & Brown, 2003), they do little to restore upper airway physiology to a more normal condition. Some have suggested that partial cuff deflation during MV is a preferred means to accomplish speech; however, while this may be useful in a select group of patients who are unable to manage full cuff deflation, it may not be the best way to restore upper airway physiology. It was suggested by Hoit et al., (2003) that the combination of increasing inspiratory time and increasing PEEP, as high as 15 cmH_20 in some subjects,

Gail is a Clinical Specialist at Passy-Muir, Inc.

produced a quality of voicing identical to using a speaking valve. The author also stated that "high PEEP is a safer alternative than a one-way speaking valve" (Hoit et al., 2003). However, it may be more likely that the subjects were performing high flow leak speech. High inspiratory flows, along with increased PEEP, may be difficult for weak patients to manage, leading to increased work of breathing, and/or breath stacking. It should be noted the authors did not have findings within the study to support the claim of improved safety with this method. In addition, encouraging speech while the ventilator is delivering an inspiratory breath is not natural speech, as natural voicing occurs during the expiratory cycle.

McGrath, Lynch, Wilson, Nicholson, and Wallace (2016) proposed an alternative method of ventilator assisted communication by using a tracheostomy tube with a subglottic suction port. The port is used to deliver a low flow of gas above the cuff, which may be inflated or partially deflated. The reported limitations to this method include limited voice quality, possible laryngeal injury with higher flows, stoma leakage of gas, and the dry gas delivery causing drying of the mucosa and hyper-adduction of the vocal folds (McGrath et al., 2016). While this method has its drawbacks, it may be a good alternative for the ICU patient who is too sick or unable to manage cuff deflation even for short periods of time. However, another consideration is that this is a specialized trach and may require a trach change for the patient.

While therapies like RMT assist with improving coughing, swallowing, and trunk strength, tasks such as walking, balance and exercise require engaging the glottis and airflow to the upper airway (Massery, 2014). Normalized voicing also requires engagement of the glottis and airflow through the upper airway. To achieve this engagement, the cuff must be completely deflated and a no-leak speaking valve placed on the tracheostomy tube to allow for 100% of exhalation to flow through the glottis, upper airway, mouth and nose. It is also important to understand how to maintain adequate ventilation with the cuff of the tracheostomy tube deflated. A thorough upper airway assessment to assure upper airway patency must be performed prior to use of a no-leak speaking valve. Some practitioners may be hesitant to try managing MV in the cuff deflation condition, concerned that adequate ventilation cannot be maintained. In a study done on "unweanable" ventilator dependent patients with neuromuscular disease, Bach reported that 91 out of 104 patients were adequately ventilated with either the cuff deflated or with cuffless tracheostomy tubes (Bach & Alba, 1990).

> One way speaking valves have long been used to allow for airflow through the upper airway for speech. Clinicians should consider the other possible benefits…

The most likely patient to manage cuff deflation is one who is medically stable, awake, and engages the voice. It might be appropriate to begin cuff deflation sessions in conjunction with sedation vacations (when sedating medications are not being used). The clinician should understand that a patient who has not felt airflow through the upper airway for several weeks, or even longer, may not achieve full cuff deflation in one session. Some ventilator adjustments that may make cuff deflation more successful include reducing or eliminating PEEP and/or changing sensitivity settings, so that the ventilator does not auto cycle.

Tips for Ventilator Application | Sudderth

Effects Of:

Cuff Inflation	Reduced Upper Airway Stimulation	Reduced Positive Airway Pressure	Tracheostomy
Reduced Laryngeal Movement/ Tethering	Loss of Voice	Reduced Swallow Function	Quality of Life
Necrosis/ Trauma	Reduced/ Lost Taste and Smell	Weak or No Cough	Weaning
Reflux	Change in Sensation	Reduced Trunk Strength/ Support	Length of Stay
Reduced Upper Airway Airflow	Negative Impact on Swallowing	Reduced PEEP	

Tips For Ventilator Application

- Monitor PIP and EVT to assess upper airway patency during deflation
- Slow cuff deflation, with frequent oral care and suctioning as needed
- Make ventilator adjustments to improve cuff deflation management

  Consider:
  - Decreasing PEEP
  - Increasing Vt in increments of 50-100 to return to pre-PMV PIP
- Assure adequate alveolar ventilation by monitoring PIP and WOB
- Use safe alarm practice

Sutt, Cornwell, Mullany, Kinneally, and Fraser (2016) reported improved lung recruitment when using the Passy Muir® speaking

valve in conjunction with MV with the PEEP reduced or turned to zero. This improvement was maintained for a period of time, even after the one-way valve was removed. The authors attribute this maintenance to the return of a more normal upper airway resistance since exhalation occurred through the larynx and upper airway. At this stage of assessment, it is very important for the SLP and RCP to work closely together and employ strategies to assist the patient in maintaining adequate ventilation. The RCP will manage the ventilator alarms and monitor ventilation, while the SLP can cue the patient to breathe in during the inspiratory cycle of the ventilator and perform an expiratory maneuver to trigger the ventilator into exhalation in the presence of the leak during cuff deflation. This coordination with the ventilator is then transitioned to coordinating respirations with voicing on exhalation and may lead to coordinating respirations and swallowing. In addition to ventilator adjustments, the process of cuff deflation should not be rushed. Some patients will take longer to manage this step due to weakness of the laryngeal and pharyngeal muscles/structures and reduced sensation. A patient may exhibit coughing, throat clearing, shortness of breath, and other signs of adjustment—all of which are a part of the process in learning to coordinate breathing with the ventilator and developing a sense of normalcy with a return of airflow through the upper airway. Additionally, good oral care and suctioning as needed are important before and during this step of the airway assessment.

Once the cuff is completely deflated, airway patency can be determined by assessing voicing on exhalation, listening for exhalation though the upper airway using a stethoscope, or by reading the peak inspiratory pressure (PIP) and/or exhaled volumes via the ventilator. The clinician can objectively document an adequate leak and upper airway patency when reading a 40-50 percent drop in PIP and/or decrease in exhaled tidal volume measured by the ventilator. These measurements would suggest that the tracheostomy tube is properly sized to allow for sufficient airflow around the tracheostomy and upwards to the upper airway. It also suggests that there is no significant obstruction above the tracheostomy tube. A no-leak speaking valve then can be placed into the ventilator circuit while mechanical ventilation continues.

Once the no-leak valve has been placed in the ventilator circuit, the RCP and SLP continue to work together to assure patient-ventilator synchrony and adequate ventilation. The SLP may provide inspiratory and expiratory cues to the patient while the RCP monitors ventilation by monitoring PIP. PIP should be closely monitored since it is the measure of adequate ventilation comparable to pre-cuff deflation and no exhaled air will return or be measured by the ventilator. It may be necessary to increase delivered volume to achieve pre-cuff deflation PIP and assure adequate alveolar ventilation; however, this step may not be needed once the patient gets stronger. At this stage, the RCP should manage the ventilator alarm settings following safe practice. Other vent specific strategies may also be utilized depending on the mode of ventilation or brand, including flow or time limiting pressure delivered breaths and consider whether it is appropriate to use leak compensation as provided by the specific ventilator.

As the aerodigestive system is returned to the more normal condition with the use of a Passy Muir Valve in-line with MV, therapies that require glottis engagement, positive sub-glottic pressure, and airflow can begin. As previously mentioned, oral intubation and reduced airflow to the airway may result in decreased sensation, in addition to disuse atrophy and muscle weakness (Mirzakhani et al., 2013). Individualized therapeutic programs may be developed, requiring that therapies be modified for each patient dependent on the level of function. Progress may be slow in some patients with multiple co-morbidities but should be pursued when medically appropriate to ameliorate deterioration as much as possible.

One way speaking valves have long been used to allow for airflow through the upper airway for speech. Clinicians should consider the other possible benefits to the patient when airflow, sensation, and positive pressure is restored to the upper airway as part of the weaning strategy for patients who require MV. Use of a Passy Muir Valve during MV also provides improved access for treatment of dysphagia and increases participation in physical therapy through improved trunk stability and postural control, which may lead to improved weaning rates, reduced time of MV, and shortened ICU length of stays. According to Grosu et al. (2012), ("Difficulties in discontinuing MV are encountered in 20% to 25% of patients who receive MV, with a staggering 40% of the time spent in the ICU devoted to weaning from MV. Hence, techniques that expedite the weaning process should have a profound effect on the overall duration of MV.") Clinicians should consider cuff deflation and speaking valve trials early in the process of weaning—not only to enhance quality of life by allowing the patient to have a voice, but to provide the benefits of restored physiology and the potential positive impact on weaning.

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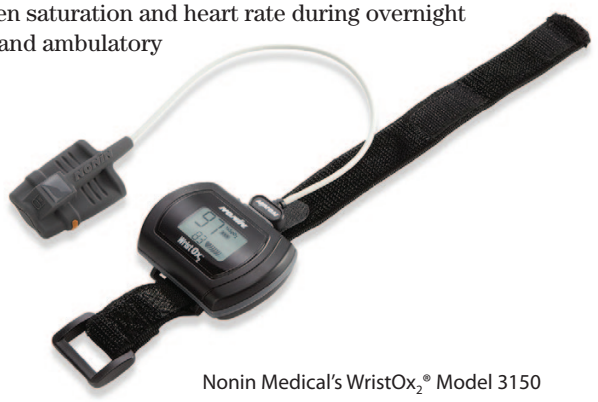
Nonin Medical's WristOx$_2$ Model 3150 Beats VirtuOx VPOD in Hypoxia Testing

Introduction

Overnight pulse oximetry studies are often used to qualify patients for long-term oxygen therapy or screen an individual for oxygen desaturations that may be associated with obstructive sleep apnea. Regardless of the specific application of continuous pulse oximetry monitoring, it is imperative to use a device that will not only be accurate when the patient is well-oxygenated, but will quickly and accurately respond to sudden and/or significant oxygen desaturations.

Nonin Medical introduced its first wrist-worn pulse oximeter (WristOx® Model 3100) in 2004. Since that time, Nonin has been an industry leader in this form factor and was the first to integrate Bluetooth® technology into its wrist-worn pulse oximeters. Due to convenience of size and comfort, the company saw rapid adoption of its wrist-worn pulse oximeter in the clinical environment, particularly for continuous monitoring of oxygen saturation and heart rate during overnight studies and ambulatory tests.



Nonin Medical's WristOx$_2$® Model 3150

The High Cost Of Missed Events

In the last several years, other wrist-worn pulse oximeters have been introduced under private label by inexpensive import manufacturers. Many of these devices are low cost and available through distributors and Medicare-approved Independent Diagnostic Testing Facilities (IDTF) throughout the United States. If these devices are missing sudden and/or significant oxygen desaturations (see Graph 1, on the following page), the cost to both the patient and the healthcare provider could be profound. Missed desaturation events could result in an incorrect diagnosis, delayed treatment, repeat studies, extended hospital stays or premature discharge, missed home oxygen prescriptions or repeat hospitalizations.

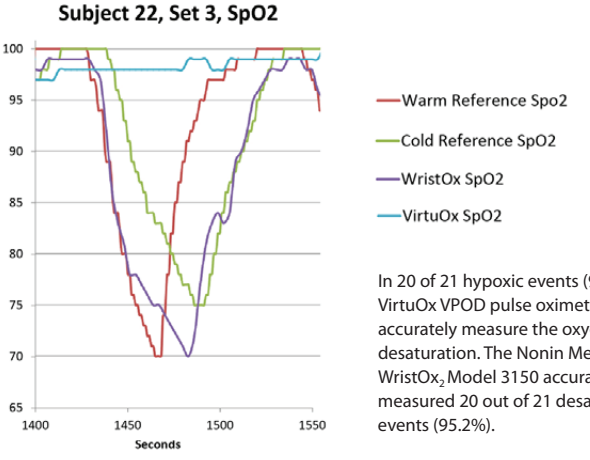
Nonin Medical WristOx$_2$ Proves To Be Superior In Capturing Oxygen Desaturation Events

In an independent lab test, hypoxia testing was performed on wrist-worn pulse oximeters from Nonin Medical (WristOx$_2$® Model 3150, Plymouth, MN) and VirtuOx (VPOD, private label, Beijing Choice, Shenzhen, China).

After obtaining Institutional Review Board (IRB) approval, Clinimark Laboratories (Boulder, CO)[1], an independent hypoxia laboratory, tested healthy volunteer participants by inducing hypoxia events down to the 70–85% SpO_2 range. These events included concurrent induced low perfusion (one arm cooled in chilled air) and labored breathing. Nellcor brand pulse oximeters (Model N600, Medtronic, Minneapolis, MN) were used as reference monitors on both the cooled (low perfusion) and warm (normal perfusion) hands.

A sample size of seven subjects was tested, obtaining a total of 21 hypoxic events with nadir value below 85% SpO_2. In 20 of 21 hypoxic events (95.2%), the VirtuOx VPOD pulse oximeter failed to accurately measure the oxygen desaturation, resulting in no reading (displayed value read zero), frozen reading (displayed value failed to track the desaturation) or no tracking (displayed values were >10% higher than the reference oximeters) when compared to the reference pulse oximeter. The Nonin Medical WristOx$_2$ Model 3150 accurately measured 20 out of 21 desaturation events (95.2%) when compared to the Nellcor reference pulse oximeters. (Table 1)

Graph 1. Example of Missed Desaturation Event by VirtuOx VPOD Wrist-Worn Pulse Oximeter



In 20 of 21 hypoxic events (95.2%), the VirtuOx VPOD pulse oximeter failed to accurately measure the oxygen desaturation. The Nonin Medical WristOx$_2$ Model 3150 accurately measured 20 out of 21 desaturation events (95.2%).

Table 1. Results by Device

Pulse Oximeter	Number of Subjects	Total Number of Hypoxic Events	Accurate Reading	No Reading	Frozen Reading	No Tracking
Nonin Medical WristOx$_2$ Model 3150	7	21	20 (95.2%)	1 (4.8%)		
VirtuOx VPOD	7	21	1 (4.8%)	6 (28.6%)	11 (52.4%)	3 (14.3%)
Nellcor N600 – cold reference	7	21	18 (85.7%)			3 (14.3%)
Nellcor N600 – warm reference	7	21	21 (100%)			

Summary

This study indicates that low-quality or low-cost import pulse oximeters may not be reliable for capturing true and significant oxygen desaturations which could, in turn, lead to costly mistakes affecting both provider and patient. The low-quality or low-cost wrist oximeter tested in this study failed to track nearly all critical hypoxic events below 85% SpO_2.

The Nonin Medical Puresat® Pulse Oximetry Technology Difference

Only Nonin Medical provides proven pulse oximetry performance in the widest range of patient conditions and settings. Nonin's clinically proven PureSAT® pulse oximetry technology uses intelligent pulse-by-pulse filtering to provide precise oximetry measurements—even in the presence of dark skin, motion, low perfusion, shortness of breath and other challenging conditions. PureSAT automatically adjusts to each patient's condition to provide fast and reliable readings clinicians can act on.

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Acid-Base Interpretation: Is it Time for a New Taxonomy?

Doug Pursley, M.Ed, RRT-ACCS, FAARC; Brandon Burk, MS, RRT-ACCS

Introduction

Proper acid-base interpretation is crucial in guiding treatment decisions at the bedside. Simply classifying a blood gas according to pre-established criteria may not result in a correct diagnosis. Acid-base values should be interpreted using all the tools available to the clinician. These include anion gap, bicarbonate gap, rules of compensation, rules of hydrolysis, and equations that predict expected PaCO2 in metabolic disorders.

Nomenclature is also an important part of defining the acid-base condition. Traditional terms such as "fully compensated" or "partially compensated" may not correctly define a disorder. For example, the time-honored meaning of the term "full compensation" implies the pH has returned to the normal range of 7.35-7.45. In actuality this only happens in mild disorders and is rarely achieved in the vast majority of cases. The term "partial compensation" can be confusing—particularly in metabolic acidosis when one is attempting to assess the degree of appropriate respiratory compensation taking place. An aspirin overdose patient with a pH of 7.46, PaCO2 15 mmHg, HCO3 10 mEQ/L, and base deficit -12 mEQ/L would be "classified" as having a partially compensated respiratory alkalosis when in actuality the patient is excessively hyperventilating in response to a metabolic acidosis. In other words, the patient has a mixed respiratory alkalosis and metabolic acidosis.

Finally, it is important to remember that when assessing metabolic disorders, the reference value for PaCO2 changes depending on the bicarbonate level. Using the standard PaCO2 reference value of 35-45 mmHg may not result in the correct interpretation.

Therefore the purpose of this article is to: 1) review some of the rules and equations that may be helpful in determining a proper acid-base interpretation, 2) discuss the difference between "interpreting" a blood gas and simply classifying it according to a set of pre-established criteria, and 3) consider the importance of using proper terminology in order to describe the true nature of a given acid-base disorder.

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Rules and Equations

Respiratory Disorders

Acute Change in HCO3 per change in PaCO2 (hydrolysis)

In acute respiratory disorders, starting at a normal PaCO2 of 40 mmHg, HCO3 will increase 1 for every 10 mmHg increase in PaCO2 and decrease 2 for every 10 mmHg decrease in PaCO2.[1] This is due to the effects of hydrolysis and has nothing to do with renal compensation. It simply represents a chemical reaction according to the following formula: $CO2 + H2O = H2CO3 = H^+ + HCO3$.

Therefore, consider the following patient. An otherwise healthy 23-year-old male with a normal PaCO2 of 40 mmHg is admitted to the ED following a narcotic overdose. He has the following blood gas: pH 7.21, PaCO2 70 mmHg, HCO3 27 mEQ/L, base excess 0 mEQ/L. The HCO3 increased from 24 to 27 as a result of hydrolysis. The patient has acute hypercarbia even though the HCO3 is slightly elevated. Traditional methods of classifying blood gases would incorrectly categorize these values as "partially compensated respiratory acidosis."

Sometimes an absence of expected hydrolysis can alert the clinician to a mixed disorder. Consider the same patient scenario but with the following values: pH 7.12, PaCO2 70 mmHg, HCO3 22 mEQ/L, base deficit -6 mEQ/L. Hydrolysis should have increased the HCO3 from 24 to 27 but instead it dropped from 24 to 22. The lower HCO3 than expected plus the base deficit points to a mixed respiratory and metabolic acidosis. Traditional classification methods would incorrectly label this an acute respiratory acidosis since the HCO3 is in the normal range.

Acute Change in pH per change in PaCO2 (predicted respiratory pH)

Starting at a pH of 7.4 and PaCO2 of 40 mmHg, pH will decrease 0.06 units for every 10 mmHg increase in PaCO2 and increase 0.10 units for every 10 mmHg decrease in PaCO2.[2] This is the so-called predicted respiratory pH and predicts what the pH will be if the only imbalance is a respiratory disorder. For example, acute hyperventilation to a PaCO2 of 20 mmHg in a patient with previously normal blood gases will produce a pH of approximately 7.60. If we add the previous rule of hydrolysis, the HCO3 would be approximately 20 mEQ/L in this patient.

It is interesting to note that the rules used to determine the acute change in pH form the foundation for determining the base excess or deficit. If a patient's actual pH is greater than their predicted respiratory pH, there will be a base excess. If the

Table 1. Expected changes in pH and HCO3 for 10 mmHg Δ in PaCO2 starting at PaCO2 of 40 mmHg

Condition	Acute	Chronic
Respiratory acidosis	• pH down by 0.06 • HCO3 up by 1 mEQ/L (hydrolysis)	• pH down by 0.03 • HCO3 up by 4 mEQ/L
Respiratory alkalosis	• pH up by 0.1 • HCO3 down by 2 mEQ/L (hydrolysis)	• pH up by 0.03 • HCO3 down by 5 mEQ/L

patient's actual pH is less than their predicted respiratory pH, there will be a base deficit.

Chronic Change in pH per change in PaCO2 (renal compensation)

In chronic respiratory disorders, pH will change by 0.03 units for every 10 mmHg chronic change in PaCO2.[3] Therefore a patient with a chronic PaCO2 of 70 mmHg can be expected to have a "compensated pH" of approximately 7.31. A patient with a chronic PaCO2 of 30 mmHg can be expected to have a "compensated pH" of approximately 7.37. This rule demonstrates that in a patient with a chronic PaCO2 > 60 mmHg, the pH can be expected to compensate to something less than 7.35. It also demonstrates that under normal conditions, respiratory alkalosis is more likely to compensate completely compared to respiratory acidosis.

Chronic Change in HCO3 per change in PaCO2 (renal compensation)

In chronic respiratory disorders, HCO3 will increase 4 mEQ/L for every 10 mmHg in PaCO2 and decrease 5 mEQ/L for every 10 mmHg decrease in PaCO2.[1] Therefore the previous patient with a chronic PaCO2 of 70 mmHg can be expected to have a HCO3 value of 32 mEQ/L. The patient with a chronic PaCO2 of 30 mmHg can be expected to have a HCO3 value of 19 mEQ/L. The rules for respiratory disorders are summarized in Table 1.

Metabolic Disorders

One Point Five Plus Eight Rule (Winter's formula)

This rule predicts the expected PaCO2 in metabolic acidosis.[1] The formula is: expected PaCO2 = (1.5 x HCO3) + 8 ± 2. Therefore, a patient with a metabolic acidosis and a HCO3 of 12 mEQ/L would be expected to have a PaCO2 of 24-28 mmHg. If this patient's PaCO2 was greater than expected, then hypoventilation is also occurring. If the patient's PaCO2 was less than expected, then hyperventilation is also occurring.

Point Seven Plus 20 Rule

This rule predicts the expected PaCO2 in metabolic alkalosis.[1] The formula is: expected PaCO2 = (0.7 x HCO3) + 20 ± 5. Therefore, a patient with a metabolic alkalosis and a HCO3 of 40 mEQ/L would be expected to have a PaCO2 of 43-53 mmHg. If this patient's PaCO2 was greater than expected, then hypoventilation is also occurring. If the patient's PaCO2 was less than expected, then hyperventilation is also occurring.

Electrolyte Calculations

Anion Gap

The anion gap is a vital part of acid-base interpretation. It signifies the amount of unmeasured or acid anions in the plasma. The anion gap is calculated by the following formula: AG = (NA + K) – (Cl + HCO3).[4] Normal anion gap is 12 mEQ/L. If the AG is greater than 20 mEQ/L, there is a 67% chance of metabolic acidosis.[1] If the AG is greater than 30 mEQ/L, there is a 100% chance of metabolic acidosis.[1] Anion gap decreases in hypoalbuminemia.

Bicarbonate Gap

The bicarbonate gap or delta gap represents the change in the anion gap from normal minus the change in bicarbonate from normal. The equation is written as follows: BG = (AG – 12) – (24 – HCO3).[4] Expanding this equation out we get: BG = [(Na+ - Cl – HCO3) – 12] – (24 – HCO3). If we simply cancel the terms in the equation we get BG = Na – Cl – 36.

Normal bicarbonate gap is 0 ± 6 mEQ/L. A BG greater than +6 mEQ/L suggests metabolic alkalosis or compensation for chronic hypercarbia. A BG less than – 6 mEQ/L suggests hyperchloremic metabolic acidosis or compensation for chronic hypocarbia.

Traditional vs. Nuanced Terminology

For many years, acid-base interpretation has been taught using the same terminology. So why change it now? Simply put, because the traditional way does not accurately describe the physiology behind acid-base homeostasis. The response to an acid-base disorder can be accurately predicted by using one or more of the rules and equations previously described in this article; however, the traditional terminology simply classifies the blood gas relative to the textbook normal values for pH (7.35-7.45), PaCO2 (35-45 mmHg), HCO3 (24 mEQ/L ± 2), and base excess/deficit (0 mEQ/L ± 2). The traditional method for classifying also tends to oversimplify the process, which ultimately leads to an incorrect interpretation/diagnosis, which could lead to improperly treating the patient.

Respiratory Acidosis

Respiratory acidosis disorders have been traditionally classified as uncompensated, partially compensated, and fully compensated. Again, these classifications do not describe what is truly happening physiologically. In a primary respiratory disorder, renal compensation occurs over a period of 48 to 72 hours.[2] Since the chances of interpreting a patient's blood gas in this particular time period is unlikely, an argument could be made that it is never appropriate to interpret a blood gas as "partially compensated." The remaining terms of uncompensated and fully compensated can be more accurately described as either acute (where there has been no renal compensation) or chronic (where there has been renal compensation). To clarify this shift in thinking, the following examples will demonstrate why using the terms acute and chronic may be a more descriptive way to interpret acid-base status.

Patient 1: A 25-year-old, otherwise healthy female with a narcotic overdose. ABG results: pH 7.17, PaCO2 80 mmHg, HCO3 28 mEQ/L, base excess + 0.3 mEQ/L. As noted earlier, this patient would have traditionally been classified as having a "partially compensated respiratory acidosis", however, when one factors in hydrolysis, there has not been renal compensation at all. The reason for the increase in HCO3 is due to hydrolysis only because of the relationship of the PaCO2 increase to the HCO3 increase. Another important component of this blood gas is that the base excess is in the normal range. If the pH and PaCO2 are out of range in opposite directions, and the base excess/

deficit is in the normal range, the interpretation will be an acute respiratory disorder the vast majority of the time. This blood gas should be interpreted as an "acute respiratory acidosis."

Patient 2: A 62-year-old male, previously diagnosed with COPD is getting a routine ABG performed at his visit to the Pulmonologist. He is currently feeling normal, with no unusual complaints. The results are: pH 7.32, PaCO2 80 mmHg, HCO3 40 mEQ/L, base excess +13 mEQ/L. This patient has the same PaCO2 as Patient 1, however, it is obvious that their blood gases aren't the same. Interestingly, the traditional classification system would call this a "partially compensated respiratory acidosis", the same as Patient 1. The difference between this blood gas, and the blood gas for Patient 1, is that there is renal compensation. Using the rules of compensation, in a chronic respiratory acidosis, for every 10 mmHg increase in PaCO2, there is a 4 mEQ/L increase in HCO3 (both increases are from normal). If one does the math on this blood gas, there is a 40 mmHg increase in PaCO2, which would cause the HCO3 to increase by 16 mEQ/L. With a chronic PaCO2 of 80 mmHg, the HCO3 should be 40 mEQ/L, which it is in this case. The traditional classification term "fully compensated" rarely applies clinically. Most compensation for acid-base disorders is only about 50%, and in the case of a respiratory acidosis that is present in Patient 2, we should never expect the pH to return to the normal range (7.35-7.45), even though there is maximal renal compensation occurring in this patient. This blood gas should be interpreted as a "chronic respiratory acidosis."

Rather than focusing on the pH, we should always assess the relationship between PaCO2 and HCO3. If the PaCO2:HCO3 increase is 10:1, then the increased HCO3 is due only to hydrolysis, and the blood gas would be interpreted as acute. If the ratio is greater than 10:1, that is 10:2, 10:3, 10:4, then there is renal compensation and the blood gas would be interpreted as chronic. Also, notice that the base excess will be increased above the normal range in "chronic respiratory acidosis" because the renal system has retained HCO3 to compensate.

Respiratory Alkalosis

The interpretation of respiratory alkalosis disorders are very similar to respiratory acidosis disorders, however, the rules are slightly different. Once again, determining whether the disorder is acute, or chronic is most important, rather than determining the degrees of compensation. Please consider the following examples:

Patient 1: A 24-year-old female with a sudden onset of shortness of breath and wheezing after being exposed to a family member's cat. Past medical history is positive for asthma, but otherwise the patient is healthy. Blood gas: pH 7.55, PaCO2 25 mmHg, HCO3 21 mEQ/L, base deficit -1 mEQ/L. The traditional classification for this blood gas would be a "partially compensated respiratory alkalosis" due to the bicarbonate moving slightly out of the normal range. Again, this classification is misleading. Remember that for every 10 mmHg decrease in PaCO2, there is a 2 mEq/L decrease in HCO3 from hydrolysis, and the base excess/deficit is in the normal range. Both of these findings indicate that there was not renal compensation, but rather the decrease in HCO3 was simply from hydrolysis. This blood gas should be interpreted as an "acute respiratory alkalosis."

Patient 2: A 45-year-old male with an anxiety disorder. Patient states that he has been feeling stressed over the past few weeks. Blood gas: pH 7.46, PaCO2 25 mmHg, HCO3 17 mEQ/L, base deficit -6 mEQ/L. The classification of this blood gas would again be a "partially compensated respiratory alkalosis" because the bicarbonate moved out of the normal range and the pH remains slightly alkalotic. While those things are technically true, when one considers the rules of compensation for a respiratory alkalosis, we find that renal compensation is "maxed out", so the term "partial compensation" is a misnomer. Given the scenario, it is likely that this patient has been hyperventilating for several days if not several weeks, leading to renal compensation. The rule in chronic respiratory alkalosis states that for every 10 mmHg decrease in PaCO2 from normal, the HCO3 will decrease 5 mEq/L from normal. Looking at this patient's blood gas, there was a 15 mmHg decrease in PaCO2, so there should be around a 7-8 mEq/L decrease in HCO3 from normal. This puts the HCO3 at 16-17 mEQ/L, just where the patient's measured values happen to be. Because this blood gas follows the rules of compensation, the interpretation should be a "chronic respiratory alkalosis."

To review: an "acute respiratory alkalosis" will follow the rules of hydrolysis, which is a decrease in PaCO2 and HCO3 in a 10:2 ratio from normal, and the base excess/deficit will be in the normal range. A "chronic respiratory alkalosis" will have renal compensation, with the PaCO2 and HCO3 decreasing in a greater than 10:2 ratio, but no more than a 10:5 ratio. Additionally, there will be base deficit outside of the normal range, demonstrating that there is indeed renal compensation.

Metabolic Acidosis

Interpreting metabolic disorders is more complex than respiratory disorders. The reason for this is that decreases in base and bicarbonate should immediate provoke respiratory compensation, which is predictable using Winter's formula: expected PaCO2 = (1.5 x HCO3) + 8 ± 2. Respiratory compensation for a metabolic disorder begins immediately, and reaches maximal compensation within 24 hours,[2] so once the bicarbonate has gone out of range, there will be a "new normal" range for PaCO2 depending on the bicarbonate concentration. Therefore, the degree of respiratory compensation should not be interpreted based on traditional normal values for PaCO2 and pH, but rather, on the expected PaCO2 from the calculation.

Another vitally important aspect of interpreting metabolic acidosis is the Anion Gap (AG) and Bicarbonate Gap (BG). Using these important calculations can assist the clinician in diagnosing metabolic disorders without obtaining an arterial blood gas since the variables needed for the equation can be obtained with a standard metabolic panel, which most patients get routinely in the hospital.

Since the normal compensatory response to a metabolic acidosis is hyperventilation, and happens nearly immediately, our recommendation is to stop using the terms "acute" or "chronic"; or partially/fully compensated. The proposed terminology would use Winter's formula to determine if the PaCO2 is compensating appropriately, or if there is an additional respiratory disorder present.

Please consider the following two examples:
Patient 1 is a 62-year-old female with diabetes. She is non-compliant with her diet and medications. ABG results: pH 7.24, PaCO2 24 mmHg, HCO3 10 mEQ/L, base deficit -15.7 mEQ/L. Electrolytes are: Na+ 145 mEQ/L, K+ 4.8 mEQ/L, Cl- 108 mEQ/L.

We know that the primary disorder here is a metabolic acidosis because of the decreased bicarbonate, base deficit, and the AG of 31.8 mEQ/L, which demonstrates that there is an increased number of fixed acids in the blood. The traditional classification would be "partially compensated metabolic acidosis." This classification is due to the fact that the PaCO2 has gone out of the textbook normal range to bring the pH back toward normal. It would not be classified as fully compensated because the pH is not in the textbook normal range. However, this classification is not describing normal, human physiology. When calculating Winter's formula [(10 x 1.5) + 8 = 23], we can see that the expected PaCO2 range is 21-25 mmHg. The actual PaCO2 from the ABG is within that range, therefore, the correct interpretation would be an "appropriately compensated metabolic acidosis", since the actual PaCO2 is within the range of the expected PaCO2.

Patient 2 is a 32-year-old male with diarrhea since attending a humanitarian trip to Guatemala five days ago. ABG: pH 7.22, PaCO2 38 mmHg, HCO3 15 mEQ/L, base deficit -11.2 mEQ/L. Electrolytes: Na+ 135 mEQ/L, K+ 3.5 mEQ/L, Cl- 108 mEQ/L.

Again, this patient has a primary metabolic acidosis, as evidenced by a decreased bicarbonate and a base deficit. The AG is 15.5 mEQ/L, which is not indicative of metabolic acidosis, however, the BG is -9 mEQ/L, which indicates that there has been a loss of base, likely from the diarrhea. Traditionally, this would have been classified as an "acute metabolic acidosis", because the PaCO2 remained in the normal range. When Winter's formula is calculated [(15 x 1.5) + 8 = 30.5], the expected PaCO2 should be 28.5-32.5 mmHg. Although the PaCO2 is within the textbook normal range, remember, with metabolic disorders, a "new normal" PaCO2 is calculated. Since the "new normal" PaCO2 should be 28.5-32.5 mmHg, and the actual PaCO2 is significantly higher (38 mmHg), the respiratory system has failed to compensate appropriately, and is therefore failing. This ABG should be interpreted as a "mixed metabolic and respiratory acidosis".

Metabolic Alkalosis

Similar to metabolic acidosis, respiratory compensation in a metabolic alkalosis should happen immediately and reach maximal compensation in 24 hours.[2] In the case of a metabolic alkalosis the respiratory response is hypoventilation, and the degree of hypoventilation is directly proportional to the increase of bicarbonate/base. This relationship can also be calculated using the Point 7 plus 20 rule (HCO3 x 0.7 + 20) that was explained earlier. The 0.7 plus 20 rule is a calculation that determines the appropriate amount of respiratory compensation in a metabolic alkalosis. Similar to Winter's formula for a metabolic acidosis, the 0.7 plus 20 rule will calculate a "new normal" PaCO2 for the given amount of bicarbonate. If the PaCO2 is outside of the calculated range, then there is a secondary respiratory disorder present.

Also, the bicarbonate gap calculation is very important in determining if there is a metabolic alkalosis (Na – Cl – 36). Remembering that the normal bicarbonate gap is 0 ± 6 mEQ/L, if the bicarbonate gap value is > 6 mEQ/L, then there is likely a metabolic alkalosis present, especially when given an ABG that demonstrates evidence of a metabolic alkalosis. The following two metabolic alkalosis cases will demonstrate these calculations and the proposed terminology.

Patient 1: A 72-year-old male, with nausea and vomiting over the past two days. ABG: pH 7.50, PaCO2 46 mmHg, HCO3 35 mEQ/L, base excess + 11 mEQ/L. Electrolytes: Na+ 144 mEQ/L, K+ 4 mEQ/L, Cl- 98 mEQ/L.

This patient has a primary metabolic alkalosis, as evidenced by the increased bicarbonate, a base excess, and an alkalotic pH. Also, if the bicarbonate gap is calculated (144-98-36), the result is +10 mEQ/L, which is indicative of a metabolic alkalosis. Now, to determine respiratory compensation, we would use the 0.7 plus 20 rule [(35 x 0.7) + 20 = 44.5]. So the "new normal", or expected PaCO2 is 39.5-49.5 mmHg. Since the patients actual PaCO2 is in the calculated range, this ABG is an "appropriately compensated metabolic alkalosis."

Patient 2: A 63-year-old female with congestive heart failure that has been hospitalized for an exacerbation. She has been receiving large doses of furosemide to alleviate her symptoms, along with non-invasive ventilation for hypoxemia. ABG: pH 7.62, PaCO2 35 mmHg, HCO3 35 mEQ/L, base excess +12.6 mEQ/L. Electrolytes: Na+ 135 mEQ/L, K+ 2.5 mEQ/L, Cl- 88 mEQ/L.

This patient also has a primary metabolic alkalosis, again with a high bicarbonate/base excess. The bicarbonate gap is +11 mEQ/L, so all of the signs point toward a metabolic alkalosis, likely from aggressive diuresis with loop diuretics. Calculating the 0.7 plus 20 rule [(35 x 0.7) + 20 = 44.5], this patients actual PaCO2 should be 39.5-49.5 mmHg. Her actual PaCO2 is 35 mmHg, which is well below what it should be, given her HCO3 level. Because of this, we can say that she is also hyperventilating, which means that she has a "mixed metabolic and respiratory alkalosis."

Mixed Disorder

Mixed disorders can be difficult to diagnose correctly because multiple rules can apply, and the context of the situation is vitally important. Consider the following example:

A 67-year-old male, 2 pack per day smoking history and known COPD diagnosis is brought to a local emergency department for shortness of breath. The patient becomes unresponsive and an ABG is drawn while the patient is breathing oxygen via nasal cannula: pH 7.17, PaCO2 100 mmHg, HCO3 35 mEQ/L, base excess + 6.9 mEQ/L, PaO2 56 mmHg. The decision is made to intubate and place on mechanical ventilation, with the tidal volume set at 10 mL/kg of predicted body weight, and a set frequency of 20/minute.

One hour after mechanical ventilation was initiated, another ABG was drawn: pH 7.52, PaCO2 38 mmHg, HCO3 30 mEQ/L, base excess + 6.8 mEQ/L. By itself, this blood gas appears to be an "appropriately compensated metabolic alkalosis, however, with the context that we are given with this patients past medical history, this diagnosis would be incorrect. Using the compensation rules for chronic respiratory acidosis, this patients "normal" blood gas would be pH 7.35, PaCO2 60 mmHg, HCO3 32 mEQ/L, base excess + 6.4 mEQ/L, which would be interpreted as a "chronic respiratory acidosis." With this diagnosis as a baseline, we can now correctly interpret both his admission blood gas, and his post intubation blood gas effectively.

The admission blood gas would be interpreted as an "acute respiratory acidosis, superimposed on a chronic respiratory acidosis" because his PaCO2 is higher, and pH lower than it is

in his normal state. The post intubation blood gas should be interpreted as an "acute respiratory alkalosis, superimposed on a chronic respiratory acidosis." This is due to the PaCO2 being lower, and pH higher than the normal blood gas in his chronic state. The reason that this is happening is due to overzealous mechanical ventilation. The clinician should decrease the set minute volume to target a PaCO2 of around 60 mmHg.

Implications for Treatment

While getting the interpretation correct should be the ultimate goal, we should consider how it will affect the treatment of patients with acid-base disorders. It can be tempting for the clinician to target a textbook normal blood gas for patients receiving mechanical ventilation, but all too often that decision will lead to another acid-base abnormality that needs to be addressed as well. Consider the mixed disorder case discussed in the last section. The patient clearly has an "acute on chronic respiratory acidosis" and needs some form of mechanical ventilation; however, once placed on a mechanical ventilator, the clinician targeted a "normal" PaCO2, which led to hyperventilation of the patient and another acid-base abnormality. It would have been more appropriate to calculate his "normal" PaCO2 in his chronic state, and target that number during mechanical ventilation.

Another example of how acid-base interpretation can affect treatment decisions is in metabolic acidosis. Using the example of "Patient 2" in the metabolic acidosis section, it is apparent that he has a metabolic acidosis from a loss of base. Once Winter's Formula is calculated and it is determined that there is also a respiratory acidosis occurring, an important decision is imminent for the clinician(s) involved. Because the PaCO2 is in the textbook normal range, clinicians might simply determine that there is not a respiratory component, which could potentially delay treatment for a critically ill patient. The clinician that recognizes the respiratory acidosis in this case, however, could aid in the patient's care by suggesting that the patient be monitored for fatigue and respiratory distress. Depending on the assessment, it might be appropriate to intubate and mechanically ventilate this patient due to "ventilatory failure," despite the patient's "normal" PaCO2.

As these examples show, properly interpreting acid-base status can make a significant difference in patient care, especially in the critically ill.

Conclusion

Complex acid-base disturbances are not unusual in critically ill patients. Consequently, proper treatment of these patients depends on an accurate acid-base diagnosis at the bedside. When acid-base imbalances are improperly interpreted or go unrecognized, adverse consequences may occur such as potentially longer hospital stays or even increased morbidity. Therefore, blood gases should be "interpreted" using the rules and assessments previously described as opposed to simply "classifying" a blood gas by systematically arranging the values according to pre-established criteria. Respiratory therapy programs have a chance to be a change agent at the grassroots level by teaching students to always "comprehensively" assess acid-base status using proper terminology.

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The Benefits of High-Flow Nasal Cannula for High-Risk Patients Versus Noninvasive Ventilation

Chris Campbell

In addition to the efficacy of a therapy the patient's comfort and tolerance are determinants of a therapy's level of success. If a patient suffers adverse effects and has to withdraw from therapy, the purpose of that therapy is then defeated. Sounds simple enough, but there are therapies that are uncomfortable and difficult to tolerate for patients that are also considered the "standard" because of a lack of research on alternatives. Recent clinical trials have proposed Nasal High Flow (NHF) therapy as an viable alternative, providing benefits such as greater patient comfort[1-4] lower costs,[5] and other physiological mechanisms not offered by COT or NIV, such as the humidification of gases which may reduce the work of breathing.[6] Furthermore, NHF therapy could avoid some of the pitfalls of NIV such as increased tidal volume which could exacerbate outcomes for patients with acute respiratory failure.[1] Until recently a significant research gap existed, namely evidence supporting the use of NHF therapy in patients at high risk of reintubation. A Spanish team led by Gonzalo Hernández (MD, PhD, Critical Care Medicine, Hospital Virgen de la Salud, Madrid) investigated the non-inferiority of NHF therapy compared with NIV for reducing postextubation respiratory failure and reintubation in patients deemed at high-risk of reintubation.[6]

This study follows-on from Hernandez et al.'s previous RCT, comparing NHF therapy to COT for patients at low risk of reintubation.[7] In this study, NHF significantly reduced the risk of reintubation within 72 hours compared with COT.[7] The results are similar to a previous study by Maggiore et al. on a general population of critically ill patients.[4]

The Study

The multicentre randomized non-inferiority clinical trial, involved 604 adults in three intensive care units in Spain (September 2012-October 2014) including critically ill patients ready for extubation.

Patients had at least 1 of the following high-risk factors for reintubation: older than 65 years; Acute Physiology and Chronic Health Evaluation II score higher than 12 points on extubation day; body mass index higher than 30; inadequate secretions management; difficult or prolonged weaning; more than 1 comorbidity; heart failure as primary indication for mechanical ventilation; moderate to severe chronic obstructive pulmonary disease; airway patency problems; or prolonged mechanical ventilation.

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The researchers used high-flow oxygen (Optiflow™, Fisher and Paykel Healthcare Ltd), which was applied immediately after extubation through specific nasal cannula. Prior to extubation the flow was initially set at 10 L/min to prime the line and titrated upwards in 5-L/min steps according to the tolerance of the patients. The mean gas flow at 12 hours was 50L/ min ±5 (SD). Temperature was initially set to 37°C, unless reported too hot by patients, and FiO_2 was regularly adjusted to the target peripheral capillary oxygen saturation (SpO_2) of greater than 92%. After 24 hours, high-flow was stopped and, if necessary, patients received conventional oxygen therapy.

Full-face mask NIV (BiPAP Vision; Respironics Inc) was continuously delivered immediately after extubation for a scheduled period of 24 hours. Afterward, NIV was withdrawn and oxygen was administered by Venturi mask. Both PEEP 4-5cm H_2O and inspiratory pressure support (8-10 cm H_2O) were adjusted to target a respiratory rate of 25/min and adequate gas exchange (arterial oxygen saturation [SaO_2] 92%, with pH of 7.35). The FiO_2 was adjusted to maintain SpO_2 at greater than 92%. Sedatives to increase tolerance to NIV were not allowed.

Both groups were treated by the same medical, nursing, and respiratory therapy staff (excluding the investigators) and received similar medical management.

The Results

The study found that the proportion requiring reintubation was 22.8% with NHF therapy vs 19.1% with NIV (absolute difference, −3.7%; 95% CI, −9.1% to ∞), and post-extubation respiratory failure was observed in 26.9% with NHF vs 39.8% with NIV (risk difference, 12.9%; 95% CI, 6.6% to ∞), therefore within the 10% non-inferiority threshold set a priori.

For the secondary outcomes, median time to reintubation was not significantly different between the two groups, but median ICU length of stay after randomization was lower in the NHF group: 3 days vs 4 days (IQR, 2-9; P=.048). In addition, adverse effects requiring withdrawal of the therapy were observed in none of the patients in the NHF group vs 42.9% of patients in the NIV group ($P < .001$).

Conclusion

In conclusion, the authors wrote that, "among high-risk adults who have undergone extubation, high-flow conditioned oxygen therapy was not inferior to NIV for preventing reintubation and

postextubation respiratory failure. High-flow conditioned oxygen therapy may offer advantages for these patients."

- NHF was non-inferior to NIV for rates of reintubation and post-extubation respiratory failure,in patients at high risk of reintubation.
- ICU length of stay was lower in the NHF group.
- No patients in the NHF group experienced adverse events requiring discontinuation of therapy.
- Median time to reintubation did not differ significantly.

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COPD and Chronic Respiratory Failure Management: Improving Outcomes and Reducing Readmissions with the Life2000h Ventilator by Combining Ventilation with Ambulation

Kelly Shepard, RRT, LRCP; Allison Wilhonen, RRT, LRCP; Raymon Gregg, BS, CRT, RPSGT

Introduction

Chronic Respiratory Failure (CRF) and COPD are major burdens to the US healthcare system, both clinically and economically. COPD is the third leading cause of death in the US, and affects an estimated 24 million Americans, with approximately only half currently diagnosed. Exacerbations and hospital readmissions account for nearly 70% of the $36 billion that is spent treating COPD annually.[1]

Increased activity provides clinicians with an opportunity to improve COPD care. Activity outcomes in COPD patients have been studied for over 20 years, and have shown as much as a 40% reduction in hospital admissions and respiratory mortality by increasing patients' activity an average of 2 hours per week.[2] While clinically beneficial, sustained activity is often difficult for patients with CRF consequent to COPD to achieve. CRF symptoms such as severe dyspnea, high work of breathing, and oxygen desaturations often prevent patients from realizing functional activity gains.

Patient Background

"Peg" is one such patient, and is the focus of this case study. Peg is a fifty-seven-year-old, Caucasian female diagnosed with CRF consequent to COPD, with a history of hospitalizations and declining lung function dating back to 2011. Peg was enrolled in the pulmonary rehabilitation program at PeaceHealth United General Hospital in Sedro Wooley, WA in February 2014. She completed the program and could walk 321 meters, while on 3 lpm of oxygen. She continued to practice her pulmonary rehabilitation exercises to the best of her abilities, and utilized oxygen at 2 lpm at rest and 3-4 lpm with exertion.

However, as of December 2015, her PFT results indicated a FEV_1 of 16% and FVC of 36% of predicted. During an exacerbation hospitalization in early 2016, her physician informed Peg that she most likely only had 3-4 months to live. She was discharged home on a Trilogy ventilator with a 4 lpm oxygen bleed-in and instructed to wear the device nocturnally and as needed during the day. Peg wore the ventilator while asleep and nearly continuously during the day, while seated in a chair. While helpful for ventilatory support, the size and weight of the ventilator, mask, and supplemental oxygen source prevented Peg from being able to be active and relegated her to a sedentary lifestyle of either lying in bed or sitting in a chair.

Treatment Recommendation

After two months of inactivity, due to her dependency on her nocturnal ventilator, Peg sought out other treatment options. Her home oxygen and respiratory management provider, Norco Medical, working in conjunction with PeaceHealth's pulmonary rehab department, recommended incorporating a Breathe NIOV device into her plan of care. Her physician agreed, and Peg was setup with a NIOV™ device for daytime use. She was later upgraded to Breathe's new Life2000h™ ventilator, which allows for higher volumes, flows and optional PEEP support.

This FDA-cleared, one-pound, palm-sized, wearable, life-support ventilator delivers a high mixture of oxygen and air through an unobtrusive nasal pillows interface, working to support patients that require mechanical ventilation. The open ventilation system unloads respiratory muscles by providing positive pressure and augmenting the patient's tidal volume.[3] Published data that supports the efficacy of Breathe ventilators demonstrates that the devices reduce dyspnea (shortness of breath), increase oxygenation, enhance exercise endurance, and reduce work of breathing. The devices feature three volume settings that allow patients to select different volumes throughout the day as their respiratory needs change—from lower support while relaxing at home to higher levels of support while exercising.

Peg was titrated on the ventilator by Norco Medical's respiratory therapist, and placed on final prescription volume settings of 180 ml, 200 ml, and 280 ml to meet her ventilation needs at low, medium, and high activity levels, respectively. These volumes helped to maintain her SpO_2 levels between 95%-98% with activity.

Outcomes Following Treatment Change

Peg has completed over six months of therapy on a Breathe ventilator. She sleeps on her Trilogy and immediately switches to her Life2000h once awake. The low profile Breathe Pillows Interface™ prevents the development of mask-related nasal bridge pressure ulcers, despite many hours of continuous daily use, and combined with the open ventilation system, Peg can talk and interact more with friends and family. The ventilator's small size and wearable form factor have allowed Peg to increase her functional activity levels, including re-engaging in some light gardening, and enabling her to take walks around her rural property. Her Norco Medical and PeaceHealth care teams

Kelly Shepard, RRT and Allison Wilhonen, RRT are part of the pulmonary rehabilitation care team at PeaceHealth United General Hospital in Sedro Wooley, WA. Raymon Gregg, CRT, RPSGT is Director of Clinical Education for Breathe Technologies, Inc. in Irvine, CA.

have noticed improvements in her overall skin coloring and a noticeable strengthening in her voice and ability to speak. She has also been able to start driving again, which has increased her feeling of independence. She was recently re-enrolled in United General Hospital's pulmonary rehabilitation program, and is utilizing her Life2000h ventilator while exercising.

Since beginning therapy, Peg has not experienced an ER visit due to an exacerbation or required a hospital admission. "It is incredible to see a patient this fragile not experience an ER visit or admission, given that she was exacerbating several times per year. It is important for her quality of life as well as the healthcare system to see a meaningful way to reduce the risk of a readmission," said Kelly Shepard, Peg's respiratory therapist at PeaceHealth.

When asked how the Life2000h has made a difference in her life, Peg emphatically states, "I honestly believe that I would not still be alive today without the help to breathe that this machine provides to me every day. Since I have started on the Breathe device, it has felt like the difference between living and simply existing."

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Oximetry Assessment of Intracardiac and Great Vessel Shunts

Bruce Toben, RRT-NPS, CPFT, FAARC

Introduction

Congenital Heart Disease (CHD) affects approximately 8 live births per 1,000 globally, with a higher prevalence in Asia (9.3 per 1,000) and Europe (8.2 per 1,000) vs. a lower incidence in the United States (6.9 per 1,000).[1] Depending on the severity that contributes to overt signs and symptoms, the diagnosis of CHD may occur in utero, after birth, during adolescence or in adulthood. Many defects that are associated with CHD are characterized by a blood flow pattern that deviates from the normal circuit of the adult circulatory system. Patients with this altered blood pathway or shunt may be asymptomatic or present in stages of increasing gravity that severely compromises cardiac output with profound hypoxemia. Included among the most common intracardiac and great vessel shunt lesions are: atrial septal defect, patent ductus arteriosus and ventricular septal defect.

Right-sided cardiac catheterization with the Oximetry Run procedure is a standard assessment technique for the detection, localization and quantification of intracardiac and great vessel left-to-right shunts in all age populations. During the oximetry run, oxygen content (ctO_2) and fractional oxyhemoglobin saturation ($\%FO_2Hb$) are measured in blood samples drawn sequentially from the pulmonary artery (PA), right ventricle (RV), right atrium (RA), superior vena cava (SVC), and inferior vena cava (IVC). A left-to-right shunt may be detected and localized if a sudden, discontinuous change or step-up in blood oxygenation is identified in one of the right heart sites assessed. A significant step-up is defined as an increase in blood oxygen content or saturation that exceeds the normal variability that might be observed if multiple samples were drawn from that cardiac chamber or great vessel.[2]

The oximetry run procedure was established by studies that were originally performed by Dexter and his associates in 1947.[3] Oxygen content was measured using Van Slyke and Neill's volumetric technology and pressures were recorded by Hamilton's optical manometer. Their results concluded that repeated specimens drawn from the RA could vary in ctO_2 by as much as 2 volumes percent (vol%), variation within the RV and PA were found to be 1 vol% and 0.5 vol% respectively. From these observations, Dexter concluded that a significant step-up is present at the atrial level when the highest ctO_2 in blood samples drawn from the RA exceeds the highest content in the vena cava by 2 vol%, at the ventricular level if the highest RV sample is 1 vol% higher than the highest RA sample, and at the level of the pulmonary artery if the PA ctO_2 is more than 0.5 vol% greater than the highest RV sample.

The studies performed by Dexter derived the acceptable variability of ctO_2 in the right heart utilizing a laboratory based analytical method. In 1980, Antman correlated ctO_2 with oxygen saturation during oximetry run procedures in patients receiving right-heart catheterizations for non-shunt related pathologies.[4] Because of the pioneering work of Dexter and the continued efforts of Antman, point-of-care (POC) whole blood oximetry (hemoximetry), which encompasses multiwavelength spectrophotometry, has replaced volumetric analysis with rapid throughput measurements of $\%FO_2Hb$ and ctO_2 for step-up shunt detection. Without compromising accuracy or precision, healthcare professionals who are not skilled in the nuances of laboratory technology, can assist in the oximetry run procedure by processing blood specimens and reporting results within 10 seconds.[5] The use of POC whole blood oximetry has simplified the technique and reduced the overall time needed to perform the right-sided cardiac catheterization procedure for step-up shunt detections.

Oximetry Run Procedure

Screening for a left-to-right shunt is commonly performed by measuring the $\%FO_2Hb$ from samples drawn from the SVC and PA. If the difference in $\%FO_2Hb$ between these samples is ≥8%, a left-to-right shunt may be present at the atrial, ventricular, or great vessel level, and a full oximetry run is often conducted.

A full oximetry run to detect a left-to-right shunt typically includes collecting samples from the following anatomic locations and measuring the $\%FO_2Hb$ and ctO_2.[2]

1. Left and/or right pulmonary artery
2. Main pulmonary artery
3. Right ventricle, outflow tract
4. Right ventricle, mid
5. Right ventricle, tricuspid valve or apex
6. Right atrium, low or near tricuspid valve
7. Right atrium, mid
8. Right atrium, high
9. Superior vena cava, low (near junction with right atrium)
10. Superior vena cava, high (near junction with brachiocephalic vein)
11. Inferior vena cava, high (just at or below diaphragm)
12. Inferior vena cava, low (at L4–L5)

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Table 1: Detection of Left-to-Right Shunts by Oximetry[2]

Level of Shunt	Mean of distal chamber samples	Mean of proximal chamber samples	Highest value in proximal chamber	Highest value in distal chamber	Approximate minimal *Q*p/*Q*s required for detection (assuming SBFI = 3 L/min/M^2)	Possible Causes of Step-Up
	%*F*O$_2$Hb	*c*tO$_2$ (vol%)	%*F*O$_2$Hb	*c*tO$_2$ (vol%)		
Atrial (SVC/IVC to RA)	≥7	≥1.3	≥11	≥2.0	1.5–1.9	Atrial septal defect; Partial anomalous pulmonary venous drainage; ruptured sinus of Valsalva; VSD with TR; coronary fistula to RA
Ventricular (RA to RV)	≥5	≥1.0	≥10	≥1.7	1.3–1.5	VSD; PDA with PR; primum ASD; coronary fistula to RV
Great Vessel (RV to PA)	≥5	≥1.0	≥5	≥1.0	≥1.3	PDA; aortapulmonic window; aberrant coronary artery origin
Any level (SVC to PA)	≥7	≥1.3	≥8	≥1.5	≥1.5	All of the above

SVC and IVC, superior and inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; VSD, ventricular septal defect; TR, tricuspid regurgitation; PDA, patent ductus arteriosus; PR, pulmonic regurgitation; ASD, atrial septal defect; SBFI, systemic blood flow index; *Q*p/*Q*s, pulmonary to systemic flow ratio.

Interpretation of the oximetry run and step-up differences relative to left-to-right shunts, are often modeled on the guidelines published by Grossman, whereby criteria developed by Antman compared both the mean %*F*O$_2$Hb of the distal chambers and the highest %*F*O$_2$Hb in the proximal chambers for significant step-up findings (Table 1).[2]

To determine a right-to-left shunt, blood specimens need to be sampled from the left heart, i.e., pulmonary vein, left atrium, left ventricle, and aorta. The pulmonary venous blood of patients with arterial hypoxemia caused by an intracardiac right-to-left shunt is fully saturated with oxygen. Therefore, the site of a right-to-left shunt may be localized by noting which left heart site is the first to show desaturation (i.e., a step-down in oxygen concentration). If the left atrial %*F*O$_2$Hb is normal but desaturation is present in the left ventricle and in the systemic circulation, the right-to-left shunt is across a ventricular septal defect. A major disadvantage of this technique is that a pulmonary vein and the left atrium must be entered. This is not as easy in adults as it is in infants, where access to the left atrium may be entered through the foramen ovale.

If the oximetry run reveals that a significant step-up is present, the pulmonary blood flow (Q_P), systemic blood flow (Q_S), and magnitude of left-to-right or right-to-left shunts may be calculated based on the Fick equation.[6]

Oximetry and Oxyhemoglobin Saturation

Many POC devices report oxyhemoglobin saturation. Blood gas analyzers calculate this value using an algorithm based on an assumed normal oxyhemoglobin dissociation curve, PO_2, pH and a preset total hemoglobin value.[7] Some whole blood oximeters use two light emitting diode wavelengths that have the capacity to only measure the hemoglobin species of oxyhemoglobin (%O_2Hb) and reduced hemoglobin (%HHb).[8] These systems, which either do not measure hemoglobin directly, or do not detect the full spectrum of hemoglobin species, report functional oxyhemoglobin saturation (SO_2). Because they do not account for concentrations of carboxyhemoglobin (%COHb) or methemoglobin (%MetHb), they inherently report oxygen saturation results with a positive bias when correlated to the laboratory's gold standard (CO-oximetry).[9] In the presence of clinically elevated %COHb and %MetHb, patient management based on functional oxygen saturation may contribute to an erroneous assessment of cardiopulmonary function and the inappropriate interpretation of the step-up calculation.[10]

Multiwavelength spectrophotometry integrated into POC whole blood oximetry or CO-oximetry is designed to report accurate and precise results of both *c*tO_2 and oxygen saturation.[11] These analyzers directly measure: %O_2Hb, %HHb, %COHb and %MetHb. The oxygen saturation value reported, which is derived from measuring all the species of hemoglobin, is termed fractional oxyhemoglobin saturation. The total hemoglobin reported is the sum of the concentrations of each hemoglobin derivative in units of g/dL, g/L or mmol/L. Some POC oximetry systems[12] contain software to tag the result with the anatomic location of the sample, calculate the magnitude of the step-up, and perform hemodynamic computations required in the right-side catheterization procedure including:

- Body surface area
- Oxygen uptake
- Stroke volume and stroke index
- Cardiac output
- Pulmonary and systemic blood flow
- Pulmonary and systemic vascular resistance
- Pulmonary-to-systemic blood flow ratio

To promote blood conservation and reduce the risk of iatrogenic anemia especially in the newborn/pediatric population, oximeters and CO-oximeters used in the oximetry run procedure should perform as intended with an instrument sample volume of ≤50 µL.[13] In addition; the analysis throughput time should be fast enough to accommodate a specimen that is free from

anticoagulants.[14] Micro sample specimens that contain even the smallest coating of a liquid anticoagulant can promote hemodilution type preanalytical errors to all results.[15] Another advantage of the throughput time is the effect to the overall length of the catheterization procedure. Having a time to result in 60 seconds, compared with less than 10 seconds, can disrupt the oximetry run flow by either delaying moving the catheter to the next anatomic location while waiting for the result, or repositioning the catheter to a previous site to resample due to analyzer malfunction or to confirm a past result. These two system design features, small sample volume and time to result, are essential considerations for choosing an optimal analyzer for right-sided catheterization procedures.

The Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS, and National Committee for Clinical Laboratory Standards) cautions the use of functional oxygen saturation calculations (SO_2) in lieu of fractional oxygen saturation measurements (%FO_2Hb). Specifically directed at the oximetry run procedure and its associated physiologic calculations, the CLSI guideline states, "Clinically significant errors can result from incorporation of such an estimated value for oxygen saturation in further calculations, such as shunt fraction, or by assuming that the value obtained is equivalent to fractional oxyhemoglobin."[16] This identical warning is also published in the Operation Manual of blood gas analyzers and the oximeters that report functional oxyhemoglobin saturation.[7, 8]

Summary

The oximetry run with a step-up or step-down assessment is an established diagnostic procedure in CHD, and is effective in detecting, localizing and quantifying left-to-right and right-to-left intracardiac and great vessel shunts. A contributing factor to ensure accuracy and efficacy in the technique is the selection of the oximetry analyzer. The ideal instrument should: a) report both %FO_2Hb and ctO_2 results, b) have rapid throughput of samples to minimize overall catheterization time, c) require a small sample volume to promote blood conservation, d) have simple instrument operational characteristics to perform tests proficiently by non-laboratory healthcare professionals, e) tag the result with the anatomic location of the sample, and f) have a low per test cost due to the multiple samples required for each oximetry run procedure. The clinical staff conducting the oximetry run procedure should be familiar with the differences between functional vs. fractional oxygen saturation to avoid potential pitfalls in step-up interpretation and ensure accuracy and consistency in the evaluation of intracardiac and great vessel shunts.

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Effect of External PEEP in Patients Under Controlled Mechanical Ventilation with an Auto-PEEP of 5 cmH_2O or Higher

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Abstract

Background: In some patients with auto-positive end-expiratory pressure (auto-PEEP), application of PEEP lower than auto-PEEP maintains a constant total PEEP, therefore reducing the inspiratory threshold load without detrimental cardiovascular or respiratory effects. We refer to these patients as "complete PEEP-absorbers." Conversely, adverse effects of PEEP application could occur in patients with auto-PEEP when the total PEEP rises as a consequence. From a pathophysiological perspective, all subjects with flow limitation are expected to be "complete PEEP-absorbers," whereas PEEP should increase total PEEP in all other patients. This study aimed to empirically assess the extent to which flow limitation alone explains a "complete PEEP-absorber" behavior (i.e., absence of further hyperinflation with PEEP), and to identify other factors associated with it.

Methods: One hundred patients with auto-PEEP of at least 5 cmH_2O at zero end-expiratory pressure (ZEEP) during controlled mechanical ventilation were enrolled. Total PEEP (i.e., end-expiratory plateau pressure) was measured both at ZEEP and after applied PEEP equal to 80 % of auto-PEEP measured at ZEEP. All measurements were repeated three times, and the average value was used for analysis.

Results: Forty-seven percent of the patients suffered from chronic pulmonary disease and 52 % from acute pulmonary disease; 61 % showed flow limitation at ZEEP, assessed by manual compression of the abdomen. The mean total PEEP was 7 ± 2 cmH_2O at ZEEP and 9 ± 2 cmH_2O after the application of PEEP ($p < 0.001$). Thirty-three percent of the patients were "complete PEEP-absorbers." Multiple logistic regression was used to predict the behavior of "complete PEEP-absorber." The best model included a respiratory rate lower than 20 breaths/min and the presence of flow limitation. The predictive ability of the model was excellent, with an overoptimism-corrected area under the receiver operating characteristics curve of 0.89 (95 % CI 0.80–0.97).

Conclusions: Expiratory flow limitation was associated with both high and complete "PEEP-absorber" behavior, but setting a relatively high respiratory rate on the ventilator can prevent from observing complete "PEEP-absorption." Therefore, the effect of PEEP application in patients with auto-PEEP can be accurately predicted at the bedside by measuring the respiratory rate and observing the flow-volume loop during manual compression of the abdomen.

Keywords: Dynamic hyperinflation, Auto-positive end-expiratory pressure, Positive end-expiratory pressure, Flow limitation, Mechanical ventilation, Respiratory rate

Background

Deciding whether to use positive end-expiratory pressure (PEEP) in mechanically ventilated patients with auto-PEEP is a daily challenge for intensivists, since in these patients the application of PEEP can increase or not the end-expiratory lung volume and end-expiratory plateau pressure [1, 2]. In some patients, here referred to as "complete *PEEP-absorbers*," the application of PEEP reduces the auto-PEEP to maintain a constant total PEEP (i.e., the sum of PEEP and auto-PEEP as measured by the end-expiratory airway occlusion), therefore reducing the inspiratory threshold load and the work of breathing without detrimental cardiovascular or respiratory effects. In others, the total PEEP rises as a consequence of PEEP application and adverse effects can occur due to the worsening of hyperinflation. The impact of total PEEP in mechanically ventilated patients becomes relevant when end-inspiratory hyperinflation or hemodynamic impairment occurs, whereas end-expiratory hyperinflation could affect inspiratory threshold load and efficiency of respiratory muscles in patients with spontaneous respiratory activity.

Flow limitation occurs when the expiratory flow cannot be increased despite the raise of alveolar pressure, as usually occurs during the increase of an expiratory effort [1]. From a

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pathophysiological point of view, application of PEEP at a level lower than the patient's auto-PEEP (e.g., 80–90 %) is expected to reduce auto-PEEP and leave total PEEP unchanged in the presence of flow limitation, while in the absence of flow limitation the applied PEEP should add to auto-PEEP and increase total PEEP [1, 3–5]. To the best of our knowledge, however, there is no clinical evidence confirming that flow limitation by itself is sufficient to prevent the increase in total PEEP when PEEP lower than auto-PEEP is applied. Indeed, the role of other factors that might predict a PEEP-absorber behavior, related to either patient characteristics (elastance, airway resistance, acute or chronic lung damage) or ventilatory setting (tidal volume, expiratory time, respiratory rate, minute ventilation), has never been studied. Moreover, the presence of flow limitation was not systematically assessed in previous clinical studies investigating the effect of applied PEEP on total PEEP and auto-PEEP in patients with respiratory failure. From these studies, we only know that, on average, total PEEP (or end-expiratory lung volume) increased by an amount lower than the applied PEEP when this was lower than auto-PEEP [5–14].

This study aimed to empirically assess the extent to which flow limitation alone explains a "complete PEEP-absorber" behavior (i.e., absence of further hyperinflation with PEEP), and to identify other factors associated with it. Moreover, we wanted to analyze the diagnostic performance of the model predicting the "complete PEEP-absorber" behavior which could improve the decision of how to use PEEP in patients with auto-PEEP.

Methods

From January to June 2013, in a network of 11 Italian intensive care units, we performed a pre-post clinical trial where all patients were studied before and after PEEP application. Patients were considered for inclusion in the study if they met all of the following criteria: (1) age ≥18 years; (2) tracheal intubation (or tracheotomy) with controlled mechanical ventilation; (3) absence of any sign of spontaneous respiratory activity (absence of triggering, passive inspiration and passive expiration, as evaluated by airway pressure and airflow waveforms); (4) persistence of expiratory flow at the beginning of each inspiration; (5) no contraindication to compression of the abdomen; (6) absence of cardiovascular instability (mean arterial pressure >60 mmHg, systolic arterial pressure <180 mmHg, heart rate >40/min and <150/min); (7) arterial oxygen saturation >90 %; and (8) intracranial pressure <20 mmHg. All patients satisfying these criteria and with auto-PEEP ≥5 cmH_2O at zero end-expiratory pressure (ZEEP) were enrolled in the study.

The primary aim of the study was to identify variables independently associated with "complete PEEP-absorber" behavior, i.e., unchanged total PEEP after application of PEEP equal to 80 % of auto-PEEP. Total PEEP was considered unchanged if its value increased up to 1 cmH_2O, which represents the accuracy level of the pressure measurement. In a secondary analysis, patients who were not "complete PEEP-absorber" were classified as "high PEEP-absorber" if the increase of total PEEP was less than 50 % of applied PEEP; otherwise, they were classified as "low PEEP-absorber." This created a three-level response variable, and the analysis was repeated to identify variables independently associated with "high PEEP-absorber" and with "complete PEEP-absorber" versus "low PEEP-absorber" response.

Ethics, consent and permissions

The protocol was approved by the Institutional Ethical Committee (Comitato Etico ASL Brescia), and informed consent was obtained from patients or their next of kin, as appropriate.

Measurements at baseline and after PEEP application

After enrollment, patients received volume-controlled ventilation with constant inspiratory flow while maintaining the tidal volume, respiratory rate and inspiratory time set by the attending physician. PEEP was set at 0 cmH_2O. Three end-expiratory and three end-inspiratory airway occlusion maneuvers, each lasting 4 s, were then performed with at least ten uninterrupted breaths between maneuvers. Peak airway pressure (P_{pk}), end-inspiratory plateau pressure (P_{plat}), total PEEP ($PEEP_{tot}$), tidal volume and inspiratory flow were measured. The mean value of each variable was used for subsequent analysis and calculation. Compliance of the respiratory system was calculated as tidal volume/(P_{plat} – $PEEP_{tot}$) and resistance of the respiratory system as (P_{pk} – P_{plat})/inspiratory flow. *We calculated auto-PEEP* as the difference between $PEEP_{tot}$ and applied PEEP [1].

After the occlusion maneuvers, the presence of flow limitation was assessed with manual compression of the abdomen [15–17]. The investigator put one hand gently on the patient's abdomen, with the palm on the umbilicus, perpendicular to the axis between the xiphoid process and the pubis. After a short period, which allowed for recognition of the expiratory phase, the investigator exerted firm but gentle compression of the abdomen in an antero-posterior direction as soon as the insufflation was finished. This compression was maintained throughout expiration. The flow-volume loops obtained during passive expiration and during manual compression of the abdomen were superimposed, and flow limitation was diagnosed when all or part of the expiratory flow during manual compression of the abdomen and passive expiration was superimposed on the flow-volume loops. Three maneuvers were performed, and patients were classified as flow limited if flow limitation was confirmed in all three maneuvers.

We then applied a PEEP equal to 80 % of the patient's auto-PEEP measured at ZEEP, while maintaining all other ventilator settings equal to those at baseline, and all measurements were repeated.

Data validation

Each enrolled patient was assessed for reliability of measurements and absence of spontaneous respiratory activity. Data were considered reliable if the difference between each of the three measurements and their average value was lower than 10 % (a difference of 1 cmH_2O was tolerated) for all airway pressure variables. Furthermore, the investigators captured images of the airway and flow waveforms during ventilation and during end-inspiratory and end-expiratory occlusions, and of the superimposed flow-volume loops obtained during manual compression of the abdomen and during passive expiration. These images were assessed and discussed by four senior authors (GN, DT, AR and MT), who had to confirm the absence of any sign of respiratory activity and the diagnosis of flow limitation. Only patients with data satisfying these validation criteria were included in the analysis.

Statistical analysis

The size of the study was decided based on considerations on the number of predictors to be tested in the predictive model. Flow-limited expiration has been reported in approximately 40

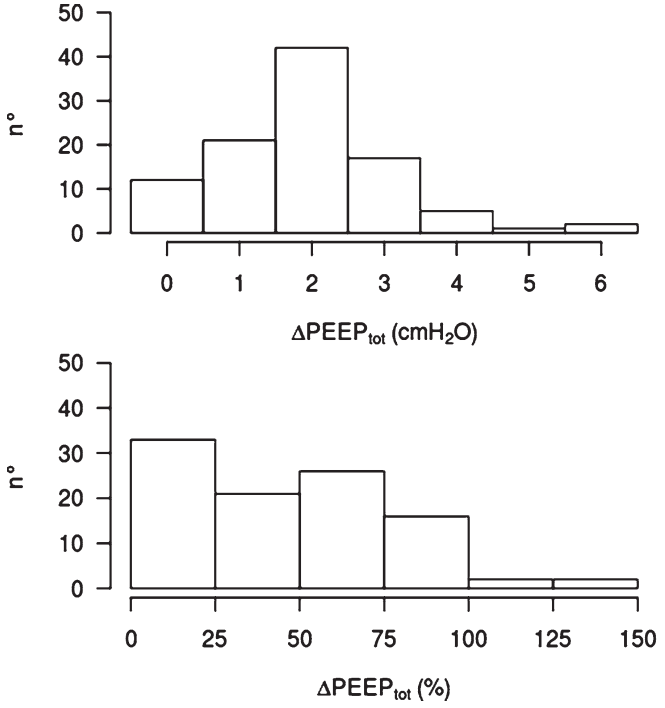

Figure 1. Frequency distribution of differences in total PEEP ($\Delta PEEP_{tot}$) in PEEP versus ZEEP phases. On the upper side the differences are shown as the absolute value in cmH_2O; on the lower side the differences are expressed as a percentage of applied PEEP. PEEP positive end-expiratory pressure, $PEEP_{tot}$ total PEEP, ZEEP zero end-expiratory pressure

% of patients with auto-PEEP [18], and we expected a similar percentage of "complete PEEP-absorber." We anticipated that the enrollment of 100 patients would give about 40 events, allowing us to evaluate up to eight explanatory variables in a logistic model with "complete PEEP-absorber" as the outcome variable [19].

Data are shown as mean and standard deviation, median and interquartile range, or count and percentage, as appropriate.

Primary analysis ("complete PEEP-absorbers" vs. other patients)

In the univariate analyses, the variables to be tested were selected a priori and differences between groups were analyzed using logistic regression. All variables with a p value lower than 0.05 were included in a multiple logistic regression model to assess their independent association with "complete PEEP-absorber" behavior, with their effect expressed as odds ratio (OR) with 95 % confidence interval (95 % CI). Multicollinearity in the regression models was assessed by the variance inflation factor (VIF). Variables with VIF higher than 5 were removed one by one from the model, beginning from the covariate with the highest VIF.

Variables showing statistical significance in the multiple regression model were kept in the final predictive model. We performed internal validation using tenfold cross-validation to investigate model overfitting and correct for it. The diagnostic performance of our predictive model after cross-validation was evaluated in terms of discrimination, using the area under the receiver operating characteristics (ROC) curve corrected for overoptimism, and calibration, assessed using the mean absolute error. We also evaluated sensitivity and specificity, as well as positive and negative predictive values.

Secondary analysis ("low" vs. "high" and "complete PEEP-absorbers")

Overall differences across the three groups were analyzed with a one-way analysis of variance for normally distributed continuous variables and a Chi-squared test for binary and nominal data. Pairwise comparisons were made with Tukey's test and Fisher's test, respectively. All variables with a p value lower than 0.05 were included in a multinomial logistic regression model to identify the variables independently associated with "high PEEP-absorber" and "complete PEEP-absorber," with "low PEEP-absorber" as the reference level.

A p value threshold of 0.05 was for used for statistical significance. Statistical analyses were performed using the R statistical software, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

Results

Of the 203 patients screened, 118 (58 %) had auto-PEEP equal or greater than 5 cmH_2O at ZEEP and were enrolled in the study. Eighteen enrolled patients did not satisfy the requirements for data validation, leaving 100 patients who were included in the analysis.

Thirty-nine percent of patients had the diagnosis of chronic obstructive pulmonary disease, and 19 % were admitted for acute exacerbation of chronic obstructive pulmonary disease. Pneumonia was diagnosed in 24 % of enrolled subjects. Simplified Acute Physiology Score 2 was 50 (40-61) at admission in intensive care unit, and Sequential Organ Failure Assessment score was 7 (5-9) on the day of the study (median and interquartile range).

Auto-PEEP at ZEEP was 7 ± 2 cmH_2O, and the applied PEEP was 5 ± 1 cmH_2O. On average, the addition of PEEP led to a total PEEP increased to 9 ± 2 cmH_2O ($p < 0.001$). Thirty-three percent of patients were "complete PEEP-absorber," 21 % were "high PEEP-absorber," and the remaining 46 % were classified as "low PEEP-absorber." The distribution of the post-pre difference in total PEEP (after application of PEEP as compared with baseline, $\Delta PEEP_{tot}$) across all patients is shown in the upper panel of Fig. 1. The lower panel of Fig. 1 shows $\Delta PEEP_{tot}$ expressed as a percentage of applied PEEP (e.g., 100 % if total PEEP increased by the full amount of applied PEEP; 0 % if the application of PEEP did not alter total PEEP). Figure 1 shows how changes in total PEEP after PEEP application vary across patients with auto-PEEP, with the majority of the patients showing changes in total PEEP that are halfway between those expected in the presence and absence of flow limitation.

The characteristics of complete, high and low PEEP-absorbers are compared in Table 1. The adjusted results of multiple logistic regression for the association between study variables and "complete PEEP-absorber" behavior are shown in Table 2. Expiratory time and minute ventilation were dropped from the model because of multicollinearity with respiratory rate. Respiratory rate and flow limitation were independently associated with "complete PEEP-absorber" behavior: Respiratory rate was inversely associated, whereas flow limitation was positively associated with the probability of being "complete PEEP-absorber." The secondary analysis, in addition to confirming the association of respiratory rate and flow limitation with "complete PEEP-absorber" pattern,

Table 1. Patients' characteristics according to PEEP-absorber behaviors, classified as in the primary and secondary analyses

PEEP-absorber	*Primary analysis*: complete PEEP-absorber vs other patients			*Secondary analysis*: "other patients" classified as high and low PEEP-absorber (3-level variable)		
	Complete	Other	p	High	Low	p
Number of patients (%)	33 (33 %)	67 (67 %)	–	21 (21 %)	46 (46 %)	–
Total PEEP at ZEEP (cmH_2O)	8 ± 3	6 ± 2	<0.001	8 ± 3	5 ± 1*,#	<0.001
Applied PEEP (cmH_2O)	7 ± 2	5 ± 2	0.001	7 ± 2	4 ± 0*,#	<0.001
Total PEEP with PEEP (cmH_2O)	9 ± 3	9 ± 2	0.65	10 ± 3	8 ± 1#	0.001
Female, n (%)	18 (55 %)	24 (36 %)	0.12	5 (24 %)	19 (41 %)	0.08
Age (years)	74 ± 8	70 ± 11	0.07	71 ± 10	69 ± 12	0.18
Body mass index (kg/m^2)	30 ± 7	28 ± 6	0.05	31 ± 7	26 ± 5*,#	0.002
Respiratory rate (1/min)	16 ± 3	22 ± 4	< 0.001	20 ± 3	22 ± 4*	<0.001
Expiratory time (s)	2.7 ± 0.7	1.5 ± 0.5	< 0.001	1.7 ± 0.5	1.4 ± 0.5*	<0.001
Minute ventilation (l/min)	7.1 ± 1.4	10.5 ± 2	< 0.001	10 ± 2	11.1 ± 2.1*	<0.001
Tidal volume (ml/IBW)	8 ± 1	8 ± 1	0.94	8 ± 1.5	8 ± 1.2	0.29
Resistance ($cmH_2O{\cdot}l^{-1}{\cdot}s$)	21 ± 5	18 ± 7	0.05	20 ± 9	18 ± 6*	0.03
Elastance (cmH_2O/l)	20 ± 5	19 ± 6	0.25	19 ± 6	18 ± 6	0.47
Flow limitation, n (%)	32 (97 %)	29 (47.8 %)	<0.001	19 (90 %)	10 (22 %)*,#	<0.001
Chronic pulmonary disease, n (%)	25 (76 %)	22 (33 %)	<0.001	12 (57 %)	10 (22 %)*,#	<0.001
History of smoking, n (%)	24 (75 %)	24 (38 %)	<0.001	9 (45 %)	15 (34 %) *	0.002
Acute pulmonary disease, n (%)	27 (84 %)	25 (37 %)	<0.001	12 (57 %)	13 (28 %)*	<0.001
PaO_2/F_iO_2 (mmHg)	203 ± 82	275 ± 132	0.01	205 ± 89	306 ± 137*,#	<0.001
Supine position, n (%)	21 (64 %)	31 (46 %)	0.16	10 (48 %)	21 (46 %)	0.26

Figures are presented as number (percentage) or mean ± standard deviation, as appropriate

PEEP positive end-expiratory pressure, *IBW* ideal body weight

* $p < 0.05$ vs "complete PEEP-absorber"; # $p < 0.05$ versus "high PEEP-absorber"

Table 2. Multiple logistic regression: adjusted associations between study variables and "complete PEEP-absorber" behavior

	Odds ratio (95 % CI)	*p* value
Respiratory rate (min^{-1})	0.59 (0.42–0.76)	<0.001
Flow limitation	18 (1.7–476)	0.03
Resistance ($cmH_2O\ L^{-1}\ s$)	0.94 (0.82–1.06)	0.29
Chronic pulmonary disease	3.2 (0.26–58)	0.38
Body mass index ($kg\ m^{-2}$)	1.1 (0.94–1.2)	0.39
Acute pulmonary disease	2.3 (0.33–17)	0.39
History of smoking	2.8 (0.28–33)	0.39
PaO_2/F_iO_2 (mmHg)	1 (0.99–1.01)	0.88

CI confidence interval

Table 3. Multinomial logistic regression: adjusted associations between study variables and "high PEEP-absorber" or "complete PEEP-absorber" behavior ("low PEEP-absorber" as reference level)

	Good PEEP-absorber		Complete PEEP-absorber	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Flow limitation	20 (3.1–131)	0.002	76 (4–1425)	0.004
Respiratory rate (min^{-1})	0.91 (0.72–1.2)	0.46	0.56 (0.4–0.79)	0.001
PaO_2/F_iO_2 (mmHg)	0.99 (0.98–1)	0.09	0.99 (0.98–1.01)	0.29
Body mass index ($kg\ m^{-2}$)	1.1 (0.95–1.3)	0.2	1.1 (0.95–1.3)	0.16
Chronic pulmonary disease	3 (0.36–24)	0.31	7.3 (0.35–150)	0.2
Acute pulmonary disease	2.1 (0.31–13.9)	0.45	3.7 (0.34–41)	0.28
History of smoking	0.6 (0.07–5.2)	0.65	2 (0.12–33)	0.64
Resistance ($cmH_2O\ L^{-1}\ s$)	1.01 (0.89–1.1)	0.93	0.94 (0.81–1.1)	0.38

OR odds ratio, *CI* confidence interval

showed that the only characteristic associated with "high PEEP-absorber" was the presence of flow limitation (Table 3).

The final predictive model to identify "complete PEEP-absorber" included flow limitation and respiratory rate, with the latter binarized as low and high using a threshold of 20/min; this corresponds to the threshold showing the best compromise between sensitivity and specificity to predict PEEP-absorber behavior in the ROC curve of the model with respiratory rate alone. The logistic regression equation of the model was: "complete PEEP-absorber" = –5 + 3.5 × respiratory rate <20/min + 2.9 × flow limitation. The model showed excellent overall predictive ability, with an area under the ROC curve of 0.92 (95 % CI 0.87–0.97). The tenfold cross-validation showed little evidence of overfitting in our predictive model. The high accuracy of the model was confirmed, with an area under the ROC curve corrected for overoptimism of 0.87 (95 % CI 0.79–0.95). The calibration of the model corrected for overoptimism was also good (mean absolute error = 0.03). Sensitivity, specificity and positive and negative predictive values are shown in Table 4, which also reports the diagnostic performance of two models with either flow limitation or respiratory rate alone. The model with both flow limitation and respiratory rate showed the best overall predictive ability, with high values across all indicators (ranging from 0.81 to 0.94).

In practice, the data may be interpreted as follows: Flow-limited patients have approximately the same probability to be "complete PEEP-absorber" or not (positive predictive value: 0.52), but patients without flow limitation almost certainly are

Table 4. Diagnostic performance of the model to identify "complete PEEP-absorber" with different combinations of respiratory rate and flow limitation

	Sensitivity (95 % CI)	Specificity (95 % CI)	Positive predictive value (95 % CI)	Negative predictive value (95 % CI)
FL	0.97 (0.84–1)	0.57 (0.44–0.69)	0.52 (0.39–0.65)	0.97 (0.87–1)
RR < 20 min^{-1}	0.91 (0.76–0.98)	0.85 (0.74–0.93)	0.75 (0.59–0.87)	0.95 (0.86–0.99)
RR < 20 min^{-1} and FL	0.88 (0.72–0.97)	0.9 (0.8–0.96)	0.81 (0.64–0.92)	0.94 (0.85–0.98)

CI confidence interval, *RR* respiratory rate, *FL* flow limitation

not "complete PEEP-absorber" (negative predictive value: 0.97). The probability to be "complete PEEP-absorber" is 0.75 when respiratory rate is lower than 20/min and increases to 0.81 when both flow limitation is present and respiratory rate is lower than 20/min. The absence of "complete PEEP-absorber" behavior can be accurately predicted based only on respiratory rate higher than 20/min (negative predictive value 0.95).

Discussion

This study shows that the application of external PEEP is associated with an increase in total PEEP even in the presence of flow limitation, if the respiratory rate is sufficiently high. Respiratory rate and flow limitation, both measurable at the bedside, can predict whether PEEP application in patients with auto-PEEP is likely to result in an unchanged total PEEP rather than in an increased total PEEP with further hyperinflation. The predictive role of a low respiratory rate is novel, and the two factors together show accurate predictive ability, with an area under the ROC curve reaching 0.87. To our knowledge, this is the first study to develop a predictive model that could be used in clinical practice to guide the difficult choice of PEEP in patients with incomplete expiration.

As expected in patients with auto-PEEP ≥ 5 cmH_2O, our study population showed a high percentage (65 %) of patients with chronic or acute lung disease, confirming a similar finding from a previous study in mechanically ventilated patients with acute respiratory failure [18]. Our sample is representative of those critically ill patients with at least 5 cmH_2O of auto-PEEP, which have different characteristics when compared to the overall population of mechanically ventilated patients.

After application of PEEP equal to 80 % of the patient's auto-PEEP, one-third of patients did not show an increase in total PEEP ("complete PEEP-absorber" behavior) and about half of patients showed an increase of less than 50 % of the applied PEEP. Most patients showed an increase in total PEEP that was halfway between that expected in the presence and absence of flow limitation. Apart from the possibility of decreased expiratory airway resistance and airway recruitment with PEEP [1], this behavior may be explained by the fact that flow limitation does not affect the lungs as a whole. Rather it should be regarded as a phenomenon occurring in some areas and not in others in the context of inhomogeneous lung disease [1, 20, 21]. As a consequence, within the same patient dynamic hyperinflation can occur in the absence of flow limitation in some lung regions, while it can be due to flow limitation in others. Therefore, it is not surprising that the increase in total PEEP exhibits a mixed behavior pattern, reaching the two extreme patterns of no change ("complete PEEP-absorber") or increase by the same amount of the PEEP applied only in some patients. An explanatory model is reproduced in Fig. 2.

Our data show that flow limitation alone is not enough to predict a complete PEEP-absorber behavior, which requires the combination of flow limitation and low respiratory rate. In our study population, the threshold of 20/min used to define low respiratory rate was chosen as the best compromise between sensitivity and specificity in the ROC curve. This threshold, however, could be different in patients with characteristics or ventilator patterns different from those of the patients enrolled in our study.

The contribution of respiratory rate to "complete PEEP-absorber" behavior has a pathophysiological basis. The development of auto-PEEP in non-flow-limited areas becomes increasingly likely with the increase of respiratory rate and consequent reduction of expiratory time. Therefore, the application of PEEP in the presence of high respiratory rate could further worsen hyperinflation in non-flow-limited areas and prevent a "complete PEEP-absorber behavior." Conversely, the reduction of respiratory rate can prevent auto-PEEP generation in the absence of flow limitation. In this case, all dynamic hyperinflation would be due exclusively to flow limitation, and the application of PEEP lower than auto-PEEP should not lead to further hyperinflation.

The prediction of the response to PEEP through evaluation of respiratory rate and flow limitation can be particularly useful when the measurement of total PEEP is not reliable or possible. This can occur when there is persistence of expiratory activity during end-expiratory occlusion [22–24], or when the mechanical ventilator does not allow end-expiratory occlusion. In addition, simply knowing that patients with high respiratory rate are not likely to be "complete PEEP-absorber" could be very important when flow limitation cannot be reliably assessed (e.g., during noninvasive ventilation in patients with respiratory failure) [25]: The use of PEEP should be cautious until the respiratory rate decreases, so that further hyperinflation can be avoided. Interestingly, while the presence of flow limitation and low respiratory rate could accurately predict a "complete PEEP-absorber" behavior, a "high PEEP-absorber" behavior was predicted with high accuracy by flow limitation alone. The clinical implication of this finding is that when PEEP is applied to a tachypneic flow-limited patient, we have in most cases an increase of total PEEP lower than half of the applied PEEP, whereas greater increases of hyperinflation are typical of patients without flow limitation.

In our study, the presence of flow limitation was assessed with the maneuver of manual compression of the abdomen, a simple technique validated in spontaneously breathing as well as sedated mechanically ventilated patients [15–17]. In mechanically ventilated patients, the manual compression of the abdomen has been shown to measure the lung volume at

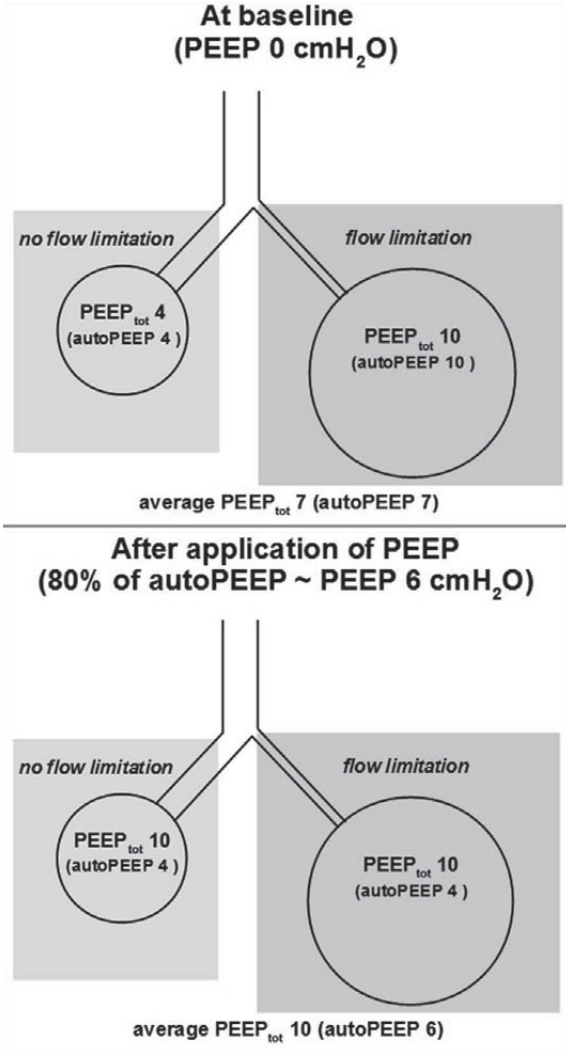

Fig. 2 Effect of PEEP on areas with and without flow limitation. In the upper part an area without flow limitation with 4 cmH2O of auto-PEEP and a flow-limited area with auto-PEEP of 10 cmH2O at ZEEP are presented. Hypothesizing that these two areas evenly contribute to the expired volume, the average auto-PEEP of this model is 7 cmH2O. When PEEP of 6 cmH2O (about 80 % of auto-PEEP) is applied to the whole respiratory system (lower part of the figure), the part of the lung without flow limitation will increase its end-expiratory pressure by the same amount of the applied PEEP, then increasing total PEEP to 10 cmH2O, without any change in auto-PEEP. On the contrary, the flow-limited region is not expected to be further hyperinflated by a PEEP lower than its total PEEP, with the result that total PEEP does not change and auto-PEEP decreases. The average result of PEEP application on the whole lung will be a rise in total PEEP from 7 to 10 cmH2O: The two parts react to PEEP as either flow-limited or non-flow-limited areas, and the overall observed response to PEEP is intermediate between them. PEEP positive end-expiratory pressure; PEEPtot total PEEP; ZEEP zero end-expiratory pressure

which flow limitation occurred with repeatability (i.e., variation among repeated measurements on the same subject under identical conditions) of 16 % and with a very good agreement with the technique of negative expiratory pressure (bias –0.16 ± 3.9 %; 95 % limits of agreement –7.8–7.5 %) [17]. In our study, we did not measure the lung volume at which flow limitation occurred, but simply we assessed whether flow limitation was present or absent. Therefore, we are confident that this approach was appropriate as a bedside evaluation of the presence of flow limitation. In situations where the maneuver of manual compression of the abdomen is impossible to perform or unreliable, it may be reasonable to assume that most of patients with chronic obstructive disease suffer flow limitation [18, 26].

Study limitations

The choice to enroll only passive patients represents both a strength and a limitation of the study. The measurement of auto-PEEP was accurate, whereas it is challenging in actively breathing patients [8, 22–24]. However, our results should be generalized with caution to actively breathing patients, even if the breathing pattern of the patients in our study is similar to that observed in acute respiratory failure of different etiologies during assisted ventilation [27–29]. We cannot exclude that, in patients without flow limitation, total PEEP could be decreased by active expiration and hyperinflation could be actively limited at the expense of an increased effort of the expiratory muscles.

We tested the effects of applied PEEP equal to 80 % of auto-PEEP at ZEEP in patients with at least 5 cmH_2O of auto-PEEP, and our results may not be generalizable to patients with lower auto-PEEP levels or in whom different levels of PEEP are applied. The individual response to PEEP depends on the level of PEEP applied, and in some patients, the "complete PEEP-absorber" behavior is observed only at PEEP levels lower than 80 % of their auto-PEEP [14].

Finally, we report findings obtained with the ventilator settings chosen by the clinicians. We did not investigate differences in the effect of PEEP application corresponding to different respiratory rates or tidal volumes in the same patient, and therefore, we cannot predict what would have been the response to PEEP if different ventilatory parameters had been used.

Conclusions

When PEEP was applied to passive mechanically ventilated patients with auto-PEEP, one-third of patients did not increase total PEEP and about half increased it less than 50 % of the applied PEEP. We found that expiratory flow limitation was associated with both high and complete "PEEP-absorber" behavior, but our results also suggest that setting a relatively high respiratory rate on the ventilator can prevent from observing complete "PEEP-absorption." Therefore, a simple evaluation of the patient's ventilation showing high respiratory rate can allow to accurately exclude a "complete PEEP-absorber" behavior. Our study suggests that it is possible to predict at the bedside if the application of PEEP in patients with auto-PEEP can maximally reduce the inspiratory threshold load without any negative impact on hemodynamics and respiratory muscle mechanics. These findings could be used in routine clinical practice to help setting external PEEP when end-expiratory occlusion is not available or reliable.

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Heart Rate Response During 6-Minute Walking Testing Predicts Outcome In Operable Chronic Thromboembolic Pulmonary Hypertension

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Abstract

Background: Six-minute walk test (6MWT) is routinely performed in chronic thromboembolic pulmonary hypertension (CTEPH) before pulmonary endarterectomy (PEA). However, the clinical relevance of heart rate response (ΔHR) and exercise-induced oxygen desaturation (EID) during 6MWT is remaining unknown.

Methods: Patients undergoing PEA in our center between 03/2013-04/2014 were assessed prospectively with hemodynamic and exercise parameters prior to and 1 year post-PEA. Patients with symptomatic chronic thromboembolic disease (mean pulmonary artery pressure (mPAP) <25 mmHg) and clinical relevant obstructive pulmonary disease were excluded. The following definitions were used: ΔHR = (peak HR – resting HR), percent heart rate reserve (HRR) = (peak HR – rest HR)/(220 – age – rest HR) x 100 and EID = $SpO_2 \leq 88$ %.

Results: Thirty-seven patients (of 116 patients screened) with mPAP of 43.2 ± 8.7 mmHg, pulmonary vascular resistance (PVR) of 605.5 ± 228.7 dyn*s/cm^5, cardiac index (CI) of 2.4 ± 0.5 l/min/m^2 and a 6MWT-distance of 404.7 ± 148.4 m and a peak VO_2 of 12.3 ± 3.4 ml/min/kg prior to PEA were included. Baseline ΔHR during 6MWT was significantly associated with PVR 1 year post-PEA using linear regression analysis (r = 0.43, p = 0.01). Multivariate analysis indicated an association of HRR during 6MWT and residual PH with a hazard ratio of 1.06 (95 % Confidence interval for hazard ratio 0.99–1.14, p = 0.08). EID was observed commonly during 6MWT but no correlations to outcome parameters were found.

Conclusions: This is the first prospective study to describe an association of ΔHR during 6MWT with pulmonary hemodynamics 1 year post-PEA. Our preliminary results indicate that HRR derived from 6MWT is of clinical significance. EID was commonly observed, albeit failed as a significant prognostic factor.

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Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined by an elevation of mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) caused by unresolved pulmonary vascular obstruction due to recurrent embolism [1, 2]. Mechanical obstruction in proximal parts of the pulmonary vascular system and secondary small-vessel arteriopathy in the non-obstructed areas are causes of disease progression and lead to extensive right ventricle (RV) dysfunction, loading and failure [1, 2]. Pulmonary endarterectomy (PEA) is the gold standard in case of surgical accessible CTEPH and offers a potential curative treatment with an improved functional outcome and high survival rates [3, 4]. Predictors of favorable outcome after PEA are important in daily clinical practice and include preoperative forced expiratory volume in 1 s (FEV1), heart-type fatty acid-binding protein (H-FABP) and cardiac index (CI) [5, 6]. In addition, 6-minute walk testing (6MWT) with measurement of the distance covered (6MWD) is performed routinely before and after PEA as a tool to assess disease severity, functional capacity or long-term outcome [7, 8]. Moreover, preoperative 6MWD correlates with 3-month survival after PEA [9]. However, the prognostic relevance of additional parameters derived from the 6MWT were not evaluated in detail before. Presently, it is unknown whether exercise-induced oxygen desaturation (EID) or heart rate response (ΔHR) during 6MWD associate with disease severity, functional or hemodynamic outcome in operable CTEPH. Nevertheless, patients with CTEPH frequently display significant EID with inadequate increase in heart rate (HR) during exercise [10]. Previously, EID has been related to reduced exercise performance and increased mortality in patients with chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis [11, 12], whereas ΔHR in pulmonary arterial hypertension (PAH) was analyzed in the context of baseline exercise capacity and functional improvements under targeted therapy [13]. Furthermore, chronotropic incompetence derived from heart rate reserve (HRR) was identified as an important and independent predictor of mortality in population based studies [14]. Moreover, parameters such as peak oxygen uptake (VO_2), peak systolic and diastolic blood pressure derived from cardio pulmonary exercise testing (CPET) are better correlated with functional class and prognosis than resting hemodynamic parameters in PAH [15]. So far, the significance of ΔHR and EID during 6MWD in comparison to CPET is remaining unknown in CTEPH.

We hypothesized that EID during 6MWD in CTEPH might be

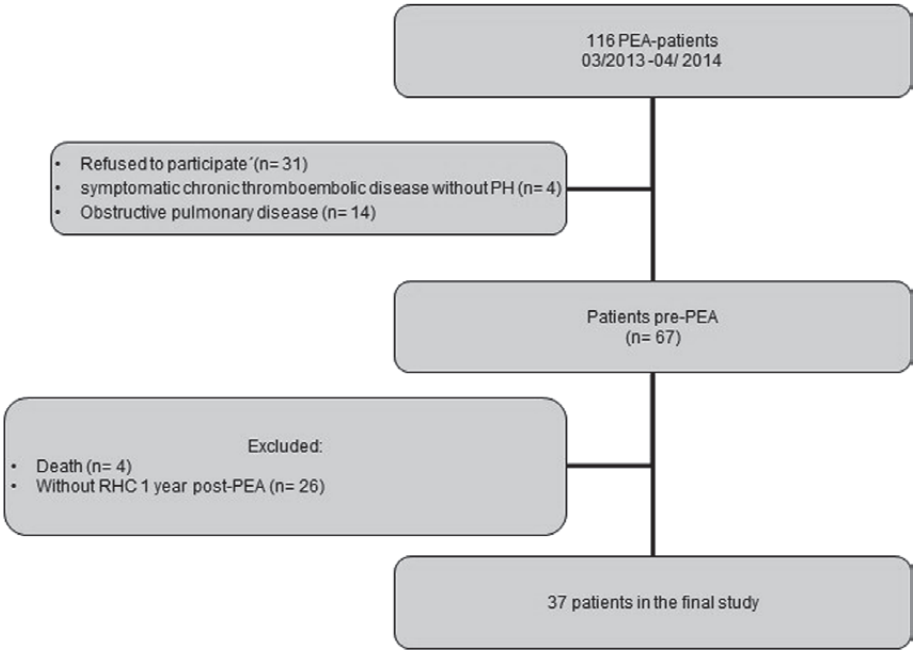

Fig. 1 Flow chart of patient selection. RHC: right heart catheterization, PEA: pulmonary endarterectomy, PH: pulmonary hypertension

of prognostic relevance and related to the extent of dyspnea. Moreover, we speculated that the ΔHR derived from the 6MWT reflects the inappropriate response of the RV with insufficient increase of the cardiac output (CO) to exercise, as it was shown for CPET [16]. Therefore, our aim was to prospectively investigate ΔHR and EID during 6MWT in patients with operable CTEPH and their associations with clinical symptoms and hemodynamic outcome 1 year post-PEA. In addition, we aim to compare ΔHR and EID assessed during 6MWT with CPET prior PEA in regard of their predictive significance.

Methods

Patients

All CTEPH patients undergoing PEA between March 2013 and April 2014 at the Department of Thoracic surgery, Kerckhoff-Clinic, Bad Nauheim, Germany were prospectively screened. After exclusion, 67 patients entered the study pre-PEA, while only patients with complete baseline and 1 year post-PEA hemodynamic data were analyzed (n = 37) (Fig. 1). Baseline and follow-up right heart catheter (RHC) were not mandatorily performed in-house, as the Kerckhoff-Clinic is a national referral center. Patients with symptomatic chronic thromboembolic disease (mean pulmonary artery pressure <25 mmHg at baseline [17]), obstructive pulmonary disease (forced expiratory volume in 1 s/vital capacity (FEV1/VC) ≤70 %) were excluded.

CTEPH was diagnosed according to current guidelines [18] and operability was assessed by a multidisciplinary board including pulmonary physicians, PEA surgeons and pulmonary radiologists. All patients received oral anticoagulants for at least 3 months and underwent PEA according to the protocol of the Kerckhoff-Clinic [19]. Residual PH 1 year post-PEA were defined by mPAP >25 mmHg and PVR >240 dyn*s/cm^5 at rest [20] while CTEPH type was classified by the surgical specimen as described previously [21].

All included patients gave written, informed consent, and the study was approved by the by the ethics committee of the Faculty of Medicine at the University of Giessen (Approval No. 67/14).

The following definitions were used: ΔHR = (peak HR – resting HR) [22], HRR = (peak HR – rest HR)/(220 – age – rest HR) x 100 [23] and EID = oxygen pulse saturation (SpO_2) ≤88 % [12, 24].

6-minute walk test

All patients performed 6MWT at the Kerckhoff-Clinic according to current guidelines [25]. Patients were instructed to walk at their own pace while standard phrases were communicated [25]. HR and oxygen pulse saturation (SpO_2) using pulse oximetry (Oximax™, N-65™, Covidien AG, USA) were measured at baseline and every minute until minute 6. In addition, patients were asked to quantify their sensation of dyspnea with the BORG scale [26]. As described previously, the respiratory therapist checked that the pulse oximeter had an acceptable signal before beginning all tests and carefully instructed the patient [12]. Patients already receiving supplemental oxygen at rest performed 6MWT with their current oxygen dosage. 6MWD was defined as the maximal achieved walk distance in m at room air or oxygen-supplemented.

Cardio-pulmonary exercise testing

Prior PEA patients performed a symptom-limited incremental CPET using a ramp protocol with an incremental rate of 5 to 15 W/min judged by the operator (Masterscreen CPX®, Carefusion®), according to current recommendations [27]. Patients receiving supplemental oxygen and exhibited a resting SpO_2 less than 88 % were excluded. Patients were asked to exercise up to their individual limit, while exercise was terminated due to exercise-limiting symptoms by the patient. Dead space ventilation (V_D/V_T) was calculated using the Bohr-formula, while absolute dead space (V_D) was assessed in milliliters [28].

Baseline parameters

Hemodynamic, laboratory, echocardiography data were collected before and after PEA in all included patients. Right heart echocardiography assessed pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) according to current recommendations [29].

Table 1 Baseline characteristics

	Baseline	One year post-PEA	*p*-value
Patients, *n*	37		
Male/female	20/17		
Age (y)	61 ± 12		
BMI (kg/m^2)	27.9 ± 5.8		
WHO functional class, (%)		b	0.7
I	none	29.6	
II	27	48.1	
III	62.2	22.2	
IV	10.8	None	
6MWT			
6MWD (m)	404.7 ± 148.4	453.4 ± 126.8	0.1
Rest SpO_2 (%)	93.9 ± 2.7	95.6 ± 2.9	0.043
Peak SpO2 (%)	88.8 ± 5.6	92.2 ± 4.5	0.003
Δ SpO2 (%)	−5.1 ± 4.4	−3.5 ± 4.1	0.15
Rest HR (beats[b]min-1)	83.8 ± 14.4	83.5 ± 13.9	0.98
Peak HR (beats[b]min-1)	117.1 ± 18.8	107.8 ± 17.1	0.041
Δ HR (beats[b]min-1)	32.6 ± 14.7	24.3 ± 12.9	0.038
HRR (%)	45.1 ± 20.6	33.4 ± 16.7	0.022
Δ Borg	4.4 ± 2.2	3.1 ± 2.4	0.006
Supplemental Oxygen (*n*, %)	9 (24.3)	3 (8.1)[b]	0.33
Lung function			
FEV1 (% pred.)	88.7 ± 13.8	88.2 ± 12.5	0.76
FEV1/FVC (% pred.)	96 ± 10.3	90.6 ± 12.1	0.05
TLC (% pred.)	99 ± 13.5	104.8 ± 16.8	0.11
VC (% pred.)	91.6 ± 13.7	94 ± 12.7	0.34
RHC			
mPAP (mm Hg)	43.2 ± 8.7	28.9 ± 10.1	0.001
RAP (mm Hg)	5.9 ± 4.1	7.2 ± 4.3	0.15
PVR (dyne[b]s/cm^5)	605.5 ± 228.7	328.1 ± 241.4	0.001
CI (l/min/m^2)	2.4 ± 0.5	2.7 ± 1.3	0.048
PAWP (mm Hg)	9.5 ± 4.6	10.6 ± 4.5	0.19
Echocardiography			
TAPSE (mm)	17.2 ± 4.3	17.5 ± 3.2	0.62
PASP (mm Hg)	69.8 ± 25.1	56.8 ± 23.7	0.041
CPET[c]			
Peak VO_2 (ml/min/kg)	12.3 ± 3.4	14.2 ± 4.2	0.33
Rest V_D/V_T	35.2 ± 7.6	32 ± 5.8	0.77
Peak V_D/V_T	39.5 ± 8.7	35 ± 11.9	0.6
Rest V_D, L	0.35 ± 0.17	0.29 ± 0.11	0.39
Peak V_D, L	0.65 ± 0.25	0.72 ± 0.21	0.55
Rest SpO_2 (%)	94.2 ± 1.7	95.1 ± 1.4	0.10
Peak SpO2 (%)	89.3 ± 1.4	90.7 ± 4.8	0.86
Δ SpO2 (%)	−4.9 ± 5.8	−4.4 ± 4.3	0.69
Rest HR (beats[b]min-1)	72.8 ± 12.2	81.2 ± 11.2	0.15

Statistical analysis

Data are presented as mean ± standard deviation (SD) for normally distributed parameters or median [interquartile range (IQR)]. As appropriate the 2-tailed T-test, paired T-test, Wilcoxon Signed Rank test, Mann-Whitney-U-test or Pearson Chi-Square test was used to test for differences between groups. Linear regression analysis was performed between follow-up hemodynamic parameters and baseline 6MWT and

Table 1 Baseline characteristics *(Continued)*

Peak HR (beats[b]min-1)	120.7 ± 21.3	122.9 ± 19.6	0.25
Δ HR (beats[b]min-1)	47.9 ± 19.4	41.7 ± 16.3	0.72
HRR (%)	54.7 ± 21.1	53.7 ± 20.2	0.92
Co-morbidities, *n* (%)			
Hypertension	24 (64.9)	Unchanged	
Coronary heart disease	4 (10.8)	Unchanged	
Renal insuffiency	4 (10.8)	Unchanged	
Jamieson-Type, %			
I	31		
II	31		
III	38		
Laboratory			
NT-proBNP (pg/ml)	488.2 [1004]	245.0 [422][a]	0.006

Values represent mean ± SD or median [IQR]. pred.: predicted, [a] = Wilcoxon Signed Rank test, [b] = Pearson Chi-Square test, [c]*n* = 34. *CI* cardiac index, *mPAP* mean pulmonary arterial pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *PAWP* pulmonary arterial wedge pressure, *TAPSE* tricuspid annular plane systolic excursion, *PASP* pulmonary artery systolic pressure, *6MWD* six-minute walking distance, VO_2 oxygen uptake, *WHO* World Health Organization, *NT-proBNP* N-terminal fragment of pro-brain natriuretic peptide, V_D absolute dead space, V_D/V_T dead space ventilation, *HR* heart rate, SpO_2 oxygen pulse saturation, *RHC* right heart catheter, *CPET* cardio-pulmonary exercise testing, *HRR* heart rate reserve, *VC* vital capacity, *FRC* functional residual capacity, *TLC* total lung capacity, *FEV1* forced expiratory volume in 1 s

CPET characteristics. In addition, all baseline parameters were analyzed univariate in a logistic regression model with residual PH as dependent variable. Then all parameters of the univariate analysis with a p-value < 0.15, were entered into a backward stepwise multivariate logistic regression model to predict residual PH 1 year post-PEA. P-value of < 0.10 was considered statistically significant in the multivariate analyses. Statistical analysis was performed using SPSS, version 21.0 (IBM, Armonk, NY).

Results

Baseline

Thirty-seven CTEPH patients with a mean age of 61 ± 12 years and a body mass index of 27.9 ± 5.8 kg/m^2 mostly in WHO functional class III were included. Patients showed impaired pulmonary hemodynamics with a precapillary pattern, substantially reduced CI and elevated PVR before PEA. Concomitant right heart echo-cardiography showed an elevated PASP and a reduced TAPSE. Lung function testing revealed no significant obstructive or restrictive ventilatory abnormalities. During 6MWT peak SpO_2 decreased to 88.8 ± 5.6 % with a Δ SpO_2 of -5.1 ± 4.4 %, HR increased to a mean peak of 117.1 ± 18.8 beats*min^{-1} while ΔHR was 32.6 ± 14.7 beats*min^{-1} and HRR was 45.1 ± 20.6 %. Sensation of dyspnea as assessed by the BORG score showed a substantial increase (Δ BORG 4.4 ± 2.2). In total, 9 patients underwent the 6MWT with supplemental oxygen (Table 1). In total, 34 patients performed CPET displaying an impaired exercise capacity while V_D and V_D/V_T exhibited a significant increase during exercise. During CPET peak SpO_2 decreased to 89.3 ± 1.4 % with a ΔSpO_2 of - 4.9 ± 5.8 %, HR increased to a mean peak of 120.7 ± 21.3 beats*min^{-1} while ΔHR was 47.9 ± 19.4 beats*min^{-1} and HRR was 54.7 ± 22.1 %.

One year post-PEA

Hemodynamic and functional parameters significantly improved 1 year post-PEA as compared to baseline. Patients presented mostly in WHO functional class I and II, resting and peak SpO_2 were significantly higher during 6MWT and peak HR, ΔHR and HRR and NT-proBNP were significantly lower 1 year post-PEA. A trend towards decrease was observed in resting V_D/V_T and V_D during CPET (Table 1). In total, 21 patients presented with residual PH displaying significantly elevated mPAP, PVR, NT-proBNP and reduced CI in comparison with non-residual PH. In addition, patients with residual PH presented to a higher degree in WHO functional class III and showed, in comparison with non-residual PH, a significant lower rest and peak SpO_2 during 6MWT. HRR was significantly higher in patients with residual PH while ΔHR showed a trend to higher values. Dyspnea as measured by BORG score was significantly increased in patients with residual PH, while the administration of supplemental oxygen did not differ between groups (Table 2). In comparison with non-residual PH no significant differences of peak VO_2, SpO_2, HR or HHR derived from CPET were shown.

Clinical relevance of exercise-induced oxygen desaturation

Baseline characteristics were analyzed according to the presence of EID during 6MWT, while pulmonary hemodynamics, exercise capacity, V_D/V_T and Jamieson-Type showed no significant differences in comparison. Interestingly, 12 out of 37 patients exhibited EID with a ΔSpO_2 of 10 ± 1.1 % (Table 3), while a rapid continuous desaturation was evident already starting at minute one of the 6MWT (Fig. 2a). BORG score at minute 3 was significantly higher in patients with EID, albeit ΔBORG and peak BORG score showed a trend to higher values in EID (Fig. 2b).

There were no significant associations between rest SpO_2, peak SpO_2 or ΔSpO_2 with hemodynamic or functional parameters 1 year post-PEA during 6MWT and CPET (data not shown).

Univariate logistic regression analysis revealed that baseline peak SpO_2 or Δ SpO_2 during 6MWT were not associated with the presence of residual PH. Univariate analysis related rest SpO_2 during 6MWT to residual PH with a hazard ratio of 0.8 (95 % Confidence interval for hazard ratio 0.6–1.06, p = 0.11). However, additional stepwise backward multivariate analysis showed that rest SpO_2 derived from 6MWT was not independently associated with the hemodynamic outcome 1 year post-PEA. In addition, rest SpO_2, peak SpO_2 or ΔSpO_2 derived from CPET failed as prognostic markers using univariate analysis (Table 4).

Table 2 Parameters 1 year post-PEA according to non-residual and residual PH

	Non-residual PH	Residual PH	*p*-value
Patients, *n* (%)	16 (43.2)	21 (56.8)	
WHO functional class, (%)		a	0.002
I	46.2	None	
II	53.8	57.1	
III	None	42.9	
IV	None	None	
6MWT			
6MWD (m)	487.6 ± 72.1	432.4 ± 148.9	0.26
Rest SpO_2 (%)	97 ± 1.9	94.8 ± 3.1	0.05
Peak SpO2 (%)	94.3 ± 4.4	90.8 ± 4.1	0.05
Δ SpO2 (%)	−2.7 ± 3.8	−3.9 ± 4.4	0.47
Rest HR (beats[a]min-1)	83.9 ± 15.1	83.2 ± 13.9	0.9
Peak HR (beats[a]min-1)	101.6 ± 15.2	111.5 ± 17.6	0.2
Δ HR (beats[a]min-1)	17.8 ± 6.3	28.3 ± 14.4	0.06
HRR (%)	24.3 ± 11.5	28.3 ± 14.4	0.05
Δ Borg	1.7 ± 1.9	3.9 ± 2.4	0.02
Supplemental Oxygen (*n*, %)	1 (6.3)	2 (9.5)	-
Lung function			
FEV1 (% pred.)	93.9 ± 12.8	83.9 ± 10.6	0.02
FEV1/FVC (% pred.)	95.8 ± 13.9	86.7 ± 9.2	0.03
TLC (% pred.)	104.2 ± 15.2	105.2 ± 18.3	0.87
VC (% pred.)	96.8 ± 14.0	92.1 ± 11.6	0.3
RHC			
mPAP (mm Hg)	19.7 ± 3.2	36 ± 7.5	0.001
RAP (mm Hg)	5.5 ± 2.4	8.7 ± 5.1	0.04
PVR (dyne[a]s/cm[5])	218.3 ± 280.9	415.9 ± 163.7	0.012
CI (l/min/m^2)	2.9 ± 0.4	2.6 ± 0.6	0.09
PAWP (mm Hg)	8.9 ± 3.8	12.2 ± 4.7	0.037
Echocardiography			
TAPSE (mm)	18.3 ± 2.7	16.7 ± 3.6	0.2
PASP (mm Hg)	50.6 ± 29.2	59.5 ± 21.9	0.5
CPET[b]			
Peak VO_2 (ml/min/kg)	15.2 ± 4.5	13.3 ± 3.9	0.36
Rest V_D/V_T	30.3 ± 5.1	35.3 ± 6.4	0.35
Peak V_D/V_T	27.7 ± 6.1	41.2 ± 12.1	0.13
Rest V_D, L	0.22 ± 0.07	0.37 ± 0.09	0.09
Peak V_D, L	0.63 ± 0.1	0.78 ± 0.26	0.39
Rest SpO_2 (%)	95.1 ± 1.3	93.7 ± 1.8	0.10
Peak SpO2 (%)	89.1 ± 7.3	89.6 ± 4.6	0.86
Δ SpO2 (%)	−5.2 ± 5.4	−3.6 ± 3.3	0.69
Rest HR (beats[a]min-1)	76.1 ± 12.4	69.9 ± 11.7	0.15
Peak HR (beats[a]min-1)	125.3 ± 22.4	116.6 ± 19.9	0.25
Δ HR (beats[a]min-1)	49.2 ± 19.3	46.7 ± 19.9	0.72
HRR (%)	55.1 ± 21.1	54.3 ± 21.8	0.92
Jamieson-Type, (%)		a	0.15
I	14.2	46.7	
II	42.9	20	
III	42.9	33.3	
Laboratory			
NT-proBNP (pg/ml)	175.0 [56–259]	389.0 [95–703]	0.18

Values represent mean ± SD or median [IQR]. [a] = Pearson Chi-Square test, [b] *n* = 34. For abbreviations see Table 1

Clinical relevance of heart rate response

During 6MWT an initial steep and then flattened HR response was observed (Fig. 2a). Baseline ΔHR during 6MWT was significantly associated with PVR 1 year post-PEA (r = 0.43, p = 0.01) (Fig. 3a). However, using linear regression analysis ΔHR showed no significant associations with mPAP (Fig. 3b) or other pulmonary hemodynamic parameters 1 year post-PEA (data not shown). There were no significant associations of rest HR, peak HR or HRR with hemodynamic parameters 1 year post-PEA (data not shown). Interestingly, HR parameters derived from CPET were not significantly associated with hemodynamic parameters 1 year post-PEA (data not shown).

Univariate logistic regression analysis revealed that baseline ΔHR and HRR during 6MWT were significantly associated with the presence of residual PH. The step-wise backward multivariate model associated HRR and Jamieson-Type with the hemodynamic outcome 1 year post-PEA. Intriguingly, no such association were found for the Δ HR or HRR during CPET (Table 4).

Discussion

In the current study we could show for the first time that additional characteristics derived from 6MWT in operable CTEPH were of clinical relevance. The novel findings of the present study include 1) that EID during 6MWT is commonly observed in operable CTEPH pre-PEA, and 2) baseline HRR, but not EID, during 6MWT is associated with the hemodynamic outcome 1 year post-PEA. To the best of our knowledge, this is the first study that evaluated specific characteristics from 6MWT in a selected cohort of operable CTEPH patients and demonstrated their impact on the hemodynamic outcome post-PEA.

CTEPH patients with reduced exercise capacity, mostly in WHO functional class III and severely impaired pulmonary hemodynamics prior PEA were prospectively included. Our cohort demonstrated the typical precapillary PH pattern with significant impairment of RV function resulting in a reduced CI, elevated PVR and mPAP [7, 30–33]. Hemodynamic parameters and exercise capacity substantially improved 1 year post-PEA, albeit 21 patients (56.8 %) presented with a residual PH. In total, a significant improvement of the functional outcome 1 year post-PEA was observed as described previously [3, 4]. However, the high rate of residual PH in our selected cohort underlined that the individual outcome post-PEA differed while rates of residual PH up to 35 % were previously reported [20, 32, 34].

Our results describe for the first time that after exclusion of obstructive pulmonary diseases, almost ~32 % of operable CTEPH exhibited a substantial EID during 6MWT prior to PEA. Further, these patients reported an enhanced, albeit not significant, increased sensation of dyspnea during 6MWT. Our

Table 3 Parameters at baseline according to exercise-induced oxygen desaturation during 6MWT

	Baseline		
	EID	Non-EID	*p*-value
Patients, *n* (%)	12 (32.4)	25 (67.6)	
WHO functional class, (%)	a		0.09
II	33.3	24	
III	41.7	72	
IV	25	4	
6MWT			
6MWD (m)	448.9 ± 206.8	383.6 ± 109.5	0.22
Rest SpO_2 (%)	92.0 ± 2.2	94.8 ± 2.1	0.002
Peak SpO_2 (%)	81.9 ± 4.4	92.1 ± 2.3	0.001
Δ SpO2 (%)	10.0 ± 1.1	2.7 ± 0.4	0.02
Rest HR (beats[a]min-1)	83.5 ± 16.4	84 ± 13.7	0.9
Peak HR (beats[a]min-1)	120.6 ± 20.7	115.5 ± 18.1	0.45
Δ HR (beats[a]min-1)	30.5 ± 5.1	30.4 ± 2.4	0.82
HRR (%)	49.5 ± 8.1	42.5 ± 4	0.53
Δ Borg	4.7 ± 0.7	4.3 ± 0.5	0.52
Supplemental Oxygen (*n*, %)	4 (33.3)	5 (20) [a]	0.38
Lung function			
FEV1 (% pred.)	83.6 ± 11.9	90.9 ± 14.1	0.15
FEV1/FVC (% pred.)	98.6 ± 10.2	94.8 ± 10.3	0.31
TLC (% pred.)	94.8 ± 16.3	100.8 ± 12.1	0.24
VC (% pred.)	85.8 ± 10.3	94.1 ± 14.4	0.1
RHC			
mPAP (mm Hg)	43.8 ± 8.2	42.9 ± 9.0	0.77
RAP (mm Hg)	4.1 ± 2.7	6.6 ± 4.4	0.8
PVR (dyne[a]s/cm^5)	640.1 ± 231.0	587.4 ± 230.5	0.53
CI (l/min/m^2)	2.5 ± 0.6	2.4 ± 0.5	0.7
PAWP (mm Hg)	9.3 ± 2.8	9.7 ± 5.4	0.8
Echocardiography			
TAPSE (mm)	16.6 ± 4.3	17.4 ± 4.3	0.63
PASP (mm Hg)	77.2 ± 30.7	66.2 ± 21.7	0.24
CPET[c]			
Peak VO_2 (ml/min/kg)	13.1 ± 1.3	12.1 ± 0.6	0.65
Rest V_D/V_T	33.0 ± 7.3	36.0 ± 8	0.48
Peak V_D/V_T	39.0 ± 12.0	40.0 ± 7.3	0.78
Rest V_D, L	0.41 ± 0.22	0.34 ± 0.14	0.4
Peak V_D, L	0.67 ± 0.33	0.65 ± 0.23	0.9
Jamieson-Type, (%)	[a]		0.72
I	25	32	
II	50	26	
III	25	42	
Laboratory			
NT-proBNP (pg/ml)	414.0 [1260.2]	836.7 [1521][b]	0.71

Values represent mean ± SD or median [IQR]. [a] = Pearson Chi-Square test, [b] = Mann-Whitney *U* Test, [c] *n* = 34.; For abbreviations see Table 1

data support the high prevalence of EID during 6MWT in CTEPH as described previously in a heterogeneous group of PH patients [35]. Furthermore, patients with residual PH showed significantly higher BORG scores and lower peak SpO_2-levels 1 year post-PEA. The cause of EID and sensation of dyspnea is multifactorial in CTEPH, including gas exchange abnormalities with exertional hypoxaemia due to increased V_D/V_T and V/Q mismatch, increased chemosensitivity as a stimulus of exercise hyperventilation and insufficient enhancement of CO due to RV dysfunction [16, 28, 36]. One can speculate that ventilatory inefficiency with an

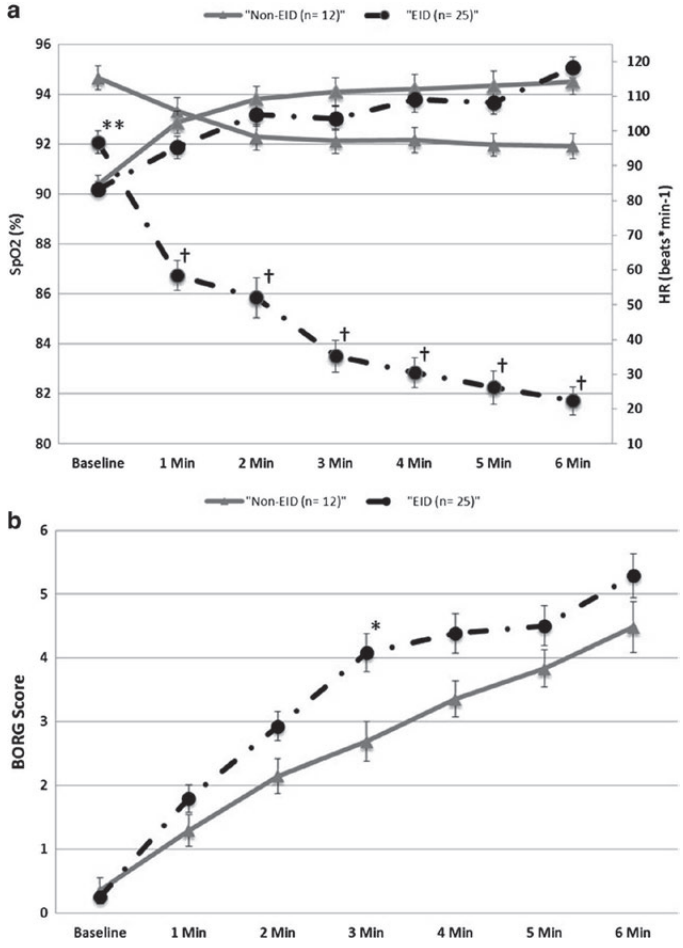

Fig. 2 a Heart rate (HR) and SpO_2 during 6MWT according to exercise-induced oxygen desaturation (EID). Data are presented as mean ± standard error of means. **p = 0.002, †p < 0.001 versus non-EID. (black line = EID; grey line = non-EID; ▲= SpO2; ●= HR). b BORG score during 6MWT according to exercise-induced oxygen desaturation (EID). Data are presented as mean ± standard error of means. *p = 0.02 versus non-EID. (black line = EID; grey line = non-EID).

increased V_D/V_T during exercise due to increased V/Q mismatch results in EID, which however couldn't be extrapolated by our data as significant correlations between EID and V_D/V_T were lacking. The absence of significant associations between EID and V_D/V_T might be related to the relatively small increase in V_D/V_T during exercise observed in our cohort, as previously peak V_D/V_T up to 50 were reported [36]. In addition, baseline resting V_D/V_T was lower than previously reported indicating that pulmonary perfusion was, overall, slightly better in our cohort [30]. Surprisingly, baseline EID was neither associated with hemodynamic parameters 1 year post-PEA nor with the presence of residual PH. Therefore our data emphasized that baseline EID failed as a surrogate marker to predict small-vessel arteriopathy, non-removable material or impaired RV reverse remodeling post-PEA which were identified as major causes of residual PH [20]. Nevertheless, EID was described as a powerful prognostic marker of overall survival in PAH, pulmonary fibrosis or COPD previously [11, 12, 37]. In addition, SpO_2-levels or EID derived from CPET failed as relevant prognostic factors in our multivariate model.

Interestingly, our data indicated for the first time that ΔHR prior PEA was related to PVR 1 year post-PEA in operable CTEPH patients. In addition, HRR during 6MWT was associated with the presence of residual PH. Even though the association of an enhanced baseline HRR with the presence of residual PH might look paradoxical at first sight, its' pathophysiologic meaning in CTEPH is explicable. In general, exercising PAH patients exhibit a limited increase in stroke volume due to systolic and diastolic impairment, increased RV afterload and impaired ventriculoarterial coupling [38], while the diastolic pressure–volume relationship determines filling and CO [39]. In CTEPH the chronic obstructions in the pulmonary circulation lead to an increase in RV afterload and eventually to an impairment in RV function [40] such that the increase in CO is compensatory achieved through increases in HR. The disproportionate, albeit enhanced ΔHR at baseline inside a cohort with an overall impaired HRR, may reflect the severity of the disease. One can speculate that an enhanced HRR at baseline was mainly mirroring the inadequate response of the RV to adapt to higher load during exercise with a further impaired overall RV function and advanced RV remodeling. Therefore, HRR was associated with the hemodynamic outcome 1 year post-PEA in patients that were less prone to RV reverse remodeling. PEA immediately reverses the increased RV afterload in CTEPH patients, while the magnitude of reverse RV remodeling after PEA has been shown to correlate with changes in hemodynamics, restoration of ventriculoarterial coupling or reduction of RV systolic wall stress [33, 40–43]. However, it has been proposed that RV remodeling is only partly reversible because of diffuse myocardial fibrosis and differed individually [40]. As previously reported, regression of concentric hypertrophy and restoration of full right and left systolic function assessed by means of Cardiac Magnetic Resonance Imaging (cMRI) require a longer period of time of up to several years [43].

Interestingly, the ΔHR and the HRR during CPET failed as prognostic marker in our cohort, highlighting the value of 6MWT in CTEPH. Being a self-paced submaximal effort test, it results in an aerobic steady-state, as opposed to CPET which is a maximal effort test. Thus differences in HRR with increased HR in more severely ill patients, as discussed above, may be observed in this test, but not at maximal effort. We therefore speculate that ΔHR and the HRR assessed during 6MWT are superior in reflecting disease severity in a selected cohort of operable CTEPH patients. As shown previously, differences of the cardiac, ventilatory and metabolic response during 6MWT in comparison with CPET in patients with PAH are occurring [15, 44]. CPET is associated with higher a minute ventilation, respiratory exchange ratio and maximal HR in comparison with 6MWT [44]. Therefore, Deboeck and coworkers concluded that 6MWT is a more realistic test for the determination of the exercise capacity than CPET and is more reflective of therapeutic interventions [44].

Limitations of the study are the small sample size and highly selected patient sample that excluded patients with obstructive pulmonary diseases. As we are a national referral center, the 1 year follow-up visit was not mandatorily performed in our center and accounts for the dropout rate of 26 patients. Furthermore, 31 patients refused participation at the time of screening due to various reasons. Taking together this drop out rate produces potential bias. In addition, since the rate of residual PH was higher than reported in the literature, a selection bias is possible. To confirm and elucidate the pathophysiological findings of our study, larger prospective studies including post-procedural cMRI and angiographies for quantification of reverse remodeling and residual perfusion impairments will be necessary.

Table 4 Baseline parameters as predictors of residual PH 1 year post PEA

	Univariate model		Multivariate model*	
	Hazard ratio (95 % confidence interval)	*p*-value	Hazard ratio (95 % confidence interval)	*p*-value
6MWT				
6MWD (m)	1.01 [0.99–1.01]	0.44	-	-
Rest SpO_2 (%)	1.25 [0.94–1.67]	0.11	-	-
Peak SpO2 (%)	0.96 [0.85–1.08]	0.46	-	-
Δ SpO2 (%)	0.99 [0.86–1.16]	0.96	-	-
Rest HR (beats*min-1)	0.99 [0.94–1.03]	0.6	-	-
Peak HR (beats*min-1)	1.03 [0.99–1.06]	0.19	-	-
Δ HR (beats*min-1)	1.10 [1.03–1.2]	0.009	-	-
HRR (%)	1.06 [1.02–1.1]	0.01	1.06 [0.99–1.14]	0.08
CPET				
Rest SpO_2 (%)	1.81 [0.86–3.76]	0.12	-	-
Peak SpO2 (%)	1.02 [0.86–1.20]	0.84	-	-
Δ SpO2 (%)	1.05 [0.86–1.27]	0.66	-	-
Rest HR (beats*min-1)	0.96 [0.90–1.02]	0.16	-	-
Peak HR (beats*min-1)	0.98 [0.95–1.01]	0.25	-	-
Δ HR (beats*min-1)	0.99 [0.96–1.03]	0.71	-	-
HRR (%)	1.00 [0.97–1.03]	0.91	-	-
Peak VO_2 (ml/min/kg)	0.95 [0.78–1.17]	0.63	-	-
RHC				
mPAP (mm Hg)	1.07 [0.98–1.16]	0.13	-	-
RAP (mm Hg)	1.01 [0.83–1.2]	0.96	-	-
PVR (dyne*s/cm^5)	1.01 [0.99–1.01]	0.19	-	-
CI (l/min/m^2)	1.10 [0.3–4.01]	0.89	-	-
PAWP (mm Hg)	1.03 [0.89–1.2]	0.67	-	-
Echocardiography				
TAPSE (mm)	0.90 [0.77–1.06]	0.2	-	-
PASP (mm Hg)	1.03 [0.99–1.07]	0.06	-	-
Other				
Nt-pro BNP (pg/ml)	1.00 [0.99–1.01]	0.97	-	-
WHO functional class	-	0.39	-	-
Jamieson-Type				
• I	Reference		Reference	
• II	4.2 [0.6–30.1]	0.15	8.9 [0.7–116.4]	0.096
• III	1.67 [0.28–3.57]	0.58	5.02 [3.23–100]	0.25

For abbreviations see Table 1. *: backward stepwise logistic regression including variables with a *p*-value <0.15 in the univariate model

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Conclusions

This is the first prospective study to describe an association of additional characteristics derived from 6MWT with the hemodynamic outcome 1 year post-PEA in a selected cohort of operable CTEPH patients. Our preliminary results indicate that ΔHR and HRR assessed during 6MWT are of clinical value in patients with operable CTEPH, and HRR during 6MWT may serve as a predictor of residual PH. EID was commonly observed in operable CTEPH, albeit failed as a significant prognostic factor.

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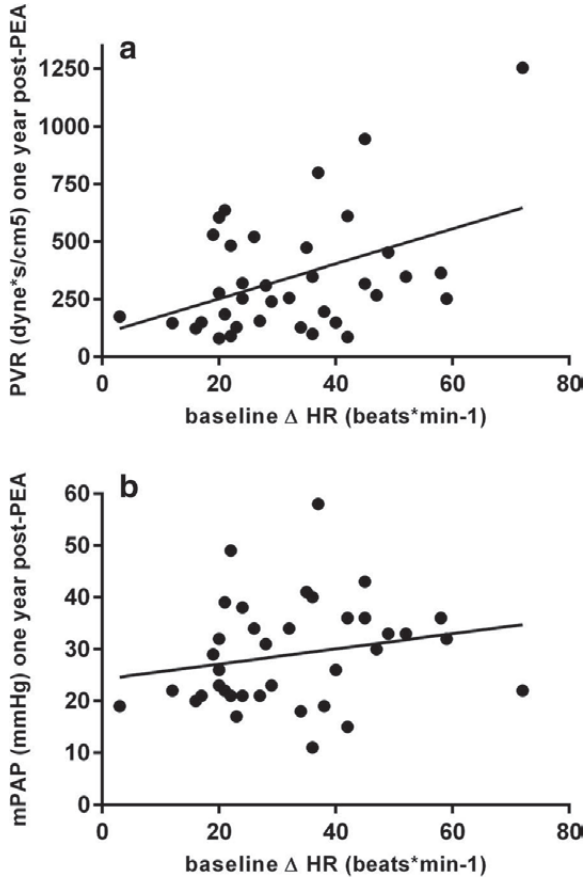

Fig. 3 Associations between baseline Δ HR and PVR ($r = 0.43$, $p = 0.01$) (**a**) and mPAP ($r = 0.21$, $p = 0.23$) (**b**) 1 year post-PEA. For abbreviations see Table 1

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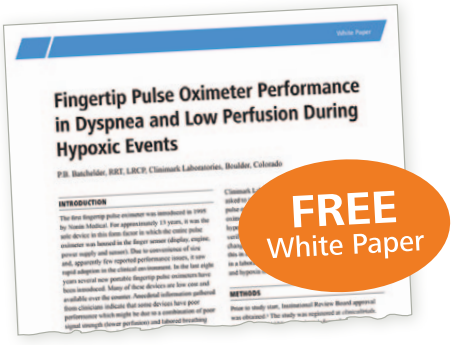

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