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Company Shows Off High IQ

nSpire Health, a leading provider of pulmonary diagnostic systems, has announced the introduction of Iris IQ, a respiratory department analytics platform. The new framework of integrated technologies eliminates incongruences between pulmonary function test results, other respiratory diagnostic exams and/or symptomology adversely affecting clinical decisions in as many as 50% of the millions of cases where pulmonary functions testing is indicated each year. Iris IQ unlocks the underlying power of Pulmonary Function Testing while helping to eliminate an estimated three billion dollars in direct and indirect healthcare costs associated with poor quality testing or lack of testing and resulting misdiagnosis and treatment of respiratory diseases. Scalable in costs for single device users to complete healthcare enterprises with several devices, the new department management platform leverages nSpire Health's patent pending PFT calibration reference standards and Iris' unique network architecture to ensure providers consistently deliver valid results for all PFT systems' clinical indications using any manufacturer's PFT device. The modular solution provides interpreting and treating physicians, respiratory therapists, and department administrators new levels of trusted insights into the complete pulmonary function testing process from pre-test staging through interpretation and result delivery including verification of instrument accuracy, precision and testing practices. "We believe the lack of practical quality management tools has been concealing the true physiologic detection capabilities of pulmonary function testing," said Michael Sims, President and CEO of nSpire Health. "Offering a comprehensive quality management solution compatible with any vendor's PFT devices raises the quality of care for all patients in all pulmonary labs." For the first time in the history of pulmonary function testing and in less than a few minutes per day end users can irrefutably validate a PFT devices output performance to a manufacturers stated specification limits (or to peer reviewed standardization criteria) for each lung function measurement output as required by the FDA and ISO and more importantly required for efficient clinical decision-making by treating physicians. Outdated simulators and biologic testing controls cost too much to use, take too long to perform, and have enormous limitations in detecting a PFT devices true accuracy and precision limits. Beyond clinical results, Iris IQ dashboards and custom reporting capabilities provide users intuitions into clinical operations, asset management and device utilization while supporting risk management and regulatory compliance. Based on real time quality assessments for every patient exam, an integrated learning management module securely provides specific corrective action training for technicians, department managers, and physicians using any browser or Iris Decision Workstation. **"Iris IQ provided us with a deeper understanding of our lung function testing quality and cost drivers while offering our team focused training on corrective action procedures for more effective and efficient patient care. We saw instant results across facilities."** said Rodney Folz, MD, PhD, Chief of Pulmonary, Critical Care, and Sleep Medicine at University Hospitals Cleveland Medical Center. According to Tad Scheiblich, Director of Product marketing, "nSpire Health is currently performing PFT Quality Webinars and free Department Quality Assessments."

FDA Approval for Device

Lonhala Magnair is the first nebulized long-acting muscarinic antagonist (LAMA) approved for the treatment of COPD in the US and the first use of the Magnair, which is based on the closed eFlow technology system, developed by PARI Pharma GmbH, to treat COPD. This technology is a virtually silent, portable, closed system nebulizer that is designed to deliver the drug in two to three minutes and allows people to breathe normally while using the device. "We are proud that the FDA has approved Lonhala Magnair as the first nebulized, long-acting muscarinic antagonist treatment option for people in the US living with COPD," said David Frawley, Executive Vice President and Chief Commercial Officer at Sunovion. **"The approval of Lonhala Magnair underscores our leadership in nebulization and the value we place on providing innovative treatment options for people living with COPD. Lonhala Magnair is an important addition to our portfolio of approved COPD therapies for people at various stages of COPD, providing the flexibility to choose handheld or nebulized products based on individual needs."** Despite the availability of several therapies, many people still struggle to control their COPD — a challenge that may be affected by the delivery method used to administer a medication, said Gary Ferguson, MD, Pulmonary Research Institute of Southeast Michigan, Farmington Hills, Michigan. "Lonhala Magnair offers an important new option that combines the efficacy of a proven medication for COPD with the attributes of a unique handheld nebulizer that allows a person to breathe normally while taking their medication. Approximately 15.7 million adults in the US report they have been diagnosed with COPD, a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or lung abnormalities usually caused by significant exposure to toxic particles or gases. The main risk factor for COPD is tobacco smoking, but other environmental exposures may contribute. The disease makes it hard for people to breathe and subsequently may limit their ability to perform some routine activities, including the proper inhalation of medication. This improper medication technique may impact treatment over time and may also result in an inadequate amount of the drug reaching the lungs, potentially worsening a person's COPD. For people with moderate-to-very-severe COPD, nebulized treatments offer an alternative to inhalers, allowing a person to breathe normally while taking their medicine. The approval is based on data from the clinical trials in the Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) program, which included GOLDEN-3 and GOLDEN-4, two Phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, efficacy and safety trials comparing LONHALA MAGNAIR with placebo in adults with moderate-to-very-severe COPD. At study endpoints, individuals treated with Lonhala Magnair demonstrated statistically significant and clinically important changes from baseline in trough forced expiratory volume in one second at Week 12 versus placebo. An additional study, GOLDEN-5, was a Phase 3, 48-week, randomized, open-label, active-controlled,

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parallel-group, multicenter safety trial designed to evaluate the long-term safety and tolerability of Lonhala Magnair in adults with moderate-to-very-severe COPD and included the active comparator Spiriva (tiotropium bromide) delivered by the HandiHaler device. Lonhala Magnair was generally well-tolerated in clinical studies, with the most common side effects being exacerbations and cough. The overall treatment emergent adverse events (TEAE) incidences were similar for glycopyrrolate and tiotropium groups over 48 weeks.

Hayek Medical Expands its Brand

Medical device company Hayek Medial is expanding its brand by starting up an Instagram account. The company, which bills itself as the 'world's home of Biphasic Cuirass Ventilation' can be found at the @hayekmedical Instagram account. The account features helpful information and photos and diagrams of its devices. You can also tag them with #HayekBCV on the social network.

Triple Therapy for COPD Cuts Exacerbations

Triple therapy reduces chronic obstructive pulmonary disease (COPD) exacerbations and improves lung function and quality of life more than dual therapy or monotherapy in patients with advanced COPD, according to a new review and meta-analysis. But triple therapy did not improve survival and was associated with an increased risk of pneumonia, Dr Weimin Yao of Guangdong Medical University in Zhanjiang, China, and colleagues found. **"Therefore, triple therapy should be limited to patients with more severe COPD symptoms that cannot be adequately managed by dual therapy,"** they conclude. Triple therapy with inhaled corticosteroids (ICS), long-acting beta-2 adrenoceptor agonists (LABA) and long-acting muscarinic receptor antagonists (LAMA) is recommended by the Global Initiative for Obstructive Lung Disease (GOLD) for GOLD group D patients who experience exacerbations after treatment with LABA and LAMA, the authors note. But previous meta-analyses have not shown clear evidence that triple therapy is more effective than dual therapy for preventing exacerbations, they add, and reviews to date have also not included studies of triple therapy with a fixed-dose-combination inhaler. The new meta-analysis includes 21 trials, six with fixed triple therapy and 15 with three treatments using three separate inhalers. Compared to LAMA monotherapy, triple therapy significantly reduced the risk of moderate or severe exacerbations (rate ratio, 0.71). Triple therapy also significantly cut exacerbation risk compared with LAMA and LABA (RR, 0.78) and ICS plus LABA (RR, 0.77). Triple therapy also was associated with improvements in trough forced expiratory volume (FEV1) and improvements in health-related quality of life. But significantly more pneumonia events occurred with triple therapy in some studies (RR, 1.53), and it was not associated with improved survival. In two trials that directly compared fixed triple therapy with separate triple therapy, there were no significant differences in any of the outcomes studied. "Considering that no survival benefit was associated with triple therapy, and increased risk of pneumonia was observed, our results might only apply to patients with symptomatic COPD, severe airflow limitation, and an exacerbation history, and any potential benefit could be lost if triple therapy is expanded to patients with mild COPD," the authors write. "Attempts should be made to identify patients with COPD phenotypes (eg, eosinophil levels, patient characteristics, and exacerbation history) most likely to respond to the triple therapy," they conclude.

Routine Spirometry Measure Useful for Monitoring Idiopathic Subglottic Stenosis

Peak expiratory flow (PEF) is a simple, efficient method for monitoring progression of idiopathic subglottic stenosis and predicting receipt of surgical intervention, researchers report. "We were surprised to find that the most simple measure of pulmonary function — peak expiratory flow — correlated with airway stenosis as closely as the more complex measures, EDI (expiratory disproportion index) and TPF (total peak flow)," said Dr James J Daniero of the University of Virginia, in Charlottesville. "This unanticipated finding provides great promise for patients to be able to self-monitor their condition by tracking biometric data obtained from a basic hand-held peak flow meter which can be recorded in a smart phone application," he said. Many patients with idiopathic subglottic stenosis (iSGS) can be treated successfully with endoscopic intervention, but more than 85% of these patients require repeated intervention within five years. EDI is highly sensitive and specific for diagnosing and monitoring iSGS, but its measurement is

complex. Dr Daniero's team evaluated the ability of PEF, relative to the validated measures of EDI and TPF, to differentiate the degree of luminal obstruction and predict the receipt of surgical intervention in 42 patients with iSGS. The mean PEFs and TPFs decreased progressively with increasing stenosis grade, while the mean EDIs increased with increasing stenosis grade. PEF had an accuracy of 85.5% (as measured by area under the curve) for predicting operative intervention in patients with iSGS. The optimal cutoff value of 4.4 L per second yielded 84.4% sensitivity and 82.0% specificity, the researchers report in JAMA Otolaryngology-Head & Neck Surgery, online November 1. By comparison, EDI had an accuracy of 85.3%, and its optimal cutoff value of 54.0 yielded 80.6% sensitivity and 80.4% specificity. TPF had an accuracy of 83.6%; with an optimal cutoff value of 7.4 L per second, it yielded 86.4% sensitivity and 78.0% specificity. "EDI is still an important measure in the diagnosis of laryngotracheal stenosis," Dr Daniero said. "EDI maintains the ability to discriminate between asthma, COPD, and other pulmonary diseases. The PEF is less specific and should be used after a diagnosis is already established to follow the longitudinal effect of progressive stenosis. It appears the TPF provides no additional benefit over PEF in this population."

Dräger Continues Its Commitment to Education

In recognition of Respiratory Care Week and the vital role that respiratory therapists (RT) play in positive patient outcomes, Dräger donated 33 Babylog VN500 Ventilators to RT schools throughout the US. This marks the fourth year of Dräger's RT school donation program, which began in 2014. Healthcare organizations have a growing need for qualified respiratory therapists (RT) to care for patients suffering from conditions and diseases that impact cardiopulmonary function. According to the US Department of Labor, employment of respiratory therapists is projected to grow 23 percent through 2026, much faster than the average for all occupations. Respiratory therapy (RT) schools are challenged with educating this next generation of professionals on the latest techniques and technologies so they are prepared to meet the demands of today's healthcare environment. **"We want our RT program graduates to be fully prepared for the challenges they will face in patient care settings, and for healthcare organizations to recognize our school for its commitment to exceptional education,"** said Monica Schibig, MA, RRT-NPS, CPFT, respiratory therapy program director, University of Missouri at Columbia. "In order to meet these goals, we must provide students the opportunity to train on advanced technologies. We are thankful to Dräger for its ventilator donation and the company's ongoing commitment to the RT profession." One specific area of care where RTs have a significant impact is the neonatal intensive care unit (NICU) caring for newborns suffering from respiratory issues. However, a recent survey of ventilation practices in the NICU found RTs in the US need greater education and experience with volume-targeted ventilation (VTV), which can reduce the risk for lung injury in preterm babies. In a recent survey of US neonatologists, only 39 percent of respondents used VTV as a primary mode of ventilation, with 62 percent citing lack of understanding or lack of training/experience as their main barriers to using this new standard of care. "We have long been committed to the RT profession and recognize that in order to enhance respiratory care delivery at the bedside, we need to support education and training of new RTs well before they receive their diplomas," said Edwin Coombs, MA, RRT-NPS, ACCS, FAARC, director

of marketing, Intensive Care, Dräger. "We hope that this latest donation of Babylog VN500 Ventilators will help RT students gain valuable knowledge and experience on advanced ventilation techniques to support positive outcomes in the NICU."

Low-Cost Program Slashes Readmission Rates for COPD

Rates of hospital readmission for acute exacerbations of chronic obstructive pulmonary disease (COPD) can be reduced significantly with a "discharge care bundle" that costs next to nothing to implement, new research shows.

Patient education and timely follow-up referrals are key, said senior author Chirag Shah, MD, from the Morristown Medical Center, Atlantic Health System, in New Jersey. "This disease has a high burden of morbidity and mortality in the United States," he said. "Keeping people out of the hospital reduces the likelihood of death but, more important, it improves their quality of life." The bundle "reduces healthcare costs and allows the hospital to use those resources for other things," he added. "I think that, ultimately, reimbursement will be a driving force for hospitals to want to keep COPD people out of the hospital." The Centers for Medicare and Medicaid Services now limits payments to hospitals with high readmission rates for a number of conditions, and paramount among them is COPD. Results from the study were presented by coauthor Moira Kendra, DNP, an acute care nurse practitioner, here at CHEST 2018. Lisa Landry was the respiratory therapist on the study. The 150 patients admitted to the Morristown Medical Center with an acute exacerbation of COPD from April to September of 2016 served as the preintervention cohort. Implementation of the evidence-based care bundle was completed in March 2017. The patients admitted from April to September 2017 served as the postintervention cohort.

Length of Each Breathing Disruption in Sleep Apnea May Predict Mortality Risk Better than Number of Breathing Disruptions

How long a person with obstructive sleep apnea (OSA) stops breathing may be a better predictor of mortality risk from OSA than the number of times they stop breathing, according to new research published online in the American Thoracic Society's American Journal of Respiratory and Critical Care Medicine. In "Apnea-hypopnea Event Duration Predicts Mortality in Men and Women in the Sleep Heart Health Study," lead study author Matthew P Butler, PhD, and colleagues report that participants who had short apneas and hypopneas (stopped breaths and shallow breaths, respectively) were at greater risk of dying over a decade of follow up than those who had long apneas. "This result seems counter-intuitive because you might expect longer periods of not breathing to be more severe," said Dr Butler, assistant professor in the Oregon Institute of Occupational Health Sciences at Oregon Health & Science University. **"On the other hand, shorter periods of disturbed breathing indicate a low arousal threshold, which would associate with sleep fragmentation, elevated sympathetic tone and greater risk for hypertension."** Previous studies have shown that the apnea-hypopnea index (AHI), the most widely used measure of sleep apnea severity, is linked to mortality and heart disease. However, according Dr Butler, AHI remains a coarse measure of sleep apnea severity and is not a good risk predictor for women. The current study found that the duration of abnormal breathing events may be a better predictor of mortality risk in both women and men. The duration of these events, the authors wrote, is easily determined from the same polysomnography studies that patients now undergo to measure AHI. The researchers analyzed the records of 5,712 adults (average age 63) who participated in the National Heart, Lung, and Blood Institute (NHLBI)'s Sleep Heart Health Study made available through the Institute's National Sleep Research Resource. This community-based study enrolled an approximately equal number of men and women and followed them for up to 11 years. The study found: Participants with the shortest duration of breathing events were 31 percent more likely to die compared to those with longer duration of breaths; this association was strongest in participants with moderate sleep apnea as measured by AHI. In this group, participants with the shortest duration of breathing events had a 59 percent increased risk of dying. "This study shows the power of 'big data' analysis to identify novel predictors of disease outcomes," said senior study author Susan Redline, MD, senior physician, Division of Sleep and Circadian Disorders at Brigham and Women's Hospital in Massachusetts. "The findings indicate that there may be several mechanisms by which sleep apnea leads to increased mortality and a need to measure several features associated with apnea occurrence. In particular, apneas of different types and event durations may result in adverse health outcomes."

ResMed's First Minimal-Contact Full Face CPAP Mask, Now Available

ResMed announced the availability of its first minimal-contact full face CPAP mask, AirFit F30, the latest addition to its AirFit mask portfolio, which helps sleep apnea patients reduce facial marks, wear glasses in bed and curl up closer to their bed partner. AirFit F30 is available for sale now in the United States and Canada. AirFit F30 fits 93 percent of patients and features a minimal-contact cushion that sits just below the nose, preventing top-of-the-nose red marks and irritation, plus reducing feelings of claustrophobia for some full face wearers. It also has ResMed's QuietAir vent, making the mask quieter than ambient noise in the bedroom. Nearly 2 to 1 patients preferred AirFit F30 over the current market leader in minimal-contact full face masks. When specifically asked about comfort, seal and ease of use, more patients picked AirFit F30 each time. AirFit F30 is also quieter than the current market leader, based on published performance (21 vs 24 dBA), with fewer sleep disruptions reported due to airflow. "AirFit F30 is a clear choice over other minimal-contact full face masks," said Jim Hollingshead, president of ResMed's Sleep business. "We're excited to now offer it, along with the rest of our full face, nasal and nasal pillows options, for an easy, comfortable, stable fit and a great night's sleep."

A Recent KPMG Study Supports that Home Non-invasive Ventilation for COPD Reduces Costs and Hospitalizations

Patients suffering from chronic obstructive pulmonary disease (COPD) with chronic respiratory failure (CRF) using home non-invasive ventilation (NIV) live longer, are less likely to be admitted to a hospital and cost Medicare significantly less than patients using other devices. These are the recently released findings from a study of four years of Centers for Medicare and Medicaid Services (CMS) data analyzed by KPMG, a global audit, tax, and advisory firm, and VieMed, a leading provider of post-acute home respiratory services, which commissioned the report. "The evidence is clear," said VieMed's CEO Casey Hoyt. **"Using a non-invasive ventilator at home coupled with a high-touch home care model saves lives, saves money, and keeps patients out of the hospital. It is time for both medical practice and health insurers, including Medicare, to catch up with changes in technology. Since the introduction of modern**

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1. Barto T, et al., Registry outcomes for HFCWO vest therapy in adult patients with bronchiectasis, Am Thor Soc Ann Meet, San Francisco, CA, May 2016, Poster P1496.

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highly sophisticated home ventilators within the last decade, NIV has become the gold standard for treating patients in the late stages of COPD." The KPMG study, "CRF/COPD 4-year CMS Data Comparison of Mortality & Cost, (2013-2016)," examined the costs and the benefits of the various respiratory assistive devices physicians commonly prescribe for patients suffering from COPD with CRF. A chief finding was that patients using NIV at home with a high-touch care model have the lowest overall costs and hospitalization rates. A high-touch care model includes multiple home visits by a certified respiratory therapist, 24-hour access to medical professionals, and enhanced coordination with physicians and other clinicians. COPD is a chronic condition that affects as many as 24 million Americans and is the country's third-leading cause of death, after cancer and congestive heart failure. Treating patients diagnosed with this progressive, chronic condition also costs the country more than $30 billion a year. The KPMG study offers compelling evidence that both outcomes and costs can be improved through home NIV with a high-touch care model. Specifically, the study examined results of untreated patients who used no respiratory device at home, patients using a bi-level positive airway pressure device (BPAP), and patients using a NIV. The study looked at mortality, the number of times patients were hospitalized and the total cost of caring for patients in each group. The analysis found that patients using a BPAP or NIV lived longer than untreated patients. For example, only 22 percent of COPD patients with CRF using NIV died, compared to 38 percent of untreated patients. Although there was little difference in the overall death rates between patients using a BPAP or NIV, there were significant differences in the cost of treating these patients and hospitalization rates.

RCI Launches Study

The Respiratory Compromise Institute announced the initiation of a clinical study aimed at better understanding the prevalence, risk factors and pathways for unplanned airway intubations as a measure of respiratory compromise. Respiratory compromise is a deterioration of respiratory function that poses a high risk of life-threatening respiratory failure, the second leading avoidable patient safety issue. General care floor patients with respiratory compromise are 29 times more likely to die. Led by Neil MacIntyre, MD, FCCP, Professor of Medicine (Pulmonary, Allergy and Critical Care Medicine) at Duke University School of Medicine, and supported by the Respiratory Compromise Institute (RCI), the study will draw on the electronic health records of patient encounters at DUHS' three hospitals: Duke University Hospital (DUH), Duke Regional Hospital (DRH) and Duke Raleigh Hospital (DRAH). The study researchers hope to assess demographic, clinical and care practice characteristics that impact the risk profile of patients 18 years or older with unplanned intubations 24 hours or more after admission or surgery on general medical and surgical floors. The source population will include patients at DUH, DRH and DRAH admitted from January 1, 2014 to December 31, 2017. DUH is a large, 957-acute care bed academic facility, providing tertiary referral care for North Carolina; DRH is a 369-bed community-based facility attending to underserved populations in Durham County, North Carolina; and DRAH is a 186-bed facility serving Raleigh, North Carolina. "Our study uses unplanned intubations as an end result of progressive respiratory compromise, which may be difficult to detect early and have a high incidence in minimally monitored care settings, such as medical and surgical floors," said Dr MacIntyre. "If we can identify which patient characteristics and aspects of clinical practice present the greatest risk, then healthcare providers will be better positioned to prevent or mitigate respiratory compromise. Furthermore, we believe that, by creating a data and analytics framework that can be adapted to other institutions, our study will serve as a model for future research."

Demographic data that investigators will be examining to assess patient risk for respiratory compromise include: age, race/ethnicity, sex, smoking and alcohol status. Researchers will also be looking at vital signs, laboratory data and clinical picture along with pre-existing medical conditions, such as diabetes, liver disease, cancer and other factors that can increase patients' risk. The impact of commonly prescribed medications, including benzodiazepines and sleep aids, will also be assessed. "Electronic health records enable us to amass large quantities of data on patients, which can and should be utilized to understand patient risk for a variety of health conditions that arise during in-hospital patient care," said Phillip Porte, Executive Director of RCI. "Innovative research like the kind being conducted by Dr MacIntyre will help us continue to deepen our understanding of and hopefully better recognize and prevent respiratory compromise, which has been the aim of the Respiratory Compromise Institute since its founding."

The study's expected completion date is end of 2018. Dr MacIntyre's co-investigators include: Armando Bedoya, MD, MMCi, Nrupen Bhavsar, PhD, MPH, and Benjamin Goldstein, PhD, MPH.

Humidifier May Help Sleep Apnea Patients Stick With CPAP Treatment

People with sleep apnea are more likely to stick with continuous positive airway pressure (CPAP) treatment when they use a built-in humidifier, a Swedish study suggests. To see what factors might influence whether patients stick with this cumbersome treatment, researchers followed 16,425 people who were prescribed CPAP between 2010 and 2017. Within one year of starting treatment, 1,527 patients, or about 9 percent, had stopped using their CPAP machines, and another 2,395 people, or almost 15 percent, were only using it an average of 2.5 hours a night instead of all night as prescribed. Patients who used CPAP machines with built-in humidifiers from the start, however, were 43 percent less likely to discontinue treatment, researchers report. "Upper-airway symptoms, such as nasal congestion, (runny nose) and mouth dryness are common in patients with sleep apnea on CPAP and are associated with CPAP failure," said lead study author Dr Andreas Palm of Uppsala University. "Humidifiers reduce these symptoms and makes the CPAP treatment more comfortable," Palm said. While CPAP machines with integrated humidifiers are now common, doctors don't always prescribe them right away, Palm noted. The study results should encourage more physicians to offer CPAP machines with humidifiers to patients right at the start of treatment, Palm said. This is already happening more often. The proportion of patients getting humidifiers at the start of CPAP treatment increased from 30 percent at the start of the study to 72 percent by the end.

Anything that helps patients continue to use their CPAP machines might be a way to lower their risk of premature death, the study also suggests. After that one-year checkup to see if patients were still using CPAP all night, researchers followed most participants for at least another 2.4 years. During this period, 378 patients died.

People who stuck with CPAP were 26 percent less likely to die than patients who discontinued treatment, the study found. In general, patients were more likely to stick with CPAP when they were older, had more severe apnea, or were overweight

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and obese but not severely obese. Women and patients with high blood pressure, on the other hand, were more likely to abandon treatment. "Although it is tempting to interpret this as meaning that CPAP reduces the risk of death, we must be very careful in interpreting this finding," said Dr Ken Kunisaki of the Minneapolis VA Health Care System and the University of Minnesota. "Many studies in all sorts of diseases have shown that people who stick with their treatment live longer, and this includes sticking with placebo/sugar-pill treatments," Kunisaki, who wasn't involved in the study, said. There are also a variety of reasons that people may discontinue CPAP, and many aren't issues that could be addressed by a humidifier, said Kristen Knutson, a researcher at Northwestern University Feinberg School of Medicine in Chicago.

VA Decision Praised

BPR Medical has welcomed the United States Veterans Health Administration (VA) decision to mandate the use of thermal fuses — also known as firebreaks — in all its home oxygen patient installations. The VA published a Patient Safety Alert requiring thermal fuses, which can prevent patient deaths and limit injuries in the event of an oxygen fire — to be installed on every stationary and portable oxygen system used by its 85,000 home oxygen patients. The change is being phased in over the next six months, with home oxygen installers' contracts being amended to reflect the new requirement. As a result of the VA's Patient Safety Alert, all the 21 regional Veterans Integrated Service Network organizations (VISNs), which oversee healthcare for veterans, will also be required to formally report fires involving home oxygen. There are no accurate figures for the number of fires involving home oxygen in the United States, however a report in 2017 by the National Fire Protection Association (NFPA) recorded a likely annual death rate of 70 people (based on figures between 2011 and 2015), equivalent to one in 20 home fire deaths. The NFPA also states that there is an average of 1,190 burns each year due to home oxygen fires, although it describes these statistics as 'likely underestimates'. Richard Radford, Managing Director, BPR Medical, said, **"Fires caused by patients smoking or being exposed to other dangers such as birthday candles, gas ovens and electrical devices while using home oxygen are an almost daily event. These fires don't just result in injuries or death for the patient but can also pose a serious risk to family and neighbors in the event of a whole house fire."**

Oximetry Results Help Determine Need for Adenotonsillectomy

Nocturnal oximetry results can be used to identify children with sleep-disordered breathing who are most likely to benefit from adenotonsillectomy, researchers report. Adenotonsillar hypertrophy leading to increased upper airway resistance is the main pathogenetic mechanism of obstructive sleep-disordered breathing (SDB) in children. But the efficacy of adenotonsillectomy in otherwise healthy children with SDB related to pharyngeal lymphoid tissue hypertrophy has not been assessed in randomized controlled trials by using oximetry, researchers say. Dr Athanasios G Kaditis from National and Kapodistrian University of Athens, Greece, and colleagues evaluated the efficacy of adenotonsillectomy in children with SDB, hypothesizing that children with SDB and abnormal nocturnal oximetry would have improved hypoxemia indices after adenotonsillectomy. Over the three-month study period, the percentage of children with an abnormal baseline McGill oximetry score (MOS >1) who achieved a normal MOS did not differ significantly between the adenotonsillectomy group and the control group. The median decline in the number of episodes per hour of oxygen desaturation of 3% or greater (ODI3) by nocturnal oximetry between baseline and follow-up was significantly greater in the adenotonsillectomy group (3.2) than in the control group (1.7), the researchers report. Moreover, children in the adenotonsillectomy group were significantly more likely than children in the control group to normalize their ODI3 at follow-up, after adjusting for baseline ODI3, age, sex and presence of obesity. A preoperative ODI3 of 3.5 episodes per hour or greater was associated with attainment of normal ODI3 in about 40% of patients after adenotonsillectomy. Three children with elevated ODI3 needed to undergo adenotonsillectomy to prevent two or more ODI3 episodes per hour in one child at the three-month follow-up, that is, the number needed to treat was three. Children in the adenotonsillectomy group had significantly greater improvements in disease-specific quality-of-life scores between baseline and three months than did children in the control group. "The present randomized controlled study reveals that nocturnal oximetry can be used in community settings to identify children with snoring and tonsillar hypertrophy who are likely to have resolution of nocturnal intermittent hypoxemia after undergoing adenotonsillectomy," the researchers conclude. "An ODI3 that is not elevated does not necessarily exclude the need for treatment, because impaired quality of life improves post-adenotonsillectomy regardless of the severity of nocturnal hypoxemia and obstructive apneas or hypopneas are not always accompanied by oxygen saturation drops," they add.

Triple Therapy for COPD More Effective Than Dual Inhalers?

Triple therapy delivered in a single inhaler reduces moderate to severe exacerbations in chronic obstructive pulmonary disease (COPD) to a greater extent than dual-inhaler therapy in patients at high risk for exacerbations, according to results from the Informing the Pathway of COPD Treatment (IMPACT) trial. The data also show that the triple therapy, a combination of the inhaled glucocorticoid fluticasone furoate, the long-acting muscarinic antagonist (LAMA) umeclidinium, and the long-acting β2-agonist (LABA) vilanterol (Trelegy Ellipta, GlaxoSmithKline), reduces the need for hospitalization from COPD compared with the dual inhaler containing umeclidinium plus vilanterol, but not compared with the inhaler containing fluticasone furoate plus vilanterol. On the basis of these new data, the US Food and Drug Administration approved the triple therapy for approval for long-term, once-daily, maintenance therapy in patients with COPD, including chronic bronchitis and/or emphysema. However, in an accompanying editorial, Samy Suissa, PhD, from McGill University, Montreal, Quebec, Canada, and Jeffrey Drazen, MD, the editor-in-chief of the New England Journal of Medicine, caution that a "peculiarity" of the study design, as well as the type of patients enrolled, may have skewed findings from the study, "falsely exaggerating the benefit of triple therapy in comparison to the LAMA-LABA comparator group."

Until more robust evidence provides a strong rationale to step up to single-inhaler triple therapy, the editorialists advise physicians to follow the updated 2017 Global Initiative for Chronic Obstructive Lung Disease guidelines, which recommend that physicians limit the addition of an inhaled glucocorticoid to patients with more symptomatic Global Initiative for Chronic Obstructive Lung Disease–defined COPD with frequent exacerbations. IMPACT was a large, phase 3, double-blind trial initially involving 10,355 patients (mean age, 65.3 years) who were randomly assigned to 52 weeks of once-daily triple

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therapy (100 µg fluticasone furoate, 62.5 µg umeclidinium, 25 µg vilanterol) or to one of two dual-inhaler therapies consisting of either 100 µg fluticasone furoate plus 25 µg vilanterol or 62.5 µg umeclidinium plus 25 µg vilanterol. "Each regimen was administered in a single dry-powder inhaler (Ellipta, GlaxoSmithKline)," write David Lipson, MD, an employee of GlaxoSmithKline in Collegeville, Pennsylvania, and colleagues.

Airgas Healthcare Receives Innovative Technology Designation

Airgas Healthcare, the specialized healthcare brand of Airgas, an Air Liquide company, announced that its INTELLI-OX portable medical oxygen cylinder has received a 2017 Innovative Technology designation from Vizient, Inc., the largest member-driven health care performance improvement company in the country. The designation was based on direct feedback from hospital representatives who interacted with the INTELLI-OX oxygen cylinder at the Vizient Innovative Technology Exchange in Denver. This is the first US award received for the INTELLI-OX design. The INTELLI-OX integrated medical oxygen cylinder features an advanced digital gauge to clearly and easily show the remaining time left at a given flow rate. It includes an integrated valve and regulator assembly, lightweight aluminum cylinder as well as visual and audible alerts when the cylinder is nearly empty and needs to be replaced. Measurements are provided in volume, pressure and time increments, simplifying readouts and eliminating guesswork for care providers. Christophe Tardieu, Airgas Senior Vice President of Healthcare, Life Sciences and Specialty Gases, commented: "We're proud to be recognized by Vizient for our innovative INTELLI-OX cylinder design. In addition to its proven reliability, our INTELLI-OX cylinders optimize the use of each cylinder to reduce turnover frequency."

ResMed to Acquire Propeller Health

ResMed, a leader in cloud-connected medical devices and out-of-hospital software-as-a-service (SaaS) business solutions, today announced it has entered a definitive agreement to acquire Propeller Health, a digital therapeutics company providing connected health solutions for people living with chronic obstructive pulmonary disease (COPD) and asthma. Named a "2017 Most Innovative Company" by Fast Company, Propeller helps people and their doctors better manage their COPD and asthma. Propeller's digital medicine platform consists of small sensors that easily attach to consumers' inhalers and pair with a mobile app to automatically track medication use and provide personal feedback and insights. Propeller's clinically validated solutions have demonstrated a 58 percent improvement in medication adherence, 48 percent increase in symptom-free days and 53 percent reduction in emergency room visits.Propeller's ability to support people in stage II and III severity levels of their COPD are complementary to ResMed's own suite of cloud-connected ventilators for those with stage III and IV COPD, including Astral, Stellar and AirCurve 10 ST-A with iVAPS — plus ResMed's new portable oxygen concentrator Mobi. "Acquiring Propeller is a significant step for ResMed toward becoming the global leader in digital health for COPD," said ResMed CEO Mick Farrell. "By working with Propeller's existing partners to offer digital solutions for respiratory care pharmaceuticals and building on our proven ability to support digital solutions at scale, we can positively impact the lives of even more of the 380 million people worldwide who are living with this debilitating chronic disease."

"Helping inhaler users improve adherence and avoid hospitalizations perfectly serves ResMed's mission: to improve people's quality of life, reduce the impact of chronic disease and save healthcare costs across the out-of-hospital care spectrum," said ResMed Respiratory Care President Richie McHale.

"ResMed shares our belief that connected health solutions create vastly better experiences and outcomes for people with chronic respiratory disease," said David Van Sickle, co-founder and CEO of Propeller. **"Joining forces enables us to accelerate the adoption of Propeller's solutions at a global scale, and serve as a powerful platform for a broad set of pharmaceutical and healthcare partners."** Propeller is privately funded, and based in Madison, Wisconsin, with an office in San Francisco. It will continue to operate as a standalone business within ResMed's Respiratory Care portfolio. There will be no immediate changes to management, locations or business processes. Van Sickle will continue in his current role, now reporting to McHale.

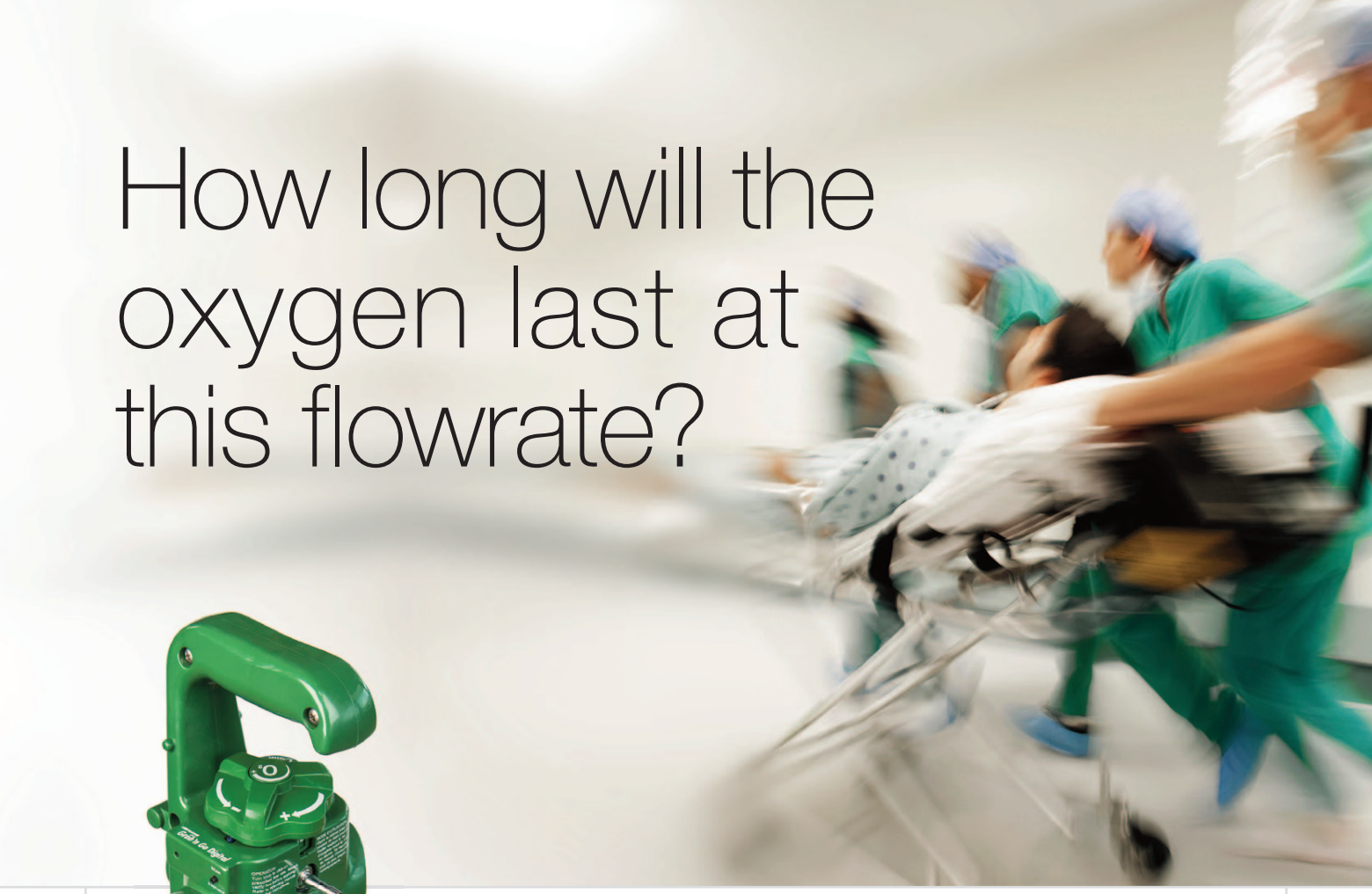
Company Wins Fifth Zenith Award

Aerogen, the global leader in aerosol drug delivery, has been recognized with the prestigious 2018 Zenith Award for respiratory care excellence by the American Association of Respiratory Care (AARC). The win represents the fifth time that Aerogen has received the award. Widely recognized as the top award of the respiratory care profession, the Zenith Award is voted on by over 47,000 AARC members based on their experience and expertise with a wide range of respiratory products. Judging criteria included outstanding service, product quality, accessibility and helpfulness of sales staff, responsiveness, truth in advertising and support of the respiratory care profession. "We are honored to be recognized by the respiratory therapy community in this way. As a fifth time recipient, we are proud to retain the confidence and trust of respiratory care professionals. Aerogen is committed to work daily to maintain this valued relationship." John Power, CEO of Aerogen. Aerogen officially received the Award at the opening ceremony for the 64th International Respiratory Congress this December in Las Vegas, NV. It will be received by two of Aerogen's long standing employees Susan Sickal, Sales Operations and Customer Support Manager and Peter Kahane, Senior Critical Care Specialist, both of whom exemplify the traits of customer centric approach and help to make Aerogen a leader in the industry.

FeNO Monitoring Gets Recommended

Circassia Pharmaceuticals, Inc., a specialty pharmaceutical company focused on respiratory disease, announced that Fractional Exhaled Nitric Oxide (FeNO) monitoring is recommended in the latest Global Initiative for Asthma (GINA) guide, "Difficult-to-Treat & Severe Asthma in Adolescent and Adult Patients – Diagnosis and Management". Asthma is a chronic inflammatory respiratory disease. During airway inflammation associated with allergic/eosinophilic asthma, higher-than-normal levels of nitric oxide (NO) are released from epithelial cells of the bronchial wall. Measuring the concentration of NO in exhaled breath, or fractional exhaled nitric oxide, can help identify airway inflammation. Circassia's innovative NIOX® technology provides objective and accurate FeNO measurement of airway inflammation, and is the only FeNO testing device in the US available at point-of-care. The new GINA guide recommends FeNO measurement as an assessment tool to determine whether patients who are on high-dose inhaled corticosteroids (ICS) or low-dose oral corticosteroids (OCS) have residual inflammation. This can provide a potential predictor of good response to anti-immunoglobulin E (anti-IgE) therapy for patients with severe, allergic asthma, and is

How long will the oxygen last at this flowrate?



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

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a tool to identify refractory type 2 inflammation in patients on high-dose ICS therapy. The guide suggests repeating FeNO measurement up to three times when asthma worsens before deciding if it is non-type 2. For patients with elevated type 2 biomarkers on high-dose ICS, FeNO monitoring is recommended to assess adherence before prescribing a biologic. Lastly, FeNO measurement is suggested as a means of monitoring tapering of oral corticosteroid treatment. Circassia announced earlier in 2018 that major insurer Aetna updated its policy to deem FeNO by NIOX as "medically necessary" as a part of comprehensive asthma diagnosis and management. NIOX testing is considered affordable and accessible for both patients and their physicians, as an estimated 80 percent of American lives have insurance coverage for NIOX testing. Asthma often begins in childhood, but can affect people of any age. The disease is characterized by attacks (exacerbations) of breathlessness and wheezing of varying severity and frequency, which if left untreated, can be life-threatening. Asthma is a common condition, with the World Health Organization estimating 235 million people have the condition worldwide. Asthma affects approximately 25 million people in the United States. GINA estimates that 17 percent of asthma patients are considered "difficult-to-treat", such that their asthma is uncontrolled despite treatment with a medium or high dose inhaled corticosteroid, with a second controller and maintenance oral corticosteroid therapy, or requires such treatment to maintain good symptom control and reduce the risk of exacerbations. An estimated 3.7 percent of asthma patients are considered "severe" in that asthma is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. According to GINA, type 2 inflammation is found in approximately half of people who have severe asthma. GINA was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute (NIH) and the World Health Organization. Embracing the issue of severe asthma was a critical goal for the GINA Board of Directors and Science Committee, as their mission remains focused on maximizing benefit for patients with asthma while minimizing healthcare provider burden.

VENTILATION ROUNDTABLE

Getinge

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

What are the new features?
We continuously provide upgrades and updates to our ventilators, and therefore make sure that Servo ventilators can be kept up-to-date and support users changing needs over the lifetime of the ventilator.

Tell us about your company's current or recent R&D efforts.
The ventilator R&D is one of the most innovative within Getinge, with investments and innovations in new therapies, functions and usability.

Discuss the training and support services you offer.
We offer in person and online training and support. Our account managers and territory managers have been through an extensive training program to insure they will be the best consultant to our customers.

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

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

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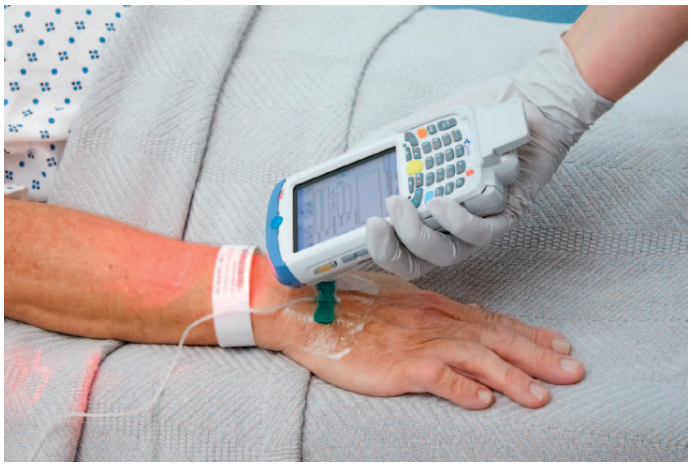

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1. www.cdc.gov/ncidod/eid/vol12no11/pdfs/06-0426.pdf 2. Respir Care 2018; 63(s10): 3016143.

Product Engineering, Quality and the Design of Mechanical Oscillation Vest Therapy

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Geoff Marcek, the Vice President of Engineering and Quality at International Biophysics.

Respiratory Therapy: Tell us a little about International Biophysics and your commitment to quality.
Geoff Marcek: International Biophysics is an FDA-registered and ISO 13485 certified medical device manufacturer. We are a 26-year-old company that manufactures, and markets medical devices across the globe. What that means, in terms of quality, for products such as the AffloVest, is that every product goes through a rigorous design and manufacturing process, inspection process, periodic audits by the FDA and other regulatory bodies to verify compliance with all the various regulations.

When we look at new technologies and applications, we really focus on what we feel are disruptive technologies and not minor incremental improvements. In the example of the AffloVest, we see a product category that doesn't have a lot of evolution over time, and we really want to bring something that really disrupts the market and results ultimately in improving patient care for the entire population that uses these types of products.

RT: The AffloVest was the first HFCWO Airway Clearance Vest on the market that uses mechanical oscillation technology as opposed to the traditional compressor-based vests. What do you see as the advantages to that?
GM: There are two types of HFCWO devices, the traditional air bladder or compressor based and mechanical (motor based). Air bladder HFCWO is an older technology and more restrictive for the patient as far as ease of use and portability, things that people would expect in today's world for something they use in their home. Mechanical oscillation vest therapy allows them to get the same type of therapy with full mobility during use and more flexibility to promote adherence to the therapy.

At this year's NACFC conference in Denver, a major HFCWO vest manufacturer, known for decades for their compressor-based technology, presented data showing that mechanical oscillation vest therapy was better than traditional compressor-based. We agree and have from the start. We are thrilled to be the leader in bringing mechanical oscillation HFCWO vest therapy to the market.

RT: In the last issue we published a recent IRB study you conducted on HFCWO vest therapy with Dr Thomas O'Brien. What are the key findings in that study?

GM: For the FDA, clearance for these devices are all classified the same, and companies are expected to provide the same safety and performance data for the FDA to review prior to clearing for sale on the market. The FDA classifies all HFCWO vests on the market as oscillation vests, which are intended to operate through vibration of the patient's abdomen and thorax. During an FDA review process, that's what their interest is, the vibration forces on the torso of the patient.

Our study challenged the hypothesis of some manufacturers that increased cephalad airflow bias was a mode of action for HFCWO vest therapy. The data we gathered does not support that hypothesis and demonstrated in fact that on some spirometry measures lung function decreased during use while wearing compressor style vests. We believe that all vests operate on the same principle, producing oscillation waveforms on the torso that can thin, mobilize and help clear secretions from the lungs.

RT: What is the product design and development process at International Biophysics?
GM: The design of the AffloVest here at International Biophysics starts with the patients and the users to gather all their feedback about HFCWO devices, and what's lacking out in the current market and what the patients and clinicians themselves would like to see. So, the first step in the design process is to gather all that customer feedback, and then feed that into design process. We then bring the product back to the users and conduct additional surveys and interviews to make sure that what we're delivering ultimately is what they are looking for.

We make sure to cover a broad range of patient factors. For example, the fact that there are many different patient sizes and anatomies led us to offer seven different sizes of AffloVests to make sure that we correctly fit every patient, regardless of their body type. And we make sure that even the motor placement on every size is anatomically correct to ensure that we're targeting the upper lobes and lower lobes of the lungs with four motors on the front and four on the back. We also consider human factors heavily in the design phase. This includes items which are relevant in a homecare environment, such as weight, noise, ergonomics, comfort, ease-of-use and electromagnetic compatibility. As a result, the AffloVest is the lightest and quietest mobile HFCWO vest on the market and is well below published threshold limits for static magnetic field exposure for certain active implantable medical devices.
Continued on page 22…

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

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Expiratory-Only Spirometers are Failing COPD Patients

Alex Stenzler

While spirometry has been used to evaluate lung function for more than 200 years, the use of flow volume loops for evaluating the forced vital capacity was only first introduced by Hyatt, Schilder and Fry in 1958.[1,2,3] During a forced exhalation, as the pressure in the lung increases, the pleural pressure forces pushing air out of the alveoli are also applied to the airways, narrowing them and exaggerating pathologies that reduce airflow. Once alveolar pressure reaches around 20 cmH_2O, increasing effort will not affect flow (Figure 1) making the flows measured the mouth effort-independent above that pressure.

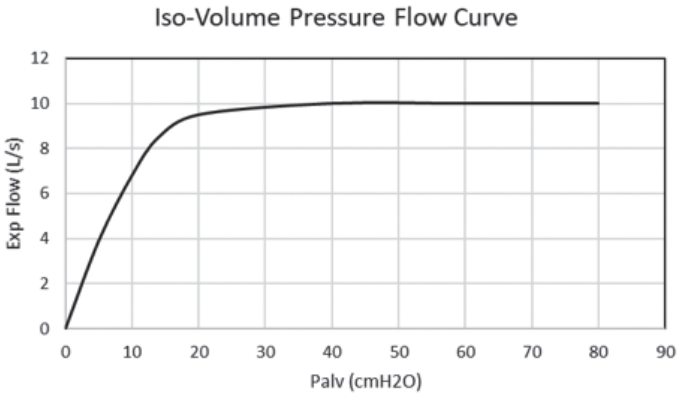

Figure 1. Iso-Volume pressure flow curve

Hyatt demonstrated that the factors that determine maximum expiratory flow were also extremely dependent on lung volume and airway caliber. This has given us the most common display of lung function testing results of a flow volume curve showing decreasing expiratory flows as lung volume decreases during a forced exhalation and reflecting the patency of the airways. An additional influence during exhalation is the continual reduction in cross sectional area from the terminal airways to the trachea, thereby increasing turbulent airflow during exhalation and resistance.

Inspiratory flow in comparison, continues to increase during inspiration until a patient reaches the most negative alveolar pressure. The rapid movement of the diaphragm and chest-wall create a large negative alveolar pressure. As air enters the alveoli, the alveolar pressure becomes less negative so that maximum negative alveolar pressure is not at Total Lung Capacity. Airflow is also influenced by the rapidly increasing cross sectional area from the trachea to the terminal airways, generating more laminar flow during inhalation and lower resistance. The negative intrathoracic pressures are also applied to the airways, which increases their diameter, reducing resistance to airflow. Peak negative alveolar pressure typically occurs in the middle of inspiration from the residual volume position, which is also close to within the tidal breathing volume range (Figure 2).

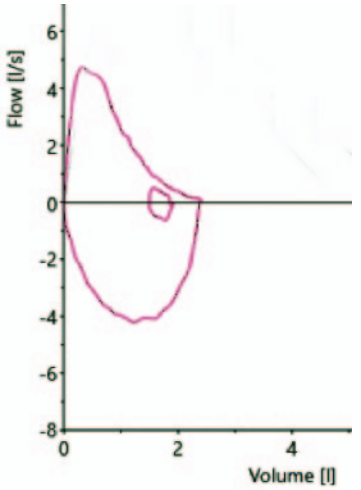

Figure 2. Maximum effort flow volume loop and tidal breath flow volume loop

Inspiratory flow therefore is rarely a cause for concern in patients with COPD as the airways are dilated during inspiration with lower resistance than during expiratory flow and it's primarily expiratory flow that limits ventilation. However, the belief that inspiratory flow is inconsequential in obstructive disease, except for the detection of upper airway disease, is misleading. The evaluation of inspiratory flow is only inconsequential when patients have a normal Functional

Alex Stenzler is the president of 12th Man Technologies, Inc. He was a Registered Pulmonary Function Technologist and has been working in the field of pulmonary function testing since 1968. He spent half of his career managing Respiratory Care Departments, COPD Clinics and Pulmonary Function Laboratories, or teaching pulmonary function technology as an Assistant Professor at the State University of New York at Stony Brook and twelve years at the Graduate School of Adelphi University. He has been the PI for two NIH and one DARPA grant and has extensive research experience. He has co-authored 16 peer-reviewed papers and one book chapter on pulmonary function testing. He holds 42 patents, most of which are related to pulmonary medicine.

Residual Capacity (FRC) and can begin inspiration from a normal resting lung volume.

The maximum flow volume loop is exactly what it states; it is the outer loop of flow at maximum effort at any lung volume. When the FRC is increased, the range of peak inspiratory flow becomes reduced. Figure 3 shows multiple forced vital capacity measurements in a subject with only very mild airway disease beginning the forced inspiratory maneuver at various lung volumes. As can be seen in the figure, as lung volume increases, the peak inspiratory flow can decrease by as much as 50% from the flow potential at a normal FRC, while tracking along the maximal curve from end exhalation.

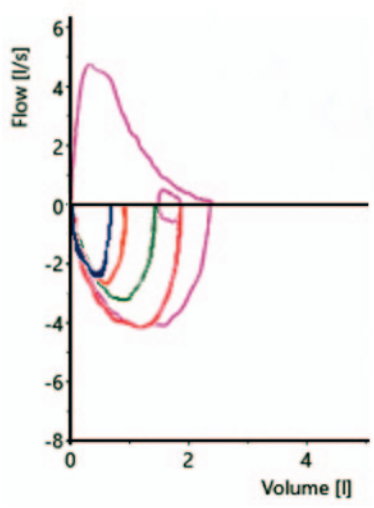

Figure 3. Forced inspiration during increasing starting lung volumes

The treatment of COPD patients with inhaled drugs has seen a significant shift to dry powder inhalers (DPIs) with some reporting use in 68% of patients.[12] The use of DPIs has been partially driven by the poor coordination of patients using metered dose inhalers (MDIs). Patients report that the use of a DPI is much easier than using an MDI. Table 1 identifies many of the COPD drugs available in DPI preparations and the flow required to deagglomerate and aerosolize the powder within the DPI device for delivery by inhalation.

Table 1. DPI Drugs Used to Treat COPD

Drug	Flow Rate	Drug	Flow Rate
Ellipa-Revlar	90 L/min	Seebri Neohaler	90 L/min
Turbohaler	60 L/min	DuoResp Spiromax	30 L/min
Spiriva Handihaler	20 L/min	Pulmicort	60 L/min
Seebri Breezhaler	90 L/min	Flovent	60 L/min
Serevent Diskus	60 L/min	Asmanex	69 L/min
Foradil Aerolizer	60 L/min	Anoro Ellipta	60 L/min
Tudorza Pressair	35 L/min	Laventair Ellipta	90 L/min
Incruse Ellipta	60 L/min	Incruse Ellipta	60 L/min
Arcapta Neohaler	60 L/min	Buventol Easyhaler	60 L/min
Breo Ellipta	60 L/min	Beclomet Easyhaler	60 L/min
Advair Diskus	60 L/min	Giona Easyhaler	60L/min
Breezhaler	50 L/min	Novolizer	60 L/min
BiResp Spiromax	60 L/min	Genuair	45 L/min

It is clear from this table that COPD patients must generate adequate peak inspiratory flow to inhale these products. Laube has demonstrated that it is not just the peak inspiratory flow but the acceleration to peak flow that is also very important, and that the minimum flow acceleration for using blister or multidose DPIs is 0.7 L/s^2.[4] With an acute progression of COPD during an exacerbation, there is further narrowing of the airways, leading to gas trapping and an increasing FRC (reduction in Inspiratory Capacity). The impact of breathing at a higher lung volume therefore results in a significant reduction in peak inspiratory flows and flow acceleration. This places patients who need their drugs more than ever, but lack the ability to aerosolize the drug within their delivery device to inhale them, in a precarious situation.

Furthermore, at a higher lung volume, not only is the peak inspiratory flow lower, but the inspired volume to carry the drug to the periphery is also smaller. It has been reported that when patients use a capsule DPI, they should inhale at least 500 mL after reaching the required inspiratory flow.[5] It is therefore not surprising that when COPD patients get into trouble, the slide to hospitalization or rehospitalization can be very rapid.

Sharma, et al, studied the peak inspiratory flow rates of COPD patients upon discharge for COPD-related hospitalization from seven US hospitals.[6] Nearly one-third of the patients had PIFRs less than 60 LPM, meaning that on discharge, these patients might not benefit from the drugs they were prescribed for treatment of their COPD. The mean PIFR for all subjects was only 71 LPM.

When we look at this data, the high rehospitalization rate for people with COPD is not surprising. If patients don't do well on a drug in DPI formulation, it may be that the drug isn't working, or it could be just that the patient couldn't aerosolize the powder and it wasn't delivered.

Understandably, it has been demonstrated that findings of decreasing inspiratory capacity (IC) is one of the most sensitive indicator of treatment failure and exacerbation in COPD.[7,8,9,10,11] If Inspiratory Capacity isn't frequently monitored in COPD patients, the very least is that peak inspiratory flow is monitored. And consider that these are free-flow peak inspiratory flow measurements and not affected by the resistance of the DPI devices that would lower the peak inspiratory flow even further. This is another important reason why COPD patients should not be monitored with spirometers that don't measure inspiratory flow and why we fail patients with COPD when we do. Therefore, spirometers that measure expiratory flow only should not be used to monitor patients with COPD.

References

1 Hyatt RE, Schilder DP, and Fry DL. Relationship between maximum expiratory flow and degree of lung inflation. J Appl Physiol. 1958; 13:331-336.

2 Fry DL, and Hyatt RE. Pulmonary mechanics. Amer J Med. 1960; 29:672-689.

3 Jordanglou J, Pride NB. Factors determining maximum inspiratory flow and maximum expiratory flow of the lung. Thorax 1968; 23:33-37

4 Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, Everard ML, Horvath I, Navalesi P, Voshaar T, Chrystyn H. What the pulmonary specialist should know about the new inhalation therapies, Eur.Respir. J. 2011;

37:1308-1331.
5 Kamin WE, Genz T, Roeder S, Scheuch G, Cloes R, Juenemann R, Trammer T. The inhalation manager: a new computer-based device to assess inhalation technique and drug delivery to the patient, J. Aerosol Med. 2003; 16:21-29.
6 Sharma G, Mahler DA, Mayorga VM, Deering KL, Harshaw Q, Ganapathy V. Prevalence of Low Peak Inspiratory Flow Rate at Discharge in Patients Hospitalized for COPD Exacerbation. Journal of the COPD Foundation 2017; 4:217-224.
7 Yetkin O, Gunen H. Inspiratory capacity and forced expiratory volume in the first second in exacerbation of chronic obstructive pulmonary disease. Clin Respir J. 2008; 2(1):36-40.
8 Tantucci C, Donati P, Nicosia F, Bertella E, Redolfi S, DeVecchi M, Corda L, Grassi V, Zulli R. Inspiratory capacity predicts mortality in patients with chronic obstructive pulmonary disease. Respir Med. 2008; 102(4):613-9.
9 Cushen B, McCormack N, Hennigan K, Sulaiman I, Costello RW, Deering B. A pilot study to monitor changes in spirometry and lung volume, following an exacerbation of Chronic Obstructive Pulmonary Disease (COPD), as part of a supported discharge program. Respir Med. 2016; 119:55-62.
10 Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, and Celli BR. Inspiratory-to-Total Lung Capacity Ratio Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2005; 171:591–597.
11 French A, Balf D, Mirocha JM, Falk JA, Mosenifar Z The inspiratory capacity/total lung capacity ratio as a predictor of survival in an emphysematous phenotype of chronic obstructive pulmonary disease. International Journal of COPD 2015; 10:1305–1312.
12 Ramadan WH, Sarkis AT Patterns of use of dry powder inhalers versus pressurized metered-dose inhalers devices in adult patients with chronic obstructive pulmonary disease or asthma: An observational comparative study. Chron Respir Dis. 2017 Aug; 14(3): 309–320.

International Biophysics interview…continued from page 18
We believe that by staying focused on the patient's experience with our product we can help improve adherence and patient outcomes.

Other engineering driven features include patient flexibility in how they program and operate the AffloVest. There are 3 different operating modes that were designed to mimic the gold standard of hand CPT and provide choices to the patient, so they can customize their treatment into different sequences and save that based on their dialogue with their physician and what they feel ultimately is working best for them with airway clearance.

RT: What are the advantages of being in full control of the product development process?
GM: The AffloVest is a sophisticated and highly-engineered product, which required a lot of investment and quite a lot of time, working with many, many suppliers, consultants, contractors, during the entire development cycle. We have three patents issued for the AffloVest, and several others that are currently pending.

Being in control of the design of the AffloVest allows us to respond quickly to patient and clinician feedback. We're able to continuously improve the AffloVest product over time and deliver a better and better product.

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Symposium Examines Benefits of Non-invasive Screening of Expiratory Flow Limitation in Chronic Obstructive Pulmonary Disease

Chris Campbell

Finding, examining and then using the most non-invasive techniques on patients should be the goal of any medical team.

Unfortunately, for some areas of medicine, the more invasive techniques are still considered the standard and so are used more often on patients.

Challenging this status quo is vital in the pursuit of medical progress.

Take, for example, the condition of chronic obstructive pulmonary disease (COPD) and the occurrence of expiratory flow limitation (EFL).

The pathophysiological significance of EFL in COPD, its measurement with non-invasive techniques, and the importance of monitoring EFL in patients with COPD were discussed at a satellite symposium sponsored by Philips Respironics and held at the 3rd Joint International Meeting of the European Respiratory Care Association (ERCA) and Journées Internationales de Ventilation à Domicile (JIVD) in Lyon, France, on March 17, 2018.

Based on this symposium, Peter Calverley from Aintree University Hospital, Lower Lane, Liverpool, Merseyside, UK and Raffaele L Dellacà from Politecnico di Milano University, Milan, Italy, compiled a report on what was discussed, entitled: Non-invasive Screening of Expiratory Flow Limitation in Chronic Obstructive Pulmonary Disease, published as a supplement on the European Respiratory and Pulmonary Diseases Journal in September 2018.

The report's takeaways included that forced oscillation technique provides an objective, non-invasive measure of tidal EFL that does not require the performance of respiratory manoeuvres and offers a simple, detailed and repeatable approach to investigating the mechanical properties of the respiratory system. The report also says that monitoring tidal EFL has the potential to identify factors limiting exercise tolerance in COPD, as well as to guide treatment decisions and thereby improve clinical outcomes in patients with COPD.

"The recognition and monitoring of EFL before and after exacerbation could potentially be used to guide or titrate treatment, reduce the duration of hospital stays and improve clinical outcomes for patients with COPD," the authors wrote.

Chris Campbell is the Senior Editor of Respiratory Therapy.

Dealing with COPD

The authors wrote about EFL and how the "gold standard" for detecting it in many medical circles involves an invasive technique that had more non-invasive alternatives.

"The hallmark of chronic obstructive pulmonary disease (COPD) is the occurrence of expiratory flow limitation (EFL) at higher lung volumes during a forced expiratory manoeuvre compared with healthy subjects,"[1] the authors wrote. "In some patients with COPD, EFL is present during tidal breathing, a condition known as tidal EFL that restricts the ability of patients to consistently achieve their relaxed end-expiratory lung volume (EELV), even at rest.[2,3] This process is a major determinant of dynamic hyperinflation and exercise limitation.[4] As the occurrence of EFL during tidal breathing may be a better indicator of dyspnoea than spirometric measurements,[5] it can be considered a clinically relevant measurement in the diagnosis and staging of COPD.[6] In the past, the measurement of tidal EFL was challenging because it was invasive, time consuming, technically demanding, difficult to standardise because of variations in previous lung volume history, and required bulky equipment and post-test analysis.[7,8] This meant that the functional assessment of COPD in clinical practice has been largely restricted to spirometry. The gold-standard method for detecting tidal EFL requires the use of an invasive oesophageal balloon, however several alternative non-invasive methods have now been proposed to measure tidal EFL, including abdominal compression, negative expiratory pressure (NEP) and the forced oscillation technique (FOT)."[9]

What is tidal expiratory flow limitation?

Tidal EFL in COPD arises because of the combined effects of reduced elastic lung recoil and increased airway resistance due to small airway inflammation, which causes a reduction in the luminal cross-sectional area.[10,11] This, in turn, according to the authors, results in gas trapping on expiration[10,12] and lung hyperinflation, a key mechanistic consequence of tidal EFL.[2]

"In healthy subjects, EELV and inspiratory capacity (IC) are maintained throughout exercise,[2]" they wrote. "Any changes that occur in EELV as a result of obstructive lung disease are reflected by changes in IC, as total lung capacity (TLC [EELV+IC]) remains unchanged during exercise.[2] In COPD, dynamic hyperinflation is the temporary and variable increase in EELV above its baseline value, which is aggravated further as expiratory time shortens, eg, during exercise, resulting in further increases in EELV.[2] Dynamic hyperinflation has been shown to be strongly associated with EFL during exhalation,[10] which in

mild COPD usually occurs during exercise.[13] However, as the condition worsens EFL and dynamic hyperinflation can also be present at rest.[13] EFL contributes independently to symptoms during COPD exacerbations (when compared to patients without EFL),[14] the most distressing of which is dyspnoea (breathlessness).[15] Patients with COPD have described dyspnoea as an unsatisfied inspiratory effort (ie, they can't get enough air in), having inspiratory difficulty or experiencing shallow breathing."[2]

New School of Thinking

The authors said the symposium discussed how new, more non-invasive techniques, have been impeded.

"New ways to non-invasively measure expiratory flow limitation in chronic obstructive pulmonary disease assessment of small airway function in clinical practice has remained a challenge for many years and progress in this area has been impeded by technical limitations related to the small size of the airways and to their location deep within the thoracic cavity.16 Several methods have been proposed to detect tidal EFL in patients with COPD, including the invasive oesophageal balloon technique, non-invasive abdominal compression, NEP and FOT.9,17,18 The challenges with some of these methods include the impact of patient position on reproducibility, eg, seated or supine (abdominal compression),19 as well the subjective nature of the assessment (NEP), which has resulted in a reassessment of the utility of FOT.8

One technique that is gaining recognition, is based on a technology that was actually firstly proposed more than 60 years ago, the authors wrote.

"DuBois et al. first introduced FOT in 1956,[20] but it is only now gaining clinical recognition. It is an objective measure that does not require the performance of respiratory manoeuvres and offers a simple, detailed and repeatable approach to investigating the mechanical properties of the respiratory system.[8,21,22] It has also been shown to be as sensitive as spirometry in detecting impairments of lung function.[22] FOT is performed at higher frequencies than regular breathing (typically between 5–25 Hz).[23,24] Reactance at 5 Hz during the expiratory phase (using the inspiratory reactance as a baseline) appears to be particularly sensitive to EFL, and this has been used in an effort to assess small airway function in patients with COPD.[25,26]

"FOT can identify EFL when a large difference in within-breath inspiratory and expiratory reactance occurs due to the development of choke points throughout the bronchial tree.[8,21] Measuring reactance over multiple breaths is preferable as it retrieves information from a longer time span than breath-by-breath measurements. As a result, aberrations in breathing pattern occurring within an individual breath are averaged over the entire measurement period, and so yield a more accurate measurement.[7] Higher values are common in patients with COPD even versus smoking controls, with high values tending to remain consistent over time.[7]"

The Importance of Assessing EFL

The authors said the symposium discussed why it's important to even assess EFL.

"The presence of EFL during a COPD exacerbation has potential clinical implications, such as signalling the presence of more severe physiological perturbations that are not detectable by spirometry,"[14] the report says. "However, EFL is often under-recognised in the clinical setting.[27] EFL in patients with COPD is associated with lower forced expiratory volume in 1 second (FEV1) and greater hyperinflation, as well as a significant correlation with worse health status, symptom score and burden of disease, as assessed by the St George's Respiratory Questionnaire.[10] Increased EFL index values at the time of hospital admission for a COPD exacerbation may signal more severe physiological perturbations not detectable by spirometry, since increased EFL has been shown to correlate with longer hospital stays.[14]

Benefits of Detection

The authors concluded their report by discussing how detecting tidal EFL can also "help to identify factors limiting exercise tolerance such as IC, as resting EFL clearly separates two populations of patients with significant differences in exercise tolerance.[28,29] Tidal EFL has been shown to correlate with the degree of breathlessness[7] and walking distance, and can be used to identify the subgroup of patients with COPD worse clinical outcomes.[30] It is also important to assess EFL in clinical practice, as a decrease in index values may relate to improvements in symptoms during recovery from an exacerbation.[14] Bronchodilators can improve dynamic airway function, allowing improved lung emptying with each breath, which is associated with improvements in dyspnoea as a result of increased IC and reduction in EELV.[2] A significant reduction of dynamic hyperinflation in patients with EFL at rest after bronchodilator administration supports the importance of categorising patients with COPD into subgroups with and without EFL, in order to predict response to bronchodilator therapy.[31,32]"

In conclusion, "identification or screening of EFL with FOT can also guide the use of continuous positive airway pressure or positive end expiratory pressure in mechanically ventilated patients with COPD, allowing targeting of the minimum pressure able to counteract the detrimental effects of intrinsic positive end expiratory pressure without unnecessarily affecting haemodynamics and/or impairing inspiratory muscle function by increasing operating volumes.[33]

"Overall, EFL could be useful for stratifying patients by the severity of their COPD or treatment responses.4 The recognition and monitoring of EFL before and after exacerbation could potentially be used to guide or titrate treatment, reduce the duration of hospital stays and improve clinical outcomes for patients with COPD."[30]

References

1 Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347–65.
2 O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3:180–4.
3 Hyatt RE. The interrelationships of pressure, flow, and volume during various respiratory manoeuvres in normal and emphysematous subjects. Am Rev Respir Dis. 1961;83:676–83.
4 Mikamo M, Shirai T, Mori K, et al. Predictors of expiratory flow limitation measured by forced oscillation technique in COPD. BMC Pulmonary Med. 2014;14:23.
5 Eltayara L, Becklake MR, Volta CA, et al. Relationship

between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1996;154:1726–34.
6 Gagnon P, Guenette JA, Langer D, et al. Pathogenesis of hyperinflation in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon. 2014:9:187–201.
7 Aarli BB, Calverley PMA, Jensen RL, et al. Variability of withinbreath reactance in COPD patients and its association with dyspnoea. Eur Respir J. 2015;45:625–34.
8 Dellacà RL, Duffy N, Pompilio PP, et al. Expiratory flow limitation detected by forced oscillation and negative expiratory pressure. Eur Respir J. 2007;29:363–74.
9 Baydur A. Expiratory flow limitation in intra and extrathoracic respiratory disorders: use of the negative expiratory pressure technique – review and recent developments. In: Oncogenesis inflammatory and parasitic tropical diseases of the lung. Chapter 6. Jean-Marie Kayembe (ed), InTech, 2013; DOI: 10.5772/53270.
10 Dean J, Kolsum U, Hitchen P, et al. Clinical characteristics of COPD patients with tidal expiratory flow limitation. Int J Chron Obstruct Pulmon Dis. 2017;12:1503–6.
11 Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:2645–53.
12 Thomas M, Decramer M, O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. Prim Care Respir J. 2013;22:101–11.
13 O'Donnell D, Revill S, Webb K. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:770–7.
14 Jetmalani K, Timmins S, Brown NJ, et al. Expiratory flow limitation relates to symptoms during COPD exacerbations requiring hospital admission. Int J Chron Obstruct Pulmon Dis. 2015;10:939–45.
15 O'Donnell DE, Elbehairy AF, Faisal A, et al. Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing. Eur Respir Rev. 2016;25:333–47.
16 Brusasco V, Barisione G, Crimi E. Pulmonary physiology: future directions for lung function testing in COPD. Respirology. 2015;20:209–18.
17 Koulouris N, Valta P, Lavoie A, et al. A simple method to detect expiratory flow limitation during spontaneous breathing. Eur Respir J. 1995;8:306–13.
18 Tantucci C. Expiratory flow limitation definition, mechanisms, methods, and significance. Pulm Med. 2013;2013:749860.
19 Ninane V, Leduc D, Kafi SA, et al. Detection of expiratory flow limitation by manual compression of the abdominal wall. Am J Respir Crit Care Med. 2001;163:1326–30.
20 DuBois AB, Brody AW, Lewis DH, Burgess BF Jr. Oscillation mechanics of lungs and chest in man. J Appl Physiol. 1956;8:587–94.
21 Dellacà RL, Santus P, Aliverti A, et al. Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J. 2004;23:232–40.
22 Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003;22:1026–41.
23 Verbanck S. Physiological measurement of the small airways. Respiration. 2012;84:177–88.
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Did You Prescribe a Wrench to Turn a Screw? The Role of Inhaler Technique in Respiratory Disease Management

Mike Hess, BS, RRT, RPFT

Adherence to medication regimens is a well-known, well-documented issue in chronic lung disease care. The reasons for this are many; from an inability to afford prescribed medications, to formulary-related barriers, to ineffective patient education on devices and dose schedules. For example, a recent cross-sectional study of nearly 3,000 European patients with COPD found over half were unable to use their devices correctly, despite having been previously educated on proper usage.[1] The issue appears at a similar rate in the asthma population,[2] highlighting the need for better education. However, even when patients are able to perfectly execute the steps involved with priming, loading, and actuating their inhalers, clinicians often fail to consider their patients' inspiratory flow characteristics when assessing technique. This omission can mask the true cause of treatment plan nonadherence, and prevents clinicians from providing effective alternatives.

Fortunately, there are multiple, easy-to-implement strategies available to evaluate virtually all aspects of inhaler device use. The InCheck DIAL (Clement Clarke International) is a reusable inspiratory flow meter that can simulate the internal resistance of various dry-powder devices on the market. The clinician sets the resistance range appropriate to the patient's device and instructs the patient to inhale maximally on a disposable mouthpiece. The resulting measurement can be used to determine if the patient is physically able to generate sufficient inspiratory flow to disaggregate the powder bolus into respirable particles. Use of the InCheck DIAL provides clinicians with customized, patient-specific data that allows for more informed clinical decision-making without adding significant time to encounters, and empowers clinicians to spend their patient education time focusing on the particular mechanics of each device, decreasing the likelihood of preparation and actuation errors.

The InCheck DIAL is also capable of measuring inspiratory flow without resistance, simulating usage of metered-dose and soft-mist inhalers (MDIs and SMIs). However, as these devices are not breath-actuated, evaluation of inspiratory characteristics alone is not sufficient to assure competency. In the case of the SMI (Respimat) device, demonstration with teach-back remains the best available solution. Clinicians should be careful to observe the patient through the entire process beginning with loading the medication cartridge, in order to determine whether the patient has the dexterity to prepare and prime the inhaler. Patients should also be observed during the inhalation phase to detect coughing or other inadvertent exhalation that reduces airway deposition.

MDIs are arguably the most difficult inhaler devices to use appropriately. Research data has consistently demonstrated the majority of MDI users experience at least one error while using their devices, with as many as 76% experiencing a critical error that affects the delivery of their medication.[3] Some of this data is decades old, indicating the exceedingly difficult nature of accurately identifying patients struggling with technique and appropriately addressing their deficiencies. The Aerosol Inhalation Monitor (Vitalograph) represents a novel, comprehensive solution to this problem. This electronic device uses a disposable MDI simulator to accurately evaluate the four major phases of MDI administration (coordination, inspiratory flow rate, inspiratory time, and breath hold). Evaluation is initiated by the patient when they 'puff' the sterile water canister of the simulator. Their inspiratory flow is sensed via pressure tubing between the simulator and the AIM unit, and visual feedback is provided in real time. When the unit detects cessation of flow, a breath hold timer starts, again providing live visual and audio feedback to help clinicians and patients time the breath hold. When the clinician observes the patient exhale, they press a button stopping the timer; the device then displays color-coded indicators (as well as variable audio tones) on an anatomical graphic of the airways, summarizing the inhalation maneuver and highlighting areas that require retraining. The process is fully automated until the end of the inspiratory hold, reducing the likelihood of operator error, and the localized feedback allows clinicians to again provide efficient, targeted education to optimize technique. AIM also comes with a DPI simulator for those who require an all-in-one solution.

At Western Michigan University Homer Stryker M.D. School of Medicine, both the AIM and InCheck DIAL are routinely utilized to ensure patients are not only *knowledgeable* about their medications, but *able* to use them properly. As the majority of our patients use at least one non-powder device, the AIM in particular has led to significant quality improvements in our practice. The integration of a dedicated respiratory therapist serving as patient educator and inhaler education tools in our practice has allowed us to markedly improve our education practices and customize our patient disease management regimens to more accurately reflect our patients' respiratory

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status. This has led to significant improvements in our COPD population's quality of life, as measured by the COPD Assessment Test (CAT), as presented in 2017 at COPD10usa.[4]

Unlike medications administered via other routes, the effectiveness of inhaled medications depends heavily on an individual's technique and abilities. Unfortunately, despite expert opinion and evidence-based practice recommendations, evaluation of inhaler technique and inspiratory flow characteristics remains overlooked and incomplete in most patients. This leads directly to increased healthcare costs, increased symptom severity and instability, and lower quality of life. This is unfortunate, considering the availability and comparatively low cost of devices such as the Aerosol Inhalation Monitor, which provide rapid, comprehensive feedback that empowers clinicians to improve personalized disease management strategies. These devices should be considered just as indispensable as otoscopes and blood pressure cuffs, and should be come just as ubiquitous in primary care and pulmonology practices alike. Patients with respiratory compromise deserve nothing less.

References

1. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J*. 2017;49(2):1601794. doi:10.1183/13993003.01794-2016.
2. Price D, Bosnic-Anticevich S, Briggs A, et al. Inhaler competence in asthma: Common errors, barriers to use and recommended solutions. *Respir Med*. 2013;107(1):37-46. doi:10.1016/J.RMED.2012.09.017.
3. Scichilone N. Asthma Control: The Right Inhaler for the Right Patient. *Adv Ther*. 2015;32(4):285-292. doi:10.1007/s12325-015-0201-9.
4. Yawn BP, Thomashow B. Abstract Presentations: COPD10usa 2017. *Chronic Obstr Pulm Dis J COPD Found*. 2017;4(4):305-319. doi:10.15326/jcopdf.4.4.2017.0162.

Severe Trauma Patient Responds Positively to Airway Pressure Release Ventilation (APRV) and Avoids Significant Complications

Ron Pasewald, BS-RRT, RRT-ACCS

The patient was a 44-year-old female admitted to the trauma ER after a T-bone motor vehicle accident. She required prolonged extrication with the Jaws of Life to free her from the vehicle. Her initial vital signs were Glasgow Coma Scale (GCS) 6, heart rate (HR) 136, blood pressure (BP) 75/40. Intubation was attempted twice in the field, both times unsuccessfully.

The patient was stabilized in the trauma ER with rapid sequence induction, Etomidate (0.2 mg/kg), Succinylcholine (1mg/kg), 2 liters of normal saline, and 4 units of packed red blood cells via mass transfusion protocol. She was also given a bedside abdominal ultrasound and a chest X-ray, which showed bilateral pneumothoraxes. The patient was prepped and bilateral 32 French chest tubes were inserted. She was immediately taken for a CT scan of her head, chest, and abdomen.

Upon secondary evaluation, the following injuries were found:

- Aortic pseudo-aneurysm and mediastinal hematoma
- Grade 5 liver, grade 3 splenic, grade 2 right kidney lacerations
- Adrenal hematoma
- Bilateral rib and sternal fracture
- Trace subarachnoid hemorrhage. (No Neuro intervention needed)
- Right nondisplaced occipital condyle fracture
- Right maxillary frontal process fracture
- Right scalp hematoma

The patient was immediately transported to the OR for abdominal exploration and repair of life-threatening injuries, which included repair and stenting of a descending thoracic aorta. Following the emergent surgery, the patient was transferred to the Surgical Intensive Care Unit (ICU) for post-operative treatment. Upon arrival into the ICU, the patient was found to be in respiratory failure, and had hypoxemia and lactic acidosis.

The Post-Surgical ICU report included the following:

Vital signs: HR 114 bpm, BP 100/50 (mAP 62 mmHg), RR 18/min, SpO_2 92%, RASS score -2
Vent settings: AC 18/420/+5/60% (8cc/kg)
Right subclavian venous access
Bilateral 32 French chest tubes
Right arterial line and 2 peripheral venous lines
IV medications: Norepinephrine 0.3 mcg/kg/min, Propofol 20 mcg/kg/min, Fentanyl 1 mcg/kg/min and 1 liter normal saline running wide open. Pt received a total of 8 units packed red blood cells, 2 units platelets, and 6 liters normal saline since admission (<12 hours).

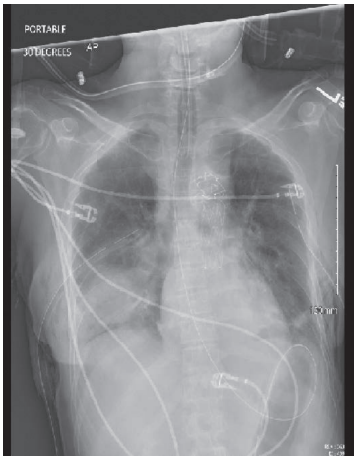
Initial Vent Settings:

AC/VC RR 18, VT 420, PEEP +8 cmH_2O, FiO_2 60%, $EtCO_2$ 54; PIP 32, PLT 28, CL 18 cc/cmH_2O, Raw 5 $cmH_2O/L/sec$ & driving pressure of 20 cmH_2O.

Initial arterial blood gas:

pH 7.24
$PaCO_2$ 59
PO_2 61
HCO_3 21
O_2 SAT 91.1
$EtCO_2$ 40
Vd/Vt = .32
PaO_2/FiO_2 ratio = 100

Upon ICU admission, the patient's chest X-ray showed the endotracheal tube 2 cm above the carina; the bilateral 32 French chest tubes were in proper position. In addition, she showed bilateral atelectasis, including a large right lower lobe (RLL) infiltrate. The RLL etiology was an infiltrate vs. atelectasis vs. pulmonary contusion.



Following an arterial blood gas (ABG) analysis, chest X-ray, and ventilator observations, the mode of ventilation was immediately

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changed to Airway Pressure Release Ventilation (APRV) with the following settings:

P High 30 cmH_2O
P Low 0 cmH_2O
T High 5.0 seconds
T Low (Auto release set @ 75%. ~.50 seconds)
FiO_2 reduced from 60% to 40% within
10 minutes of mode change

On observation, the PEF was -60 lpm. Expiratory flow was terminated @ 75% using the Auto release feature. This resulted in a termination of expiratory flow at the -45 lpm mark. This calculated the T-LOW to approximately .50 seconds. Expiratory maneuver performed, with a resultant "Auto PEEP" of 16 cmH_2O measured. Driving pressure was calculated at 14 cmH_2O. There was no spontaneous breathing effort witnessed and released tidal volumes were noted to be 400-450 cc. RR 10 releases/ minute. MVe 4.5-5.0 lpm.

Subsequent Arterial Blood Gas Analysis Reports

ABG results 2 hours post APRV (FiO_2 .40)

pH 7.39	$EtCO_2$ 38
$PaCO_2$ 50	Vd/Vt = .24
PaO_2 69	PaO_2/FiO_2 ratio = 172
HCO_3 26	Release volumes 450-500 cc
O_2 SAT 94.7	

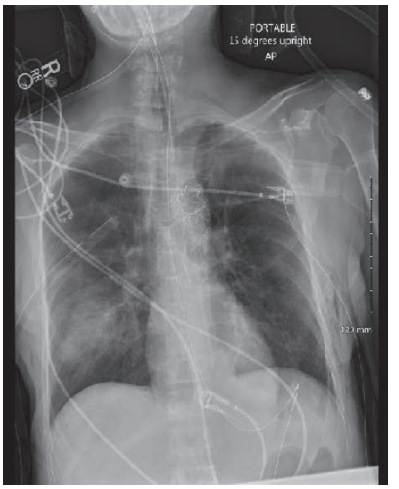
ABG results 6 hours post APRV (FiO_2 .40)

pH 7.40	$EtCO_2$ 30
$PaCO_2$ 40	Vd/Vt = .25
PaO_2 80	PaO_2/FiO_2 ratio = 200
HCO_3 24	Release volumes 450-500
O_2 SAT 96.6	

Results 12 hours post APRV (FiO_2 .40)

pH 7.34	$EtCO_2$ 30
$PaCO_2$ 40	Vd/Vt = .25
PaO_2 148	PaO_2/FiO_2 Ratio = 370
HCO_3 21	Release volumes 500-550 cc
O_2 SAT 99.0	Spontaneous volumes 200-300 cc

A follow-up chest X-ray was taken 12 hours after the patient was admitted to the ICU and 12 hours after the change to Airway Pressure Release Ventilation.



With marked improvement in the chest X-ray and ABG results, the patient's sedation was weaned for a neurological examination, in which the GCS score was noted to be 10. The patient was able to follow verbal commands and moved all extremities; no head lift was performed due to cervical precautions.

Once the patient was alert and making spontaneous breathing efforts, her mean BP rose greater than 75, which allowed her to be weaned off the Norepinephrine within 1 hour. The Fentanyl infusion was reduced to 0.25 mcg/kg/ min for pain control.

Throughout the shift, the release volumes on APRV continued to climb, representing increased lung volumes. The Vd/ Vt ratio also improved, representing improved efficiency in alveolar ventilation. The chest X-ray confirmed these bedside assessments.

Efforts to start weaning the patient from the ventilator began by adjusting the T-High setting to 6.5 seconds to facilitate spontaneous efforts. By stretching the T-High setting to 6.5 seconds, the patient augmented approximately 30-40% of the MVe. At this point, the APRV settings were:

P High 30
P Low 0
T High 6.5
T Low (Auto release set @ 75%. ~.60 seconds)
FiO_2 30%

The patient was weaned off APRV via the "drop and stretch" method. The P-High setting was lowered 4 cmH_2O every 2-3 hours and the T-High setting was extended out by one additional second with each P-High change. Weaning was continued to the following settings, where it was then decided to extubate the patient:

P High 10 cmH_2O
P Low 0
T High 10 seconds
T Low (Auto release set @ 75%. ~.60 seconds)
FiO_2 30%

The patient's total time on mechanical ventilation utilizing APRV was approximately 24 hours in total.

After a successful extubation and 12-hour period of observation in the ICU, the patient was transferred to the general rehabilitation ward for strength and conditioning training. Following a period of 10 days on the general floor, the patient was transferred to rehabilitation and was then transferred home two weeks later.

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24 Dellacà R, Kaczka DW. Oscillation mechanics of the respiratory system: applications to lung disease. Crit Rev Biomed Eng. 2011;39:337–59.
25 Kanda S, Fujimoto K, Komatsu Y, et al. Evaluation of respiratory impedance in asthma and COPD by an impulse oscillation system. Intern Med. 2010;49:23–30.
26 Paredi P, Goldman M, Alamen A, et al. Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. Thorax. 2010;65:263–7.
27 Junhasavasdikul D, Telias I, Grieco DL, et al. Expiratory flow limitation during mechanical ventilation. Chest. 2018; DOI: 10.1016/j.chest.2018.01.046 [Epub ahead of print].
28 Diaz O, Villafranca C, Ghezzo H, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J. 2000;16:269–75.
29 Koulouris NG, Kaltsakas G, Palamidas AF, Gennimata SA. Methods for assessing expiratory flow limitation during tidal breathing in COPD patients. Pulm Med. 2012;2012:234145.
30 Aarli BB, Calverley PMA, Jensen RL, et al. The association of tidal EFL with exercise performance, exacerbations, and death in COPD. Int J Chron Obstruct Pulmon. 2017;12:2179–88.
31 Tantucci C, Duguet A, Similowski T, et al. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. Eur Respir J. 1998;12:799–804.
32 Dellacà RL, Pompilio PP, Walker PP, et al. Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. Eur Respir J. 2009;33:1329–37.
33 Dellacà RL, Rotger M, Aliverti A, et al. Noninvasive detection of expiratory flow limitation in COP

Significant Predictors of Medically Diagnosed Chronic Obstructive Pulmonary Disease in Patients with Preserved Ratio Impaired Spirometry: a 3-Year Cohort Study

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Abstract

Background: Preserved ratio impaired spirometry (PRISm) is an incompletely understood respiratory condition. We investigated the incidence and significant predictive factors of chronic obstructive pulmonary disease (COPD) in PRISm patients.

Methods: From 11,922 subjects registered in the Korea National Health and Nutrition Examination Survey, never or light smokers, young subjects, and those already medically diagnosed with COPD (defined by ICD-10 code and prescribed medication) were excluded. The 2666 remaining subjects were categorized into PRISm (normal forced expiratory volume in the first second [FEV_1]/force vital capacity [FVC] [≥ 0.7] and low FEV_1 (< 80%); n = 313); normal (n = 1666); and unrevealed COPD groups (FEV_1/FVC ratio < 0.7; n = 687). These groups were compared using matched Health Insurance Review and Assessment Service data over a 3-year follow-up.

Results: COPD incidence in PRISm patients (17/1000 person-year [PY]) was higher than that in normal subjects (4.3/1000 PY; P < 0.001), but lower than that in unrevealed COPD patients (45/1000 PY; P < 0.001). PRISm patients visited hospitals, took COPD medication, and incurred hospitalization costs more frequently than normal subjects, but less frequently than unrevealed COPD patients. In the overall sample, age, FVC, FEV_1, dyspnea, and wheezing were significant predictors of COPD, but in PRISm patients, only age (OR, 1.14; P = 0.002) and wheezing (OR, 4.56; P = 0.04) were significant predictors.

Conclusion: PRISm patients are likely to develop COPD, and should be monitored carefully, especially older patients and those with wheezing, regardless of lung function.

Keywords: Chronic obstructive pulmonary disorder, Prognosis, Spirometry

Background

Despite the escalating prevalence and economic burden of chronic obstructive pulmonary disease (COPD), many COPD cases remain undiagnosed worldwide [1-3]. A lack of awareness of COPD, lack of educational programs concerning COPD, poor physician adherence to guidelines, and low usage of pulmonary function tests leads to under-diagnosis of COPD [4,5]. Many studies have reported that patients with early COPD or even pre-COPD (e.g., smokers or subjects with impaired lung function) have respiratory symptoms and utilize medical support [6,7]. This has emphasized early-diagnosis and early-treatment of COPD. However, subjects with preserved ratio impaired spirometry (PRISm) are often missed. PRISm patients do not meet COPD criteria [8], with a preserved ratio of force expiratory volume in the first second [FEV_1]/forced vital capacity [FVC] (> 0.7), but have reduced FEV_1 (< 80%, predicted), yet exhibit increased respiratory symptoms, decreased activity, increased comorbidity, and increased mortality [7, 9-14]. Wan et al. described PRISm as a COPD subtype with increased emphysema and gas trapping [15]. Lung density on computed tomography is significantly associated with lung function in PRISm [16]. Thus, some aspects of PRISm are associated with COPD development with worsening of lung function; but the COPD incidence in PRISm patients has rarely been reported.

Tobacco smoking, ageing, air pollution, poor nutritional status, impaired lung function, and underlying asthma are established risk factors for COPD [17,18]. However, the risk factors associated with COPD in PRISm remain unknown. We sought to elucidate the incidence of COPD in PRISm patients and to identify the significant risk factors for COPD in PRISm, using Korean national cohort data.

Methods

Subjects and study design

We used the cross-sectional the Korea National Health and Nutrition Examination Survey (KNHANES) data of 2007–2009 and KNHANES-matched Health Insurance Review and Assessment (HIRA) cohort data of 2006–2012. A total of 11,922 subjects were available in KNHANES. Among them, never- or light-smokers (< 10 pack-years), young subjects (< 40 years), and patients already medically diagnosed with COPD (based on the ICD-10 code and prescribed medication in HIRA), were excluded (n = 9256). We categorized the remaining 2666 subjects into 3 groups based on spirometry (Fig. 1). The normal group (n = 1666) had a normal FEV_1/FVC ratio (≥ 0.7) and normal spirometry (FEV_1 ≥ 80% predicted). PRISm subjects (n = 313) had a normal FEV_1/FVC ratio (≥ 0.7) and decreased lung function (FEV_1 < 80% predicted). Unrevealed COPD subjects had a decreased FEV_1/FVC ratio (< 0.7), regardless of FEV_1 and FVC. KNHANES data did not include post-bronchodilator FEV_1 and FVC, which are

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recommended in the guidelines [8, 19]; we therefore used pre-bronchodilator FEV_1 and FVC values.

KNHANES and HIRA data

KNHANES data were derived from a national large-scale cross-sectional survey conducted by the Korean government, via the Korea Centers for Disease Control and Prevention. This data were obtained from a well-designed national program with complex, multistage probability sample extraction to reflect the total population of Korea. KNHANES data include age, sex, height, weight, self-reported smoking history, self-reported co-morbidity (answers to the following questions: do you have [the disease, e.g., asthma] diagnosed by a doctor?), results of spirometry tests obtained using Korean classic guidelines [20], and self-reported respiratory symptoms (answers to the following questions: do you have [symptom, e.g., cough for 3 months]?). We enrolled subjects based on age, smoking history (in pack-years, PY), and lung function in the KNHANES data. Other baseline characteristics were also obtained from the KNHANES data.

Subjects enrolled in the KNHANES database have KNHANES-matched HIRA data. HIRA data were obtained from claims from the national health insurance system, which uniquely covers virtually all residents in Korea. It contains the diagnostic code, medical utilization (including hospital admission history and prescribed medication), and costs for several years [21].

Parameter definition

Contrary to the established spirometry-based diagnostic criterion for COPD (FEV_1/FVC < 0.7), "medically diagnosed COPD" was defined by diagnostic code and prescribed medication [22, 23]. Medically diagnosed COPD patients met all of the following criteria: 1) age ≥ 40 years; 2) ICD-10 codes for COPD or emphysema (J43.0×-J44.x, with the exception of J43.0 as primary or secondary [within fourth position] diagnosis); and 3) the use of more than 1 of the following COPD medications at least twice per year: long-acting muscarinic antagonist, long-acting beta-2 agonist (LABA), fixed-dose inhaled corticosteroid with LABA, short-acting muscarinic antagonist (SAMA), short-acting beta-2 agonist (SABA), SAMA with SABA, phosphodiest erase-4 (PDE-4) inhibitor, systemic beta agonist, or methylxanthine.

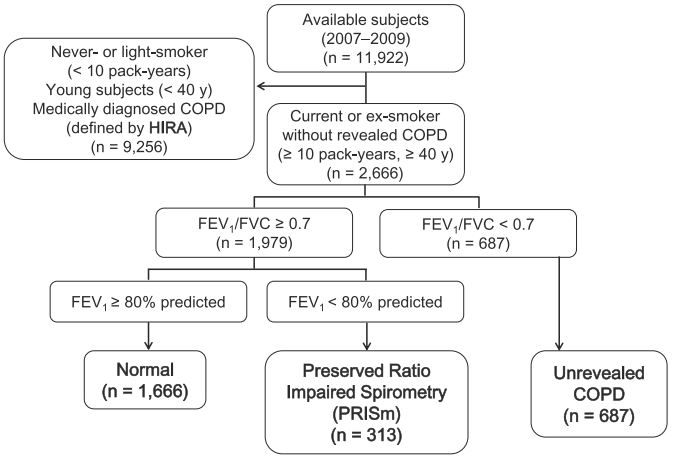

Fig. 1 Subject selection and group assignment based on the KNHANES and HIRA data. KNHANES, Korea National Health and Nutrition Examination Survey; HIRA, Health Insurance Review & Assessment; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume for 1 s; FVC, forced vital capacity

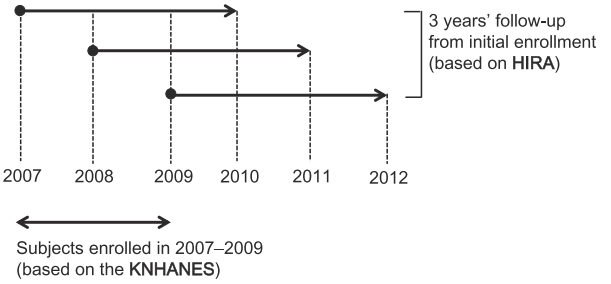

Fig. 2 Scheme of study and summary of data presentation. KNHANES, Korea National Health and Nutrition Examination Survey; HIRA, Health Insurance Review & Assessment

Hospitalization cost was defined as any medical utilization costs for inpatient services, confined to admissions with an ICD-10 code for COPD (J43.x–J44.x, except J430) or COPD-related diseases (pneumonia: J12.x–J17.x; pulmonary thromboembolism: I26, I26.0, and I26.9; dyspnea: R06.0; or acute respiratory distress syndrome: J80). Costs were presented in US dollar (USD), using an exchange rate of 1 USD = 1090 Korean Won (exchange rate as on February 9, 2018).

Chronic bronchitis was defined as self-reported chronic cough or sputum persisting for at least 3 months, in at least 2 consecutive years.

Outcomes

We analyzed the 3-year follow-up outcomes from HIRA data (Fig. 2). The incidence of medically diagnosed COPD was the primary outcome. Hospital visits, number and type of prescribed medication, and hospitalization cost were secondary outcomes. Furthermore, we sought to identify significant factors that predicted a COPD diagnosis by group.

Ethics

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (number: 3–2017-0395). The requirement for obtaining informed consent from the patients was waived due to the retrospective nature of this study.

Statistical analyses

We compared the baseline characteristics, COPD incidence, hospital visits, medication use, and hospitalization cost between groups using χ^2 tests (categorized variables) and analysis of variance with Bonferroni post-hoc test (continuous variables). Univariate and multivariate logistic regression analyses were conducted to identify factors that predicted COPD diagnosis. In multivariate analysis, only factors found significant in univariate analysis were included as co-variables. FEV_1/FVC was not used in multivariate analysis, because of increased multicollinearity (variance inflation factor = 23.81). $P < 0.05$ was considered to indicate statistical significance.

Results

Demographics of subjects by group

Unrevealed COPD subjects (64.48 ± 9.54 years) were significantly older than subjects in the normal (54.57 ± 10.52 years; $P < 0.001$) and PRISm (55.97 ± 10.85 years; $P < 0.001$) groups. Most subjects were men, and the sex distribution was similar among groups. Height and weight were less in the unrevealed COPD than in the normal and PRISm subjects. Smoking PY was heavier in the unrevealed COPD group than in the normal and PRISm groups. However, PRISm subjects were more often current-smokers

(61.7%) than were normal (51.5%; P = 0.003) and unrevealed COPD (53.4%; P = 0.045) subjects. Hyperlipidemia was less common in the unrevealed COPD (6.8%) than in the normal group (10.0%; P = 0.048). Acute coronary syndrome was more common in the unrevealed COPD (2.3%) than in the normal (1.0%; P = 0.042) group. Diabetes mellitus was significantly more prevalent in PRISm (20.1%) than in normal (10.4%; P < 0.001) and unrevealed COPD (12.2%; P = 0.003) subjects. Pulmonary tuberculosis and asthma was particularly prevalent in the unrevealed COPD group (Table 1).

FVC was significantly lower in the PRISm (72.55 ± 9.45%) than in the normal (92.96 ± 10.02%; P < 0.001) and unrevealed COPD (88.51 ± 15.02%; P < 0.001) groups. FEV_1 followed a similar pattern. However, the FEV_1/FVC ratio was significantly lower in the unrevealed COPD (0.61 ± 0.09) than in the normal (0.79 ± 0.05, P < 0.001) and PRISm (0.77 ± 0.06, P = 0.035) groups. Wheezing was more prevalent in PRISm (11.8%) patients than in normal subjects (7.0%; P = 0.009), but less prevalent than in the unrevealed COPD group (22.4%, P < 0.001). Other respiratory symptoms followed a similar pattern (Table 1).

COPD incidence, medication and hospital utilization, and cost

The COPD incidence in PRISm subjects (17.0/1000 person year [PY]) was significantly higher than that in normal subjects (4.4/1000 PY; P < 0.001); however, that in unrevealed COPD individuals (45.1/1000 PY) was significantly higher than that in PRISm individuals (P < 0.001). The PRISm group (13.1%) significantly more often visited the hospital than the normal group (7.3%; P = 0.002), but less often than the unrevealed COPD group (24.6%; P < 0.001). The type and number of prescribed medications followed a similar pattern. Hospitalization cost in the PRISm group (398.61 ± 1975.51 USD) was almost double that in the normal group (186.17 ± 1411.24 USD; P = 0.297); however, that in the unrevealed COPD group (750.71 ± 3216.02 USD; P = 0.041) was larger than that in the PRISm group (Table 2).

Comparison of baseline characteristics, medical utilization, and costs between subjects with and without medically diagnosed COPD

Among the 2666 subjects, 131 patients (4.9%) were medically diagnosed with COPD during the 3 years' follow-up. Subjects with medically diagnosed COPD were older and shorter, weighed less, had a heavier smoking history, and more often had a history of pulmonary tuberculosis and asthma than the remaining patients. Although data are not shown, other co-morbidity was not significantly different between groups. Subjects with medically diagnosed COPD had more markedly impaired lung function and severe symptoms than subjects without medically diagnosed COPD. They also more frequently visited hospitals, more frequently used COPD medication, and had greater hospitalization cost than subjects without medically diagnosed COPD (Table 3).

Table 1 Demographics of subjects according to the group

	Normal	PRISm	Unrevealed COPD	*P*-value	*P*-value*	*P*-value+	*P*-value‡
Age	54.57 ± 10.52	55.97 ± 10.85	64.48 ± 9.54	< 0.001	0.083	< 0.001	< 0.001
Male, *n* (%)	1560 (93.6)	286 (91.4)	654 (95.2)	0.063	0.426	0.432	0.054
Height (cm)	167.14 ± 6.94	166.79 ± 6.94	165.97 ± 6.56	< 0.001	0.998	<.0.001	0.236
Weight (kg)	68.29 ± 9.91	68.66 ± 11.6	63.7 ± 9.8	< 0.001	0.998	< 0.001	< 0.001
Smoking history							
Current smoking, *n* (%)	858 (51.5)	193 (61.7)	367 (53.4)	0.004	0.003	0.999	0.045
Pack-years	28.62 ± 17.11	33.20 ± 20.34	36.58 ± 21.14	< 0.001	< 0.001	< 0.001	0.026
Co-morbidity, *n* (%)							
Hypertension	453 (27.2)	91 (29.1)	209 (30.4)	0.269	0.998	0.336	0.999
Hyperlipidemia	166 (10.0)	34 (10.9)	47 (6.8)	0.035	0.998	0.048	0.092
Stroke	48 (2.9)	14 (4.5)	18 (2.6)	0.252	0.414	0.999	0.368
Acute coronary syndrome	17 (1.0)	8 (2.6)	16 (2.3)	0.019	0.077	0.042	0.999
Diabetes mellitus	174 (10.4)	63 (20.1)	84 (12.2)	< 0.001	< 0.001	0.624	0.003
Pulmonary tuberculosis	124 (7.4)	21 (6.7)	109 (15.9)	< 0.001	0.999	< 0.001	< 0.001
Asthma	20 (1.2)	15 (4.8)	65 (9.5)	< 0.001	< 0.001	< 0.001	0.024
Lung function test							
FVC % predicted	92.96 ± 10.02	72.55 ± 9.45	88.51 ± 15.02	< 0.001	< 0.001	< 0.001	< 0.001
FEV_1% predicted	94.66 ± 9.14	72.8 ± 6.72	74.18 ± 16.57	< 0.001	< 0.001	< 0.001	0.035
FEV_1/FVC	0.79 ± 0.05	0.77 ± 0.06	0.61 ± 0.09	< 0.001	< 0.001	< 0.001	0.006
Respiratory symptoms, *n* (%)							
Cough for more than 3 months	1 (0.1)	2 (0.6)	19 (2.8)	< 0.001	0.047	< 0.001	0.091
Sputum for more than 3 months	4 (0.2)	2 (0.6)	18 (2.6)	< 0.001	0.999	< 0.001	0.104
Dyspnea	10 (0.6)	3 (1.0)	31 (4.5)	< 0.001	0.999	< 0.001	0.012
Wheezing	116 (7.0)	37 (11.8)	154 (22.4)	< 0.001	0.009	< 0.001	< 0.001
Chronic bronchitis	4 (0.2)	2 (0.6)	21 (3.1)	< 0.001	0.717	< 0.001	0.054
Total	1666	313	687				

Data are presented as mean ± standard deviation or number (percentage)
* *P*-value for comparison between normal and PRISm group; + *P*-value for comparison between normal and unrevealed COPD group; ‡ *P*-value for comparison between PRISm and unrevealed COPD group
PRISm preserved ratio impaired spirometry, *COPD* chronic obstructive pulmonary disease, FEV_1 forced expiratory volume for 1 s, *FVC* forced vital capacity

Significant factors for COPD diagnosis in subjects overall

Multivariate analysis of all subjects showed that the possibility of COPD diagnosis was increased to 10.0% with every year's increase in age (odds ratio [OR], 1.10; 95% confidence interval [CI], 1.07–1.13; P < 0.001). A 1% increase in FVC and FEV_1 was significantly associated with a 3% increase and 5% decrease in COPD diagnosis, respectively (FVC [OR, 1.03; 95% CI, 1.01–1.05; P = 0.006] and predicted FEV_1 [OR, 0.95; 95% CI, 0.93–0.96; P < 0.001]). Dyspnea (OR, 3.73; 95% CI, 1.23–7.68; P = 0.017), and wheezing (OR, 2.90; 95%CI, 1.76–4.78; P < 0.001) were significant predictive factors of a COPD diagnosis (Table 4).

Comparison of baseline characteristics, medical utilization, and costs between PRISm patients with and without medically diagnosed COPD

Among the 316 subjects with PRISm, 16 patients were medically diagnosed with COPD during the 3-year follow-up period. Subjects with medically diagnosed COPD were older, shorter, weighed less, more often had asthma and decreased FVC, and more frequently had dyspnea and wheezing. Due to frequent hospital and medical utilization, their hospitalization cost was greater than that of subjects without medically diagnosed COPD (Table 5).

Significant factors for COPD diagnosis in PRISm

In multivariate analysis of subjects with PRISm, the possibility of COPD diagnosis was increased to 14.0% for every year that subjects aged (OR, 1.14; 95% CI, 1.05–1.24; P =0.002). Wheezing (OR, 4.56; 95% CI, 1.08–19.35; P =0.040) was a significant factor for a diagnosis of COPD in PRISm patients (Table 6).

Discussion

We investigated the incidence of COPD in PRISm patients and sought to identify significant risk factors of COPD in PRISm patients. We found that PRISm patients were 4 times more likely to receive a COPD diagnosis than a normal group. Sood et al. have also reported a high COPD incidence in PRISm patients (about double that in the normal population) [24]. We also showed that PRISm patients paid more hospital visits, used more prescribed COPD medications, and accounted for an increased economic burden. Despite not meeting COPD criteria, these patients require careful observation because of their risk for COPD development and concomitant medical utilization. PRISm occurs in about 6.6–17.6% of the general global population [15,25,26]; nevertheless, PRISm remains poorly understood. Many clinicians miss this "unclassified" or "non-specific" group, and discharge them without explanation, warning, or follow-up appointment. Detecting and treating these early-stage patients is requisite.

Some subjects with PRISm might have underlying restrictive lung disease. Significantly lower FVC (72.55 ± 9.45%) in PRISm patients than in normal (92.96 ± 10.02; P < 0.001) and unrevealed COPD (88.51 ± 15.02; P < 0.001) subjects supports this supposition. However, Wan et al. reported that a true restrictive pattern, defined by total lung capacity, was not frequently observed in PRISm [10]. This should be elucidated in further studies. Subjects in the PRISm group had a heavier smoking history, more severe respiratory symptoms and decreased lung function, and more frequent co-morbidity than the normal population; these differences were less marked when compared to the unrevealed COPD group. However, we found that the prevalence of current smoking in the PRISm group was higher than that in both the normal and unrevealed COPD groups. It may be that many current-smokers in the PRISm group did not experience respiratory symptoms, did not visit hospitals, and were not warned to stop smoking. Current-smokers in the PRISm group may develop COPD unless they stop smoking, as previously shown [24]. Doctors should check the smoking status in PRISm patients more carefully, and should strongly recommend that they stop smoking.

Although age, lung function, dyspnea, and wheezing are significant predictive factors of COPD in the subjects overall,

Table 2 COPD incidence, medication and hospital utilization, and cost

	Normal	PRISm	Unrevealed COPD	*P*-value	*P*-value*	*P*-value+	*P*-value‡
COPD incidence (/1000PY)	4.4	17.0	45.1	< 0.001	< 0.001	< 0.001	< 0.001
OPD visit, *n* (%)	51 (3.1)	22 (7.0)	131 (19.1)	< 0.001	0.002	< 0.001	< 0.001
No. of OPD visit	0.10 ± 0.91	0.48 ± 2.96	1.86 ± 6.37	< 0.001	0.243	< 0.001	< 0.001
Hospitalization, *n* (%)	79 (4.7)	29 (9.3)	83 (12.1)	< 0.001	0.004	< 0.001	0.571
ER visit, n (%)	23 (1.4)	12 (3.8)	36 (5.2)	< 0.001	0.008	< 0.001	0.999
ICU admission, n (%)	12 (0.7)	6 (1.9)	19 (2.8)	< 0.001	0.122	< 0.001	0.999
Total hospital visit, n (%)	121 (7.3)	41 (13.1)	169 (24.6)	< 0.001	0.002	< 0.001	< 0.001
ICS, n (%)	4 (0.2)	5 (1.6)	20 (2.9)	< 0.001	0.003	< 0.001	0.651
ICS + LABA, n (%)	2 (0.1)	11 (3.5)	50 (7.3)	< 0.001	< 0.001	< 0.001	0.063
LAMA, n (%)	–	4 (1.3)	44 (6.4)	–	–	–	< 0.001
SAMA, n (%)	12 (0.7)	12 (3.8)	36 (5.2)	< 0.001	< 0.001	< 0.001	0.999
SABA, n (%)	14 (0.8)	11 (3.5)	54 (7.9)	< 0.001	< 0.001	< 0.001	0.029
Systemic bronchodilator, n (%)	28 (1.7)	11 (3.5)	72 (10.5)	< 0.001	0.094	< 0.001	< 0.001
Methylxanthine, n (%)	33 (2.0)	17 (5.4)	101 (14.7)	< 0.001	0.001	< 0.001	< 0.001
Total prescribed medication, n (%)	57 (3.4)	26 (8.3)	127 (18.5)	< 0.001	< 0.001	< 0.001	< 0.001
Hospitalization medical Cost (for 3 years) (USD)	186.17 ± 1411.24	398.61 ± 1975.51	750.71 ± 3216.02	< 0.001	0.297	< 0.001	0.041

Data are presented as mean ± standard deviation or number (percentage)

* *P*-value for comparison between the normal and PRISm group; + *P*-value for comparison between normal and unrevealed COPD group; ‡ *P*-value for comparison between PRISm and unrevealed COPD group

PRISm preserved ratio impaired spirometry, *COPD* chronic obstructive pulmonary disease, *PY* person-year, *OPD* outpatient department, *ER* emergency room, *ICU* intensive care unit, *ICS* inhaled corticosteroid, *LABA* long-acting beta-2 agonist, *LAMA* long-acting muscarine antagonist, *SAMA* short-acting muscarine antagonist, *SABA* short-acting beta-2 agonist

Table 3 Comparison of baseline characteristics, medical utilization, and costs between subjects with and without medically diagnosed COPD

	Subjects with medically diagnosed COPD	Subjects without medically diagnosed COPD	*P*-value
Age	68.58 ± 7.77	56.70 ± 11.00	< 0.001
Male, n (%)	123 (93.9)	2377 (93.8)	0.954
Height (cm)	164.04 ± 6.25	166.94 ± 6.86	< 0.001
Weight (kg)	60.35 ± 9.89	67.5 ± 10.2	< 0.001
Smoking history			
Current smoking, n (%)	67 (51.2)	1351 (53.3)	0.631
Pack-years	41.1 ± 23.69	30.7 ± 18.52	< 0.001
Co-morbidity, n (%)			
Pulmonary tuberculosis	28 (21.4)	226 (8.9)	< 0.001
Asthma	3 (26.0)	66 (2.6)	< 0.001
Lung function test			
FVC % predicted	81.14 ± 15.77	89.85 ± 12.85	< 0.001
FEV_1% predicted	66.37 ± 19.36	87.87 ± 14.17	< 0.001
FEV_1/FVC	0.59 ± 0.16	0.75 ± 0.09	< 0.001
Respiratory symptoms, n (%)			
Cough for more than 3 months	14 (10.7)	8 (0.3)	< 0.001
Sputum for more than 3 months	11 (8.4)	13 (0.5)	< 0.001
Dyspnea	23 (17.6)	21 (0.8)	< 0.001
Wheezing	60 (45.8)	247 (9.7)	< 0.001
Chronic bronchitis	14 (10.7)	13 (0.5)	< 0.001
OPD visit, n (%)	116 (88.6)	88 (3.5)	< 0.001
No. of OPD visit	10.88 ± 11.77	0.07 ± 0.59	< 0.001
Hospitalization, n (%)	67 (51.2)	124 (4.9)	< 0.001
ER visit, n (%)	35 (26.7)	36 (1.4)	< 0.001
ICU admission, n (%)	17 (13.0)	20 (0.8)	< 0.001
Total hospital visit, n (%)	131 (100)	200 (7.9)	
ICS, n (%)	25 (19.1)	4 (0.2)	< 0.001
ICS + LABA, n (%)	54 (41.2)	9 (0.4)	< 0.001
LAMA, n (%)	42 (32.1)	6 (0.2)	< 0.001
SAMA, n (%)	44 (33.6)	16 (0.6)	< 0.001
SABA, n (%)	60 (45.8)	19 (0.8)	< 0.001
Systemic bronchodilator, n (%)	75 (57.3)	36 (1.4)	< 0.001
Methylxanthine, n (%)	110 (84.0)	41 (1.6)	< 0.001
Total prescribed medication, n (%)	131 (100.0)	79 (3.1)	–
Hospitalization medical Cost (for 3 years) (USD)	4041.23 ± 6633.39	166.17 ± 1286.46	< 0.001
Total	131	2535	

Data are presented as mean ± standard deviation or number (percentage)
COPD chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume for 1 s, *FVC* forced vital capacity, *OPD* outpatient department, *ER* emergency room, *ICU* intensive care unit, *ICS* inhaled corticosteroid, *LABA* long-acting beta-2 agonist, *LAMA* long-acting muscarine antagonist, *SAMA* short-acting muscarine antagonist, *SABA* short-acting beta-2 agonist

only age and wheezing were significant predictive factors for a COPD diagnosis in PRISm patients. Both age [27] and wheezing [28] are well-known predictive factors for COPD.

Lung function was not a significant predictive factor of COPD in PRISm. Low FEV_1 was a significant predictive factor of COPD overall, but not in PRISm patients specifically. The preserved ratio which is shown in PRISm means that these patients rarely have an extremely reduced FEV_1. In fact, Table 1 shows a relatively small standard deviation of FEV_1 in PRISm patients, as compared to other groups, although the number of subjects was small. It implies FEV_1 in PRISm has small predictive power for prognosis. Thus, it is necessary to monitor PRISm subjects carefully, even in the absence of severe reduced FEV_1.

Additionally, relatively preserved FVC was a significant predictive factor for COPD in the overall cohort using multivariate analysis, but not in PRISm patients. The reasons why preserved FVC is significant risk factor for COPD are as follows. Before adjustment, FVC in subjects with medically diagnosed COPD (81.14 ± 15.77%) was significantly lower than that in subjects without COPD (89.85 ± 12.85%; P < 0.001). We can easily assume that preserved FVC will be protective factor for COPD, however results were contrary to that in multivariate analysis with adjustment. This indicates that other associated co-variables affected the findings of FVC in multi-variate analysis. We speculated FEV_1 might be contributing factor for this confusing result. The decline in FEV_1 was much larger than that in FVC in Table 3, and FVC is unavoidably influenced by changes

Table 4 Significant factors for COPD diagnosis in all subjects

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)	**1.11**	**(1.09,1.13)**	**< 0.001**	**1.10**	**(1.07,1.13)**	**< 0.001**
Male	1.02	(0.49,2.13)	0.954			
Height (cm)	0.95	(0.92,0.97)	< 0.001	1.01	(0.97,1.05)	0.786
Weight (kg)	0.93	(0.91,0.95)	< 0.001	0.98	(0.95,1.01)	0.143
Smoking history						
Current smoking	0.92	(0.65,1.3)	0.631			
Pack-years	1.02	(1.01,1.03)	< 0.001	1.01	(1.00,1.02)	0.059
Co-morbidity						
Pulmonary tuberculosis	2.78	(1.79,4.31)	< 0.001	1.17	(0.66,2.10)	0.587
Asthma	13.11	(8.27,20.79)	< 0.001	1.88	(0.97,3.64)	0.060
Lung function test						
FVC % predicted	**0.95**	**(0.94,0.97)**	**< 0.001**	**1.03**	**(1.01,1.05)**	**0.006**
FEV_1% predicted	**0.93**	**(0.92,0.94)**	**< 0.001**	**0.95**	**(0.93,0.96)**	**< 0.001**
FEV_1/FVC	0.001	(0.001,0.001)	< 0.001			
Self-reported respiratory symptoms						
Cough for more than 3 months	37.80	(15.55,91.87)	< 0.001	2.40	(0.24,24.32)	0.458
Sputum for more than 3 months	17.78	(7.81,40.52)	< 0.001	0.48	(0.02,10.90)	0.647
Dyspnea	**25.49**	**(13.68,47.49)**	**< 0.001**	**3.07**	**(1.23,7.68)**	**0.017**
Wheezing	**7.83**	**(5.42,11.31)**	**< 0.001**	**2.90**	**(1.76,4.78)**	**< 0.001**
Chronic bronchitis	23.21	(10.67,50.5)	< 0.001	2.76	(0.07,109.05)	0.588

Statistically significant data are presented as bold
COPD chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume for 1 s, *FVC* forced vital capacity, *OR* odds ratio, *CI* confidence interval

in FEV_1. Therefore, we speculated that FEV_1, as a co-variable, might have affected the FVC findings in multivariate analysis with adjustment.

Unrevealed COPD implies a significantly impaired FEV_1/FVC ratio, meeting the standard COPD spirometry criteria for airway obstruction, but without a clinical diagnosis of COPD, no hospital visits, and no use of COPD medication to date. The number of subjects with unrevealed COPD was double that of the PRISm group in this study. Coultas et al. showed a similar proportion of undiagnosed COPD (79.7%) in the USA [3]. Chung et al. have shown that, in Korea, 97% of COPD cases are undiagnosed [2], or misdiagnosed [29]; their diagnosis and treatment should be addressed, because unrevealed COPD also leads to more hospital visits, increased medication use, and an increased economic burden [30].

Woodruff et al. showed that smokers with normal lung function commonly experience respiratory symptoms and exacerbations. They suggested a new entity that includes smoking-related chronic pulmonary disease [6]. Other recent studies also suggest that the pre-COPD stage is clinically and medically important [31,32]. We assume that PRISm may also be a pre-COPD-stage chronic pulmonary disease. PRISm patients should be advised to have regular check-ups to monitor COPD development, and more so if they have advance aged or wheezing, irrespective of the severity of lung function decrease (FEV_1).

This study had some limitations. First, "medically diagnosed COPD" may be considered artificial. "COPD incidence" is not an accurate term, but in this study reflects the incidence of medically diagnosed COPD as defined by the HIRA data, which includes insurance claims but not pulmonary function test data. However, the previously reported COPD incidence (2.6–9.2/1000 PY) [27,33-35] is not markedly different from that in this study (4.4/1000 PY in normal; 17.0/1000 PY in PRISm). "Medically diagnosed COPD" with hospital visits and medication use is more relevant than COPD diagnosed based only on impaired lung function (FEV_1/FVC < 0.7), without medical utilization. Therefore, this artificial definition may be appropriate for use in this study. Second, this cohort study did not include follow-up pulmonary function tests, because the KNHANES conducted pulmonary function tests in different populations each year.

Conclusions

PRISm is likely to develop into COPD over time, and it leads to frequent hospital visits, increased medication use, and greater hospitalization costs. Subjects with PRISm should be carefully monitored for COPD development, especially when they are older or have wheezing, regardless of lung function.

References

1. Rhee CK, Kim K, Yoon HK, Kim JA, Kim SH, Lee SH, Park YB, Jung KS, Yoo KH, Hwang YI. Natural course of early COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:663–8.
2. Chung K, Kim K, Jung J, Oh K, Oh Y, Kim S, Kim J, Kim Y. Patterns and determinants of COPD-related healthcare utilization by severity of airway obstruction in Korea. BMC Pulm Med. 2014;14:27.
3. Coultas DB, Mapel D, Gagnon R, Lydick E. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med. 2001;164:372–7.
4. Cooke CE, Sidel M, Belletti DA, Fuhlbrigge AL. Review: clinical inertia in the management of chronic obstructive pulmonary disease. COPD. 2012;9:73–80.
5. Glaab T, Banik N, Rutschmann OT, Wencker M. National survey of guideline-compliant COPD management among

Table 5 Comparison of baseline characteristics, medical utilization, and costs between PRISm with and without medically diagnosed COPD

	PRISm with medically diagnosed COPD	PRISm without medically diagnosed COPD	*P*-value
Age	70.06 ± 7.48	55.21 ± 10.49	< 0.001
Male, n (%)	16 (100.0)	270 (90.9)	–
Height (cm)	162.95 ± 6.9	167.0 ± 6.89	0.023
Weight (kg)	61.58 ± 13.13	69.04 ± 11.41	0.012
Smoking history			
Current smoking, n (%)	8 (50.0)	185 (62.3)	0.325
Pack-years	36.63 ± 14.16	33.02 ± 20.62	0.490
Co-morbidity, n (%)			
Pulmonary tuberculosis	1 (6.3)	20 (6.7)	0.940
Asthma	4 (25.0)	11 (3.7)	< 0.001
Lung function test			
FVC % predicted	64.83 ± 10.86	72.96 ± 9.2	< 0.001
FEV_1% predicted	69.77 ± 9.16	72.97 ± 6.55	0.188
FEV_1/FVC	0.76 ± 0.06	0.77 ± 0.06	0.182
Respiratory symptoms, n (%)			
Cough for more than 3 months	0	2 (0.7)	–
Sputum for more than 3 months	0	2 (0.7)	–
Dyspnea	2 (12.5)	1 (0.3)	< 0.001
Wheezing	6 (37.5)	31 (10.4)	0.001
Chronic bronchitis	0	2 (0.7)	–
OPD visit, n (%)	15 (93.8)	7 (2.4)	< 0.001
No. of OPD visit	8.81 ± 10.15	0.03 ± 0.18	< 0.001
Hospitalization, n (%)	9 (56.3)	20 (6.7)	< 0.001
ER visit, n (%)	5 (31.3)	7 (2.4)	< 0.001
ICU admission, n (%)	2 (12.5)	4 (1.4)	0.002
Total hospital visit, n (%)	16 (100.0)	25 (8.4)	–
ICS, n (%)	4 (25.0)	1 (0.3)	< 0.001
ICS + LABA, n (%)	8 (50.0)	3 (1.0)	< 0.001
LAMA, n (%)	4 (25.0)	–	–
SAMA, n (%)	8 (50.0)	4 (1.4)	< 0.001
SABA, n (%)	8 (50.0)	3 (1.0)	< 0.001
Systemic bronchodilator, n (%)	9 (56.3)	2 (0.7)	< 0.001
Methylxanthine, n (%)	11 (68.8)	6 (2.0)	< 0.001
Total prescribed medication, n (%)	16 (100.0)	10 (3.4)	–
Hospitalization medical Cost (for 3 years) (USD)	3647.51 ± 4773.55	223.58 ± 1535.45	0.012
Total	16	297	

Data are presented as mean ± standard deviation or number (percentage)
PRISm preserved ratio impaired spirometry, *COPD* chronic obstructive pulmonary disease, FEV_1 forced expiratory volume for 1 s, *FVC* forced vital capacity, *OPD* outpatient department, *ER* emergency room, *ICU* intensive care unit, *ICS* inhaled corticosteroid, *LABA* long-acting beta-2 agonist, *LAMA* long-acting muscarine antagonist, *SAMA* short-acting muscarine antagonist, *SABA* short-acting beta-2 agonist

pneumologists and primary care physicians. COPD. 2006;3:141–8.

6. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Engl J Med. 2016;374:1811–21.
7. Vaz Fragoso CA, Gill TM, McAvay G, Yaggi HK, Van Ness PH, Concato J. Respiratory impairment and mortality in older persons: a novel spirometric approach. J Investig Med. 2011;59:1089–95.
8. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Arch Bronconeumol. 2017;53:128–49.
9. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. Thorax. 2010;65:499–504.
10. Wan ES, Hokanson JE, Murphy JR, Regan EA, Make BJ, Lynch DA, Crapo JD, Silverman EK, Investigators CO. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study. Am J Respir Crit Care Med. 2011;184:57–63.
11. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the third

Table 6 Significant factors for COPD diagnosis in PRISm

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)	**1.14**	**(1.08, 1.21)**	**< 0.001**	**1.14**	**(1.05, 1.24)**	**0.002**
Male						
Height (cm)	0.93	(0.87, 0.99)	0.025	1.03	(0.92, 1.16)	0.564
Weight (kg)	0.94	(0.9, 0.99)	0.013	0.95	(0.89, 1.02)	0.153
Smoking history						
Current smoking	0.61	(0.22, 1.66)	0.329			
Pack-years	1.01	(0.99, 1.03)	0.490			
Co-morbidity						
Pulmonary tuberculosis	0.92	(0.12, 7.35)	0.940			
Asthma	8.67	(2.41, 31.23)	0.001	5.87	(0.94, 36.56)	0.058
Lung function test						
FVC % predicted	0.93	(0.89, 0.97)	0.001	1.01	(0.95, 1.09)	0.694
FEV_1% predicted	0.95	(0.9, 1.01)	0.071			
FEV_1/FVC	0.001	(0.001, 35.7)	0.183			
Self-reported respiratory symptoms						
Cough for more than 3 months						
Sputum for more than 3 months						
Dyspnea	42.29	(3.61, 494.74)	0.003	8.88	(0.65, 121.7)	0.102
Wheezing	**5.15**	**(1.75, 15.14)**	**0.003**	**4.56**	**(1.08, 19.35)**	**0.040**
Chronic bronchitis						

Statistically significant data are presented as bold
COPD chronic obstructive pulmonary disease, *PRISm* preserved ratio impaired spirometry, *FEV_1* forced expiratory volume for 1 s, *FVC* forced vital capacity, *OR* odds ratio, *CI* confidence interval

National Health and nutrition examination. J Intern Med. 2003;254:540–7.
12. Wan ES, Cho MH, Boutaoui N, Klanderman BJ, Sylvia JS, Ziniti JP, Won S, Lange C, Pillai SG, Anderson WH, et al. Genome-wide association analysis of body mass in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2011;45:304–10.
13. Soriano JB, Miravitlles M, Garcia-Rio F, Munoz L, Sanchez G, Sobradillo V, Duran E, Guerrero D, Ancochea J. Spirometrically-defined restrictive ventilatory defect: population variability and individual determinants. Prim Care Respir J. 2012;21:187–93.
14. Mannino DM, Holguin F, Pavlin BI, Ferdinands JM. Risk factors for prevalence of and mortality related to restriction on spirometry: findings from the first National Health and nutrition examination survey and follow-up. Int J Tuberc Lung Dis. 2005;9:613–21.
15. Wan ES, Castaldi PJ, Cho MH, Hokanson JE, Regan EA, Make BJ, Beaty TH, Han MK, Curtis JL, Curran-Everett D, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. Respir Res. 2014;15:89.
16. Diaz AA, Strand M, Coxson HO, Ross JC, San Jose Estepar R, Lynch D, van Rikxoort EM, Rosas IO, Hunninghake GM, Putman RK, et al. Disease severity dependence of the longitudinal association between CT lung density and lung function in smokers. Chest. 2018;153:638–45.
17. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374:733–43.
18. Zeng G, Sun B, Zhong N. Non-smoking-related chronic obstructive pulmonary disease: a neglected entity? Respirology. 2012;17:908–12.
19. Yoon HK, Park YB, Rhee CK, Lee JH, Oh YM, Committee of the Korean CG. Summary of the chronic obstructive pulmonary disease clinical practice guideline revised in 2014 by the Korean academy of tuberculosis and respiratory disease. Tuberc Respir Dis (Seoul). 2017;80:230–40.
20. Sim YS, Lee JH, Lee WY, Suh DI, Oh YM, Yoon JS, Lee JH, Cho JH, Kwon CS, Chang JH. Spirometry and bronchodilator test. Tuberc Respir Dis (Seoul). 2017;80:105–12.
21. Kim S, Kim J, Kim K, Kim Y, Park Y, Baek S, Park SY, Yoon SY, Kwon HS, Cho YS, et al. Healthcare use and prescription patterns associated with adult asthma in Korea: analysis of the NHI claims database. Allergy. 2013;68:1435–42.
22. Lee J, Lee JH, Kim JA, Rhee CK. Trend of cost and utilization of COPD medication in Korea. Int J Chron Obstruct Pulmon Dis. 2017;12:27–33.
23. Chung SM, Lee SY. Evaluation of appropriate Management of Chronic Obstructive Pulmonary Disease in Korea: based on Health Insurance Review and Assessment Service (HIRA) claims. Tuberc Respir Dis (Seoul). 2017;80:241–6.
24. Sood A, Petersen H, Qualls C, Meek PM, Vazquez-Guillamet R, Celli BR, Tesfaigzi Y. Spirometric variability in smokers: transitions in COPD diagnosis in a five-year longitudinal study. Respir Res. 2016;17:147.
25. Mannino DM, Doherty DE, Sonia Buist A. Global initiative on obstructive lung disease (GOLD) classification of lung disease and mortality: findings from the atherosclerosis risk in communities (ARIC) study. Respir Med. 2006;100:115–22.
26. Quanjer PH, Brazzale DJ, Boros PW, Pretto JJ. Implications of adopting the global lungs initiative 2012 all-age reference equations for spirometry. Eur Respir J. 2013;42:1046–54.
27. Terzikhan N, Verhamme KM, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam study. Eur J Epidemiol. 2016;31:785–92.
28. Smith OO, Helms PJ. Genetic/environmental determinants

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Low Tidal Volume Ventilation with Low PEEP During Surgery May Induce Lung Inflammation

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Abstract

Background: Compared to conventional tidal volume ventilation, low tidal-volume ventilation reduces mortality in cased of acute respiratory distress syndrome. The aim of the present study is to determine whether low tidal-volume ventilation reduces the production of inflammatory mediators in the lungs and improves physiological status during hepatic surgery.

Methods: We randomly assigned patients undergoing hepatectomy into 2 groups: conventional tidal-volume vs. low tidal-volume (12 vs. 6 $mL \bullet kg^{-1}$ ideal body weight) ventilation with a positive end-expiratory pressure of 3 cm H_2O. Arterial blood and airway epithelial lining fluid were sampled immediately after intubation and every 3 h thereafter.

Results: Twenty-five patients were analyzed. No significant changes were found in hemodynamics or acid-base status during the study. Interleukin-8 was significantly elevated in epithelial lining fluid from the low tidal-volume group. Oxygenation evaluated immediately after admission to the post-surgical care unit was significantly worse in the low tidal-volume group.

Conclusions: Low tidal-volume ventilation with low positive end-expiratory pressure may lead to pulmonary inflammation during major surgery such as hepatectomy.

Trial registration: The effect of ventilatory tidal volume on lung injury during hepatectomy that requires transient liver blood flow interruption. UMIN000021371 (03/07/2016); retrospectively registered

Keywords: Cytokines, Hepatectomy, Systemic Inflammatory Response Syndrome, Ventilator-Induced Lung Injury, Micro-sampling Method

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Background

In acute respiratory distress syndrome (ARDS), ventilation with a low tidal volume (V_T) reduces mortality compared to a conventional V_T [1, 2]. Recent studies have shown that ventilation with a conventional tidal volume is also associated with sustained cytokine production in the lungs in patients without lung injury at the onset of mechanical ventilation [3-6]. Furthermore, incidences of lung injury have been reported after major surgery in those without any pre-existing lung diseases [7]. In those studies [3-6], the protective ventilation strategy consists of low V_T ventilation, relatively high positive end-expiratory pressure (PEEP), and lung recruitment maneuver. During hepatectomy, however, surgeons require low PEEP to reduce bleeding from cut surface of the liver [8]. Our question was: when high PEEP, one part of lung protective approaches, is unavailable, does the low tidal volume ventilation strategy have utility? To answer the question, we proposed a study that aimed to evaluate the effect of low tidal volume ventilation during surgery under the condition with a restricted PEEP level (3 cmH_2O).

We conducted a prospective, randomized controlled study on patients undergoing hepatic surgery under two different V_T ventilation conditions assigned randomly to determine whether low V_T ventilation reduces lung injury and improves lung physiology during hepatic surgeries. The primary outcome of the present study was the change in pro-inflammatory cytokine concentrations in the lungs. Secondary outcomes were oxygenation during and immediately after the surgery and the duration of hospital stay after the surgery. We hypothesized that (a) proinflammatory mediators increase in the circulation after hepatic surgery with the Pringle maneuver that causes a temporal hepatic blood flow interruption; (b) airway inflammation is induced when a conventional V_T is used during surgery; and (c) compared to conventional V_T ventilation, low V_T ventilation during hepatectomy reduces airway inflammation and prevents lung injury under a condition of a limited PEEP.

Methods

General protocol and patients

This prospective, randomized, controlled study was performed at Yokohama City University Hospital. The data were collected from October 2008 to September 2009, with approval from the institutional review board (Date of IRB approval: 08-01-2007; approval number: 07-021), and written informed consent was obtained from all the patients preoperatively.

Patients aged between 20 and 85 years, undergoing hepatectomy, were considered eligible for enrolment in this study. Patients with an American Society of Anesthesiologists' physical status (ASA-PS) value of 3 and above, pre-existing lung disease, tumor in the portal vein or inferior vena cava, requirement of bile duct or gastrointestinal tract repair, or requirement of additional surgical procedures other than hepatectomy were excluded.

Patients were randomly assigned to those ventilated with a V_T of 12 mL per predicted body weight (kg) (TV12) or with a V_T of 6 mL per predicted body weight (TV6). The assignment was performed using a random number table by an investigator who was not involved in data collection and was notified to anesthesiologists who were not involved in the study using an envelope method. The investigators who collected the data and samples were blinded to the ventilation settings at any time of the experiment. Mechanical ventilation was performed in a volume-controlled mode, with the ratio of the duration of inspiration to the duration of expiration (I/E) of 1:2 and an end-inspiratory pause time of 10 %, using an anesthesia machine (Drager Fabius GS, Drager Medical, Telford, PA, USA). The patients did not receive premedication. Propofol 2 mg•kg^{-1}, vecuronium 0.1 mg•kg^{-1}, and fentanyl 100 µg was administered to facilitate orotracheal intubation with a cuffed tube. General anesthesia was maintained with sevoflurane 0.6-1.5 % and was supplemented by epidural anesthesia with mepivacaine.

The target arterial partial oxygen pressure (PaO_2) of approximately 150 mmHg was attained by adjusting the inspired oxygen fraction (F_IO_2) and the arterial partial carbon dioxide pressure ($PaCO_2$) was maintained between 35 and 45 mmHg by changing the ventilation frequency referring to the previous blood gas analysis and end-tidal carbon dioxide pressure. PEEP was applied at 3 cm H_2O in both the groups. Ephedrine was administered when the systolic blood pressure dropped below 80 mmHg. Methyl-prednisolone (8 mg•kg^{-1}) was administered intravenously prior to the Pringle maneuver (obstruction of both branches of the hepatic artery and portal vein). Muscle relaxation was reversed with neostigmine and atropine when surgery was completed. Lungs were recruited manually with approximately 20 cmH_2O for 15 to 20 s prior to extubation in both groups.

Blood sampling and blood gas analysis

Arterial blood was drawn just prior to bronchoscopic microsampling (BMS), and blood gas analysis (BGA) was performed (model 860, Chiron Diagnostics, Emeryville CA, USA) every 3 h thereafter. Whole blood was centrifuged at 4°C at 3000 RPM, and the plasma was aliquoted and stored at –80°C until use. When the patient arrived in the post-anesthetic care unit (PACU), BGA was repeated.

Bronchoscopic microsampling method

Epithelial lining fluid sampling

Epithelial lining fluid (ELF) was collected with BMS probes using a previously reported method [9]. Briefly, a BMS probe was inserted into the channel of a fibreoptic bronchoscope that was inserted into the tracheal tube. The tip of the BMS probe was attached to a segmental bronchus of the right middle lobe under optical guidance of a bronchoscope for 20 s. The BMS probe was then withdrawn from the bronchoscope. These procedures were repeated 3 times using 3 different BMS probes. The tips of

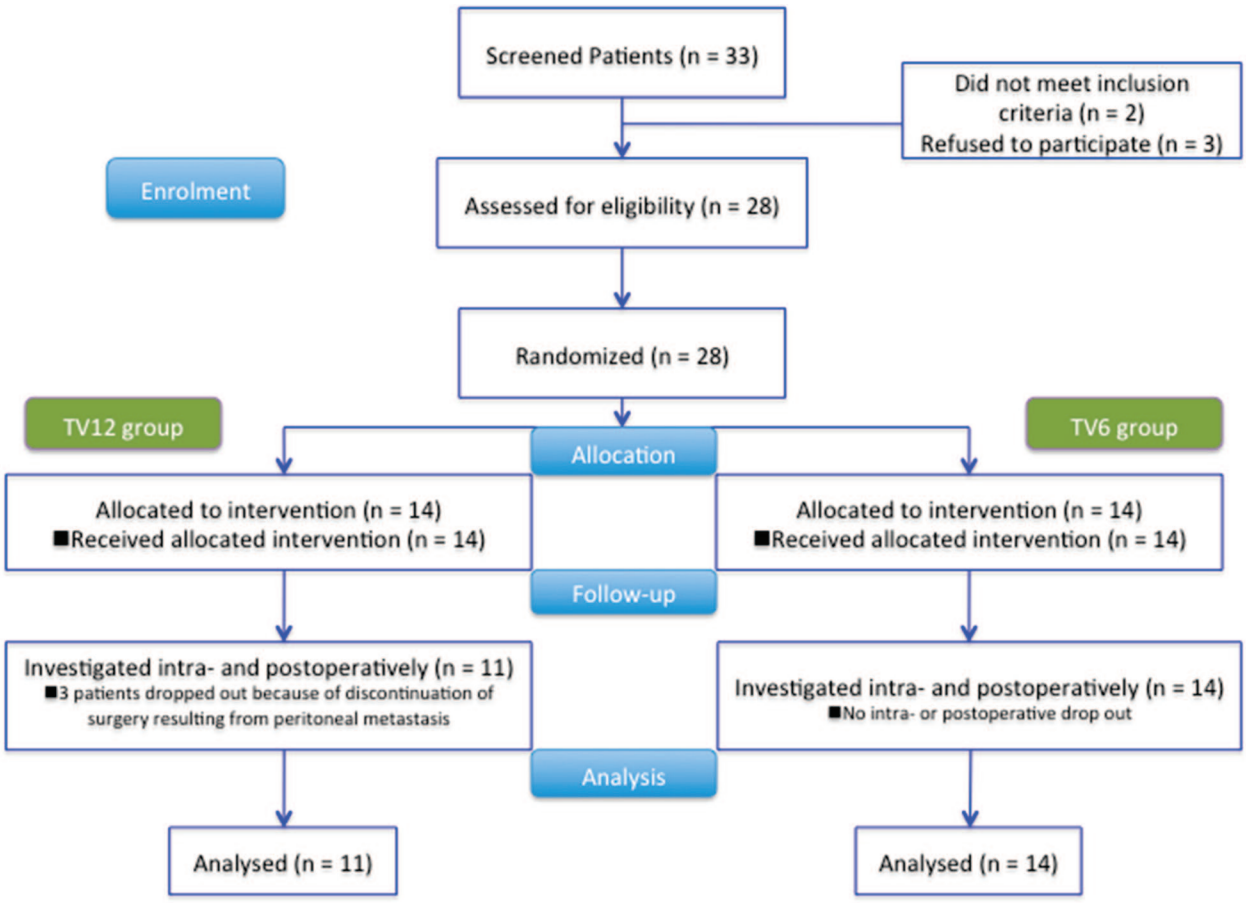

Fig. 1 Consort flow diagram for the present study

the BMS probes, made of cotton, were inserted into pre-weighed test tubes. The tubes were sealed, weighed again with the probe tips, and stored at –80°C. The collections were performed immediately after intubation and after 3 and 6 h.

Determination of the sample weight and ELF extraction

One milliliter of distilled water was added to each test tube containing BMS probes. The tubes were centrifuged at 4°C for 10 min, and the supernatant was collected and aliquoted. The BMS probes were dried on a bench top at room temperature for 3 days and weighed. The weight of the collected sample was calculated using the following formula:

$S = (T + P_1) – T – P_2$, where S is the sample weight, T is the weight of the tube, $(T + P_1)$ is the weight of the tube and the BMS probes after sampling, and P_2 is the weight of the dried probes after extraction. A sample dilution factor (DF) in distilled water was then calculated as follows:

$DF = (S + 1000) / S$,

where S is the sample weight in milligrams.

Measurements of mediator concentrations in the blood and ELF

Cytokines and adhesion molecules were measured using an enzyme-linked immunosorbent assay (ELISA). Tumor necrosis factor (TNF)-α (Quantikine® Human TNF-α/ TNFSF1A, R&D Systems, Minneapolis, MN, USA), interleukin (IL)-8 (EH2IL8, Thermo Scientific, Rockford, IL, USA), and intercellular adhesion molecule (ICAM)-1 (EH5400, Thermo Scientific) levels were measured according to the manufacturer's instructions.

Clinical data collection

Preoperative data were collected from routine clinical documentation that was stored in the institutional medical record system. Intraoperative physiological and ventilatory data were recorded in a data sheet.

Statistical analysis

All data were statistically analyzed using Statcel 2nd edition (OMS Publishing, Tokorozawa, Japan). The student t-test and Mann-Whitney U test were used to assess quantitative variables. Variables measured only once were compared using an unpaired t-test. Variables that were measured repeatedly were compared using two-way repeated measures analysis of variance (ANOVA) followed by Bonferroni post hoc. Results were expressed as mean ± standard deviation; $p < 0.05$ was considered significant.

Table 1 Patient characteristics and the baseline P/F ratio

	TV 12	TV 6	*P*-value
Age,year[a]	69 (60/68)	63 (59/72)	0.3
Gender (male/female)[b]	8/3	10/4	0.94
Body weight,kg	57.5 ± 10.2	62.7 ± 10.7	0.25
Height,cm	164.5 ± 10.1	166.1 ± 6.9	0.66
Body mass index,kg•m^{-2}	21.2 ± 2.7	22.6 ± 2.6	0.22
Operation time, min	512.8 ± 113.9	419 ± 199.3	0.23
Anesthesia time, min	606.1 ± 128.0	525.2 ± 207.3	0.32
Blood loss, mL	852.0 ± 465.0	852.0 ± 466.4	0.39
Baseline P/F ratio	501.6 ± 23.9	435.8 ± 27.6	0.09
Liver resection amount, %	38.5 ± 8.8	33.0 ± 17.4	0.38
Pringle maneuver, times[c]	3 (3/5.5)	4 (3/6)	0.75
Length of hospital stay after operation, days	12.5 ± 5.6	15.2 ± 9.0	0.38

Values are indicated as the mean ± SD otherwise indicated
Age [a]is represented as the mean (range), gender [b]as a number, and Pringle maneuver [c]as median (25th and 75th percentiles)

Results

Patient demography

A total of 28 patients were enrolled, and 14 patients were assigned to each group (Fig. 1). Three patients in the TV12 group were excluded because the operation was terminated before the completion of the study due to dissemination of tumor to the peritoneum. No differences were present in the demographic or clinical data between the groups (Table 1).

Physiological parameters

No significant differences were found in pH, bicarbonate concentration, heart rate, or blood pressure between the groups (Fig. 2). The F_IO_2 was set between 0.3 and 0.5 in all patients. There was no significant difference in the P/F ratio (Fig. 3a) or the $PaCO_2$ (Fig. 3b) between the two groups at any time point. Peak airway pressure was significantly higher in the TV12 group than in the TV6 group (Fig. 3c). To maintain the $PaCO_2$ within the normal range, ventilation frequency was greater in the TV6 group than in the TV12 group (Fig. 3d). All patients were extubated in the operating room and were spontaneously breathing when they arrived at the PACU. The P/F ratio evaluated just after admission to the PACU was higher in the TV12 group than in the TV6 group (417 ± 92 versus 315 ± 49, $p = 0.009$) (Fig. 4).

Biological parameters

No significant difference was found in the plasma concentration of IL-8 ($p = 0.17$) (Fig. 5a). TNF-α was below the detection limit (1.6 pg•mL^{-1}) in the plasma and ELF samples obtained from all the patients. Elastase activity in the plasma was minimal in both the groups. ICAM-1 in the plasma was significantly higher in the TV6 group than in the TV12 group ($p = 0.03$; Fig. 5b). The concentration of IL-8 in the ELF was significantly higher in the TV6 group than in the TV12 group at 6 h ($p = 0.03$) (Fig. 6a). No significant difference was found in ICAM-1 ($p = 0.31$) or elastase activity ($p = 0.7$) in the ELF between the groups (Figs. 6b, c).

Sharing our data

Data supporting our findings are available upon request.

Discussion

Main findings

The main findings of this study are:

1. Low tidal-volume ventilation during hepatectomy induced an increase in the concentration of IL-8 in the ELF collected during hepatectomy.
2. Low tidal-volume ventilation during hepatectomy resulted in a lower P/F ratio after surgery.

These were contrary to our hypothesis that low V_T – ventilation would reduce lung inflammation and preserve physiological lung functions following major surgery, compared to conventional ventilation.

The mechanism of lung injury

Our hypothesis was based on studies that showed the benefits of low V_T ventilation in ARDS patients [1]. A considerable number of ARDS cases originate from extrapulmonary complications

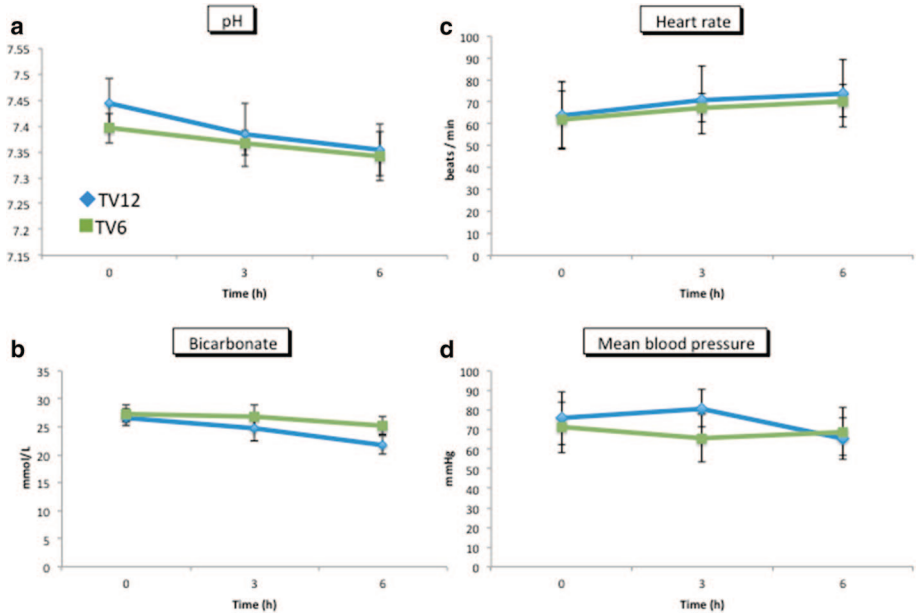

Fig. 2 Changes in hemodynamics and BGA data. pH (**a**) and bicarbonate (**b**) were analyzed by blood gas analyses, whereas heart rate (**c**) and mean blood pressure (**d**) were obtained from a bedside monitor. Mean ± standard deviation. No significant differences were observed in BP, HR, or BGA between the groups

including pan-peritonitis, cholecystitis, multiple injury, and massive transfusion. Severe systemic inflammation is a common occurrence in these conditions. Ischemia-reperfusion of organs or other parts of the body are the leading causes of systemic inflammation. The liver is one of the largest organs in the human body; approximately 25 % of the entire blood flows into the liver. Therefore, repeated hepatic ischemia-reperfusion may be a major cause of systemic inflammation. Takeuchi and colleagues showed polymorphonuclear cell (PMN) recruitment in the lungs, proinflammatory cytokine elevation in the blood and lung homogenates, and pulmonary edema in mice after 90 min of liver ischemia and reperfusion [10]. Our previous study showed that lung injury occurs following repeated hepatic ischemia and reperfusion with high V_T ventilation in rats [11]. Taken together, hepatic surgeries performed with the Pringle maneuver is a potential leading cause of lung injury; therefore, reducing V_T during hepatectomy is a reasonable strategy to prevent lung injury.

Protective ventilation during surgery

Recently, several studies have been conducted regarding V_T and lung functions during surgery. Michelet and colleagues showed that concentrations of IL-8, IL-6, and TNF-α in the plasma were lower in patients who underwent esophagectomy with lower V_T ventilation (5 mL·kg^{-1}, PEEP 5 cm H_2O) than in those who underwent esophagectomy with higher V_T ventilation

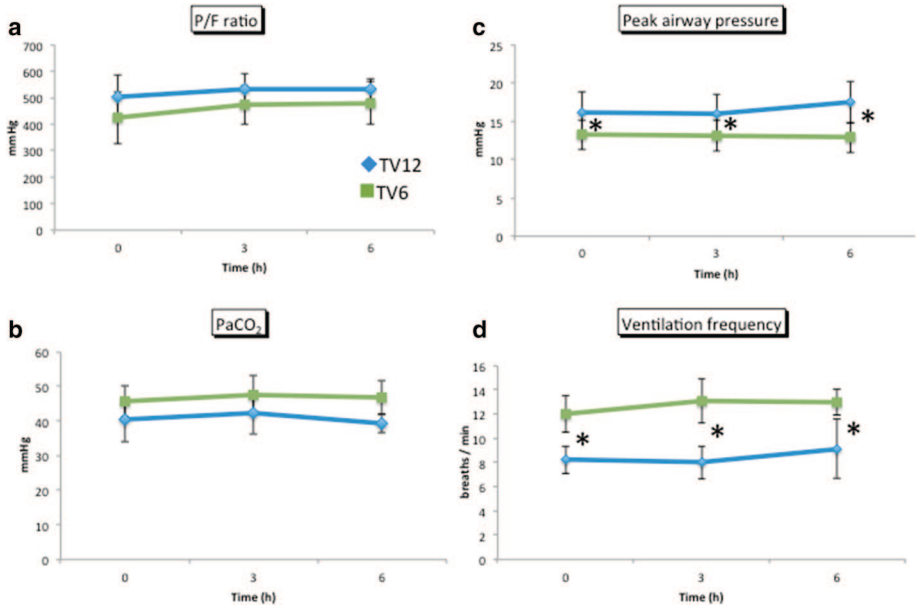

Fig. 3 Changes in arterial blood gases, airway pressure, and ventilation frequency. **a** Changes in the P/F ratio were calculated by PaO_2 analyzed by a blood gas analyzer and FIO_2. **b** Changes in $PaCO_2$ were analyzed by a blood gas analyzer. **c**, **d** Changes in peak airway pressure and ventilator frequency. Mean ± standard deviation. Peak airway pressure was significantly higher in the TV12 group. Ventilation frequency was greater in the TV6 group than in the TV12 group

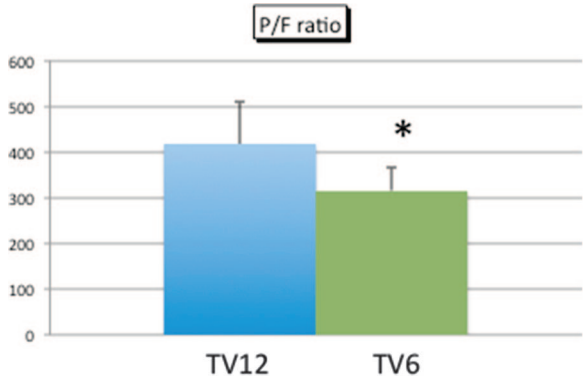

Fig. 4 Postoperative P/F ratio in the PACU. Mean ± standard deviation. The P/F ratio evaluated just after admission to the PACU was higher in the TV12 group than in the TV6 group ($p = 0.009$)

(9 mL·kg^{-1}, PEEP 0 cm H_2O) during one-lung ventilation [12]. Wolthuis and colleagues showed that the concentration of IL-8 in broncho-alveolar lavage (BAL) fluid was significantly lower in patients ventilated with a low V_T (6 mL·kg^{-1}, PEEP 10 cm H_2O) than in those ventilated with a large V_T (12 mL·kg^{-1}, PEEP 0 cm H_2O) during elective surgery [13]. Severgnini and colleagues reported that low V_T ventilation (6-8 mL·kg^{-1}, PEEP 6-8 cm H_2O) during abdominal surgery improved postoperative pulmonary function and reduced the modified Clinical Pulmonary Infection Score as compared with a standard ventilation strategy (10-12 mL·kg^{-1}, PEEP 0 cm H_2O) [14]. A recent, randomized controlled trial showed that ventilation with a V_T of 6 to 8 mL per kg of predicted body weight with a PEEP of 6 to 8 cm of H_2O and a recruitment maneuver reduced major pulmonary complications after abdominal surgery compared to ventilation with a V_T of 10-12 mL per kg of predicted body weight with no PEEP and no recruitment maneuver [15]. These studies reported that low V_T ventilation during surgery results in reduced inflammation

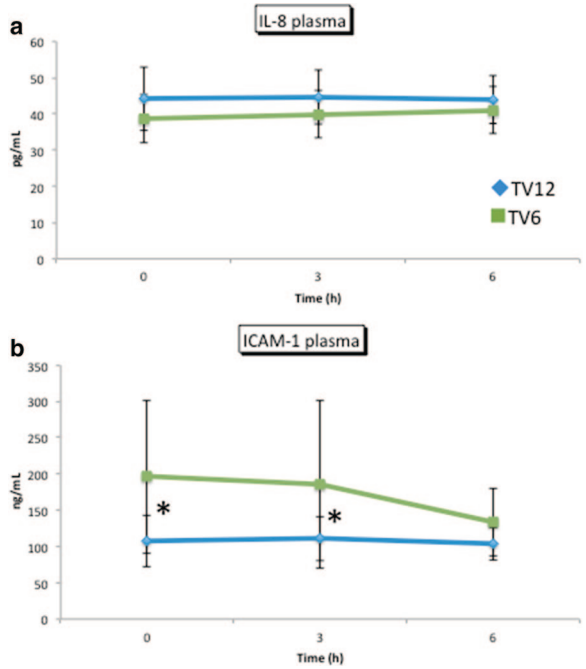

Fig. 5 Plasma concentrations of IL-8 and ICAM-1. Mean ± standard deviation. No significant differences were observed in the plasma concentration of IL-8 between the groups ($p = 0.17$). Plasma ICAM-1 was significantly higher in the TV6 group than in the TV12 group ($p = 0.03$)

or better lung functions after the surgery as compared with relatively higher V_T ventilation. We should note that relatively higher PEEP and/or lung recruitment maneuver were applied to the groups that are ventilated with lower V_T in those papers [12-15].

The results of the present study were in contrast to those of previous studies in terms of the correlation between the level of V_T and the post-surgical lung function. The most plausible reason for the discrepancy is the level of PEEP that was applied in the present study. We used relatively low PEEP (3 cmH_2O) in both the groups, which may have influenced the results. Recently, there are a few papers that focused on the relationship between PEEP level during surgery and postoperative pulmonary complications in otherwise healthy patients. Ladha et al. retrieved anesthesia records and compared ventilation settings with respiratory complications [16]. Protective ventilation defined as a median PEEP of 5 cmH_2O or more, a median tidal volume of less than 10 mL·kg^{-1} of predicted body weight, and a median plateau pressure of less than 30 cmH_2O was associated with a decreased risk of postoperative respiratory complications. de Jong et al. retrieved anesthesia records and compared median PEEP of < 5 cmH_2O, = 5 cmH_2O, or > 5 cmH_2O with respiratory outcome [17]. Application of PEEP > 5 cmH_2O was associated with a significant lower odds of respiratory complications and decreased hospital length of stay in patients undergoing major abdominal surgery but not in patients undergoing craniotomy. These findings suggest that special consideration such as application of PEEP of 5 cmH_2O or higher is necessary especially when abdominal surgery is undergone. More recently, a meta-analysis revealed that a protective lung ventilation, low V_T ventilation concomitant with PEEP and intermittent recruitment maneuver, showed a significant reduction in incidences of postoperative lung infection, atelectasis, acute lung injury, and length of hospital stay; whereas, low V_T alone failed to reduce some of the incidences [18]. In the present study, low V_T ventilation with low PEEP applied to patients undergoing hepatectomy failed to improve pulmonary function, which is consistent with the previous findings [16–18]. Moreover, it is important to understand that optimal V_T or PEEP for otherwise healthy patients undergoing surgery could be different from those for ARDS patients with a baby lung.

Mechanism of deteriorated lung function

After 6 h of ventilation, we found that IL-8 in the ELF was higher in the TV6 group than in the TV12 group. Previous studies have shown an increase in IL-8 levels in atelectatic lungs. Lung collapse results in increased IL-8 levels in BAL fluid and the re-expansion of the lungs further increases IL-8 levels in rabbits [19]. One-lung ventilation resulted in an IL-8 increase in the ELF of the non-ventilated lungs [20]. These observations suggest that the increase in IL-8 levels in the ELF in the low V_T group in the present study was due to a repeated lung collapse and re-opening of the lungs (atelectrauma) during surgery due to low V_T ventilation concomitant with low PEEP. ICAM-1 in the plasma was significantly higher in the TV6 group than in the TV12 group. Plasma ICAM-1 is associated with poor clinical outcomes in patients with acute lung injury [21]. In that study, however, plasma ICAM-1 level is also elevated in the patients with hydrostatic pulmonary edema, who basically have minimal lung injury. In the present study, mean plasma ICAM-1 concentrations in the TV12 and TV6 were from 107 to 117 ng/mL and from 133 to 196 ng/mL, respectively. These values were identical to that for the patients with hydrostatic pulmonary edema in the previous

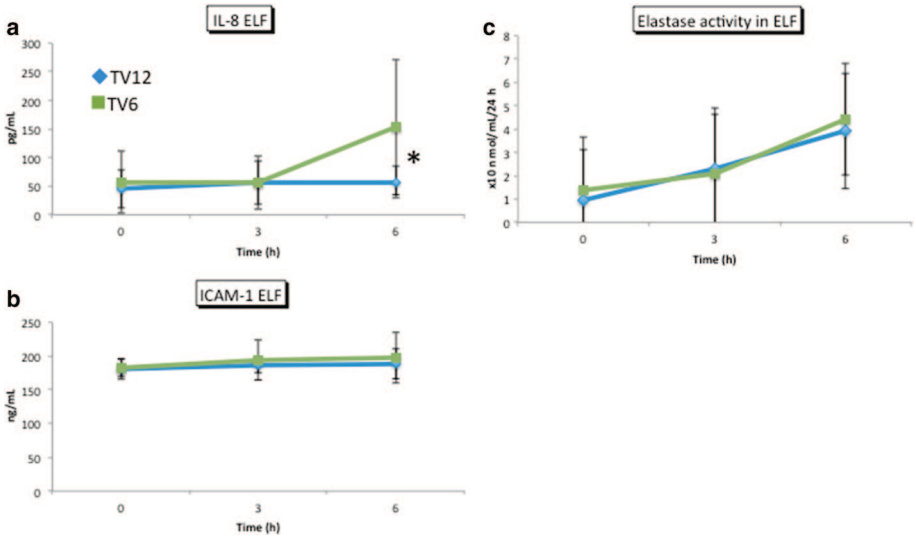

Fig. 6 Concentrations of IL-8, ICAM-1, and elastase activity in the ELF. Mean ± standard deviation. The concentration of IL-8 in the ELF was significantly higher in the TV6 group than in the TV12 group ($p = 0.04$) and the post hoc analysis revealed a significant difference at 6 h ($p = 0.03$). No significant difference was observed in ICAM-1 ($p = 0.31$) or elastase activity ($p = 0.7$) in the ELF

study (median 177 ng/mL) [21], suggesting that the effects of plasma ICAM-1 in the present study on lung injury are minimal in both groups.

Advantages of BMS method over BAL collection

Historically, BAL fluid has been used to assess the biochemical status of the airway; however, we collected bronchial ELF using the BMS method to assess lung inflammation in this study. There are a few advantages of BMS method over BAL collection. First, concerns have been raised related to patient safety during BAL collection, including desaturation during the procedure, surfactant breakdown, and a spreading of localized pathology. In fact, Bauer and colleagues showed a decrease in the PaO_2/F_IO_2 ratio after BAL collection, regardless of the BAL volume used [22]. Second, it is not possible to quantitate the concentration of biomarkers in the airway because the exact dilution factor may not be obtained in this way. Lastly, it is inappropriate to obtain repeated BAL measurements within a short period of time because the biomarkers are washed out. In the BMS method, ELF is collected using an absorptive probe guided by a fiberoptic scope; thus, we were able to safely and repeatedly collect biochemical markers from the patients' airways. In contrast to BAL, BMS has the following advantages when used to determine the biochemical status of the airway: oxygenation can be maintained during and after the procedure; alveolar surfactant is preserved; quantification of the biochemical markers is possible; and samples can be repeatedly obtained within a short duration [9].

Limitations of the study

The present study has a few limitations. First, we did not find a relevant paper to refer to in terms of the standard deviations of the two groups and thus we did not perform power analysis. Accordingly, there may be type-two error in the results of the study. Second, a steroid was administered prior to the Pringle maneuver. It is mandatory to administer a steroid for hepatectomy at our institute, regardless of the study; however, this may have limited systemic inflammation in both of the groups. In fact, in both groups, TNF-α levels in the plasma were below the detection limit, and IL-8 levels in the plasma during the surgery were similar to that of baseline values. Third, in the previous paper, the median plasma sICAM-1 concentrations for survivor and non-survivor among patients with ARDS were 338 ng/mL and 737 ng/mL, respectively [21], whereas the plasma ICAM-1 values of our patients in each group were far fewer than those values in the previous paper namely those of survivors. This fact suggests that although there was significant difference in plasma ICAM-1 in two groups in our study, the extent of the increase in ICAM-1 may not have clinical or biological significance. However we have not proven this and slightly elevated plasma ICAM-1 in the TV6 group may be the cause of lower P/F ratio after the surgery. Lastly, postoperative oxygenation difference was the only clinical outcome between the groups. No patient experienced hypoxia post-operatively because each patient received supplemental oxygen at the PACU. However, the data suggest some patients, especially those in the TV6 group (mean P/F ratio of about 300), may have experienced hypoxia unless supplemental oxygen was applied. We may consider this as clinically significant.

Conclusion

In conclusion, V_T of 6 mL·kg^{-1} predicted body weight ventilation with a PEEP of 3 cmH_2O during hepatectomy caused inflammation in the airway and reduced oxygenation after the surgery, whereas V_T of 12 mL·kg^{-1} ventilation with a PEEP of 3 cmH_2O did not. There appears to be more lung inflammation with low tidal volume with low PEEP, which may be due to repeated alveolar collapse and re-expansion (i.e., atelectrauma). Our study supports the findings of other investigations looking at lung protective ventilation during surgery, mainly that low PEEP levels may be harmful. Careful consideration is warranted when enforcing a lung-protective strategy during major surgery.

References

1. Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med. 1995;152:1835–46.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute

respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
3. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care. 2010;14(1):R1.
4. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, et al. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. Crit Care. 2010;14(2):R39.
5. Wilson MR, Patel BV, Takata M. Ventilation with "clinically relevant" high tidal volumes does not promote stretch-induced injury in the lungs of healthy mice. Crit Care Med. 2012;40:2850–7.
6. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308:1651–9.
7. Kilpatrick B, Slinger P. Lung protective strategies in anaesthesia. Br J Anaesth. 2010;105 Suppl 1:i108–16.
8. Huntington JT, Royall NA, Schmidt CR. Minimizing blood loss during hepatectomy: a literature review. J Surg Oncol. 2014;109:81–8.
9. Nishimura T, Hasegawa N, Watanabe M, et al. Bronchoscopic microsampling to analyze the epithelial lining fluid of patients with pulmonary Mycobacterium avium complex disease. Respiration. 2008;76:338–43.
10. Takeuchi D, Yoshidome H, Kurosawa H, et al. Interleukin-18 exacerbates pulmonary injury after hepatic ischemia/reperfusion in mice. J Surg Res. 2010;158:87–93.
11. Ota S, Nakamura K, Yazawa T, et al. High tidal volume ventilation induces lung injury after hepatic ischemia-reperfusion. Am. J Physiol Lung Cell Mol Physiol. 2007;292:L625–31.
12. Michelet P, D'Journo XB, Roch A, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology. 2006;105:911–9.
13. Wolthuis EK, Choi G, Dessing MC, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. Anesthesiology. 2008;108:46–54.
14. Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013;118:1307–21.
15. Futier E, Constantin JM, Paugam-Burtz C, IMPROVE Study Group, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369:428–37.
16. Ladha K, Vidal Melo MF, McLean DJ, et al. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. BMJ. 2015;351:h3646.
17. de Jong MA, Ladha KS, Melo MF, et al. Differential Effects of Intraoperative Positive End-expiratory Pressure (PEEP) on Respiratory Outcome in Major Abdominal Surgery Versus Craniotomy. Ann Surg. 2015;22 [Epub ahead of print].
18. Yang D, Grant MC, Stone A, et al. A Meta-analysis of Intraoperative Ventilation Strategies to Prevent Pulmonary Complications: Is Low Tidal Volume Alone Sufficient to Protect Healthy Lungs? Ann Surg. 2016;263(5):881–7.
19. Nakamura M, Fujishima S, Sawafuji M, et al. Importance of interleukin-8 in the development of reexpansion lung injury in rabbits. Am J Respir Crit Care Med. 2000;161:1030–6.
20. Komatsu Y, Yamamoto H, Tsushima K, et al. Increased interleukin-8 in epithelial lining fluid of collapsed lungs during one-lung ventilation for thoracotomy. Inflammation. 2012;35:1844–50.
21. Calfee CS, Eisner MD, Parsons PE, et al. Soluble intercellular adhesion molecule-1 and clinical outcomes in patients with acute lung injury. Intensive Care Med. 2009;35:248–57.
22. Bauer TT, Torres A, Ewig S, et al. Effects of bronchoalveolar lavage volume on arterial oxygenation in mechanically ventilated patients with pneumonia. Intensive Care Med. 2001;27:384–93.

Oxygen Versus Air-Driven Nebulisers for Exacerbations of Chronic Obstructive Pulmonary Disease: a Randomised Controlled Trial

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Abstract

Background: In exacerbations of chronic obstructive pulmonary disease, administration of high concentrations of oxygen may cause hypercapnia and increase mortality compared with oxygen titrated, if required, to achieve an oxygen saturation of 88-92%. Optimally titrated oxygen regimens require two components: titrated supplemental oxygen to achieve the target oxygen saturation and, if required, bronchodilators delivered by air-driven nebulisation. The effect of repeated air vs oxygen-driven bronchodilator nebulisation in acute exacerbations of chronic obstructive pulmonary disease is unknown. We aimed to compare the effects of air versus oxygen-driven bronchodilator nebulisation on arterial carbon dioxide tension in exacerbations of chronic obstructive pulmonary disease.

Methods: A parallel group double-blind randomised controlled trial in 90 hospital in-patients with an acute exacerbation of COPD. Participants were randomised to receive two 2.5 mg salbutamol nebulisers, both driven by air or oxygen at 8 L/min, each delivered over 15 min with a 5 min interval in-between. The primary outcome measure was the transcutaneous partial pressure of carbon dioxide at the end of the second nebulisation (35 min). The primary analysis used a mixed linear model with fixed effects of the baseline $PtCO_2$, time, the randomised intervention, and a time by intervention interaction term; to estimate the difference between randomised treatments at 35 min. Analysis was by intention-to-treat.

Results: Oxygen-driven nebulisation was terminated in one participant after 27 min when the $PtCO_2$ rose by > 10 mmHg, a predefined safety criterion. The mean (standard deviation) change in $PtCO_2$ at 35 min was 3.4 (1.9) mmHg and 0.1 (1.4) mmHg in the oxygen and air groups respectively, difference (95% confidence interval) 3.3 mmHg (2.7 to 3.9), $p < 0.001$. The proportion of patients with a $PtCO_2$ change ≥4 mmHg during the intervention was 18/45 (40%) and 0/44 (0%) for oxygen and air groups respectively.

Conclusions: Oxygen-driven nebulisation leads to an increase in $PtCO_2$ in exacerbations of COPD. We propose that airdriven bronchodilator nebulisation is preferable to oxygen-driven nebulisation in exacerbations of COPD.

Trial registration: Australian New Zealand Clinical Trials Registry number ACTRN12615000389505. Registration confirmed on 28/4/15.

Keywords: Air, Bronchodilator agents, Hypercapnia, Nebulisation, Oxygen

Background

In acute exacerbations of chronic obstructive pulmonary disease (AECOPD), administration of high concentration oxygen may cause profound hypercapnia and increase mortality, compared with oxygen titrated to achieve an oxygen saturation of between 88 to 92%.[1,2] Titrated oxygen regimens require two components: titrated supplemental oxygen to achieve a particular target arterial oxygen saturation measured by pulse oximetry (SpO_2), and bronchodilators delivered by either air-driven nebulisation or metered-dose inhalers with a spacer. Oxygendriven nebulisation inadvertently exposes patients to high concentrations of inspired oxygen, particularly with prolonged or repeated use as may occur in patients with severe exacerbations during long pre-hospital transfers or if the mask is inadvertently left in place.

We have shown that air-driven bronchodilator nebulisation prevents the increase in arterial partial pressure of carbon dioxide ($PaCO_2$) that results from use of oxygen-driven nebulisers in patients with stable COPD.[3] However, there are only two small non-blinded randomised controlled trials of air compared to oxygen-driven nebulisation in patients admitted to hospital with AECOPD.[4,5] These trials reported that administration of a single bronchodilator dose using oxygen-driven nebulisation increases the $PaCO_2$ in COPD patients who have baseline hypercapnia.

Robust determination of the risks of oxygen-driven nebulisation in AECOPD could identify whether widespread implementation of air-driven nebulisers, or use of metered-dose inhalers through a spacer, are required to ensure safe delivery of bronchodilators to this high-risk patient group. The objective of this study was to compare the effects on $PaCO_2$ of air- and oxygen-driven bronchodilator nebulisation in AECOPD. Our hypothesis was that two doses of oxygen-driven bronchodilator nebulisation would increase the $PaCO_2$ compared with air-driven nebulisation in patients hospitalised with an AECOPD.

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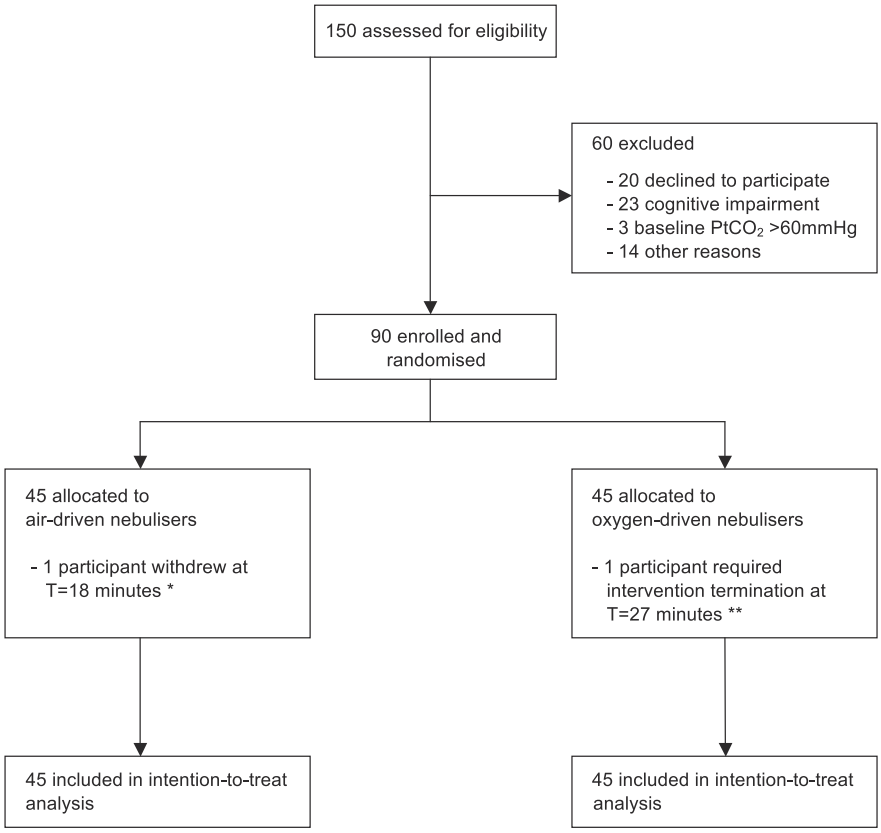


* Withdrew after feeling flushed.

** $PtCO_2$ rose >10mmHg prompting termination of oxygen-driven nebulisation, a pre-defined safety criterion.

Figure 1. Participant flow through the study and allocation of interventions

Methods

Trial design and patients

This was a parallel-group double-blind randomised controlled trial at Wellington Regional Hospital, New Zealand. The full study protocol is available in the online supplement.

Participants were hospital inpatients, ≥40 years of age, with an admission diagnosis of AECOPD. Exclusion criteria included requirement for ≥4 L/min of oxygen via nasal cannulae to maintain SpO_2 between 88 to 92%; current requirement for non-invasive ventilation (NIV); baseline transcutaneous partial pressure of carbon dioxide ($PtCO_2$) > 60 mmHg; inability to provide written informed consent; and any other condition which at the Investigator's discretion, was believed may present a safety risk or impact on the feasibility of the study results. Written informed consent was obtained before any study-specific procedures. The study was undertaken on the ward during the hospital admission. Ethics approval was obtained from the Health and Disability Ethics Committee, New Zealand (Reference 14/NTB/200). The full study protocol (original and updated version) can be found on the OLS.

Intervention

After written consent, participants had continuous $PtCO_2$ and heart rate monitoring using the SenTec® (SenTec AG, Switzerland) device and oxygen saturation (SpO_2) measured by pulse oximetry (Novametrix 512, Respironics, Carlsbad, USA). Participants were randomised to receive two nebulisations, both driven either by air or oxygen, at 8 L/min, each delivered over 15 min with a five minute break in-between. Randomisation was 1:1 by a block randomised computer generated sequence (block size six), provided in sealed opaque envelopes by the study statistician who was independent of recruitment and assessment of participants.

The participants and blinded investigator, who recorded heart rate and $PtCO_2$ were masked to the randomised treatments. If both oxygen and air ports were available in hospital on the wall behind the participant, these were used for driving nebulisation. If only oxygen ports were available, identical portable oxygen and air cylinders were placed behind the participant's bed prior to randomisation and used instead. Both the participant and blinded investigator faced forward for the full duration of the study. In addition, the blinded investigator sat towards the end of the bed — ahead of the participant, such that they could not see the participant's interventions. Likewise, the blinded investigator and patient could not view the SpO_2 on the Sentec device, as this was covered during the interventions, or the pulse oximeter which could only be viewed by the unblinded investigator. Interaction between blinded and unblinded investigators would only occur if a rise in $PtCO_2$ of ≥10 mmHg was demonstrated (a predefined safety criterion to abort intervention).

An initial 15 min wash-in and titration period was administered by the unblinded investigator using nasal cannulae, if required, to ensure that participant's SpO_2 were within 88 to 92%. If

Table 1 Participant Characteristics

	Mean (SD)		*P*
	Oxygen *N*=45[a]	Air *N*=45[a]	
Age (years)	70·4 (10·3)	72·3 (8·3)	0.34
Age at diagnosis of COPD (years)	58·6 (12·1) *N* = 40	58·8 (12·2) *N* = 44	0.92
BMI (kg/m^2)	27·2 (7·7)	25·5 (8·9)	0.33
Smoking pack years	39·3 (31·1)	51·2 (39·2)	0.11
FEV_1 (L)	0·81 (0·33) *N* = 35	0·85 (0·31) *N* = 37	0.69
FEV_1% predicted	35·0 (11·5) *N* = 35	34·0 (11·8) *N* = 37	0.73
mMRC	2·38 (1·09)	2·33 (1·04)	0.84
Baseline Transcutaneous Data			
$PtCO_2$ (mmHg)	38·0 (7·7)	37·2 (6·8)	0.59
SpO_2 (%)	92·6 (2·4)	92·6 (2·3)	0.93
Heart Rate (per minute)	89·6 (15·7)	87·0 (16·0)	0.89
Baseline capillary blood gas			
pH	7·42 (0·04) *N* = 43	7·44 (0·03) *N* = 41	0.11
$PcapCO_2$ (mmHg)	40·2 (7·0) *N* = 43	38·5 (5·9) *N* = 41	0.23
	N/45 (%)		*P*
	Oxygen	Air	
Male	17 (38)	24 (53)	0.20
Ethnicity			0.49
European	24 (53)	31 (69)	
Māori	7 (16)	4 (9)	
Pacific	5 (11)	4 (9)	
Other	9 (20)	6 (13)	
Previous Ventilation (ever)	12 (27)	3 (7)	0.02
Previous Ventilation Type			0.03
NIV	10 (22)	3 (7)	
Intubation	2 (4)	0 (0)	
Previous hypercapnia	23 (51)	17 (38)	0.29
Home Oxygen	2 (4)	1 (2)	0.99
Home Nebulisers	5 (11)	12 (27)	0.10
Comorbidities			
Heart Failure	8 (18)	3 (7)	0.20
Asthma	6 (13)	2 (4)	0.27
Bronchiectasis	3 (7)	4 (9)	0.99

COPD Chronic Obstructive Pulmonary Disease, *BMI* Body Mass Index, *FEV_1* Forced Expiratory Volume in 1 s at time of randomisation, *mMRC* Modified Medical Research Council dyspnea scale, *$PtCO_2$* Transcutaneous partial pressure of carbon dioxide, *SpO_2* peripheral oxygen saturation, *$PcapCO_2$* Capillary partial pressure of carbon dioxide, *NIV* non-invasive ventilation
[a]Unless indicated

saturations were ≥ 88% on room air, no supplemental oxygen was required. Randomisation was performed after the 15 min wash-in period, when both patient and blinded investigator were already in a forward-facing position to maintain blinding. The unblinded investigator recorded SpO_2 on a separate pulse-oximeter from then onwards.

Immediately before the first nebulisation, denoted by the baseline reading at time-point zero, $PtCO_2$, SpO_2 and heart rate were recorded. Participants then received two administrations of 2.5 mg salbutamol by nebulisation, delivered by either air or oxygen — each for 15 min duration at a flow rate of 8 L/min. Hudson RCI Micro Mist Nebuliser Masks (Hudson RCI, Durham, North Carolina, USA) were used. The nebulisations were delivered by the unblinded investigator at time zero and at 20 min, allowing for a five minute interval between nebulisations. Recordings were continued for 45 min after completion of the last nebulisation (80 min after baseline). Measurements of $PtCO_2$, SpO_2 and heart rate were recorded at five minute intervals, and at six minutes after the start of each nebulisation, in view of the British Thoracic Society (BTS) guideline's recommendation for limiting oxygen-driven nebulisation to six-minutes in ambulance care, if air-driven nebulisation is unavailable.[6]

Immediately before the first nebulisation and just before completion of the second nebulisation, at 35 min, a capillary blood gas sample was taken from the fingertip for measurement of $PcapCO_2$ and pH.

Oxygen delivery

During the wash-in and between the nebulisations oxygen was titrated, if required, via nasal prongs to maintain oxygen saturations between 88 to 92%. Participants in the air-driven group who were receiving oxygen at the start of nebulisation continued to receive titrated supplemental oxygen via nasal prongs underneath the nebuliser mask. Those in the oxygen-driven group had the prongs removed at the start, and reapplied after the completion of each nebulisation. At 35 min, oxygen was delivered via nasal prongs to participants at the flow rate they last received during titration (i.e. at 35 min and 20 min in the air-driven and oxygen-driven groups, respectively). From 35 min until 80 min, the oxygen flow rate was only increased (or initiated) if a participant's SpO_2 fell below 85%.

Outcomes

The primary outcome was originally planned to be $PcapCO_2$ at 35 min, at completion of the second nebulisation. However, after the first 14 participants had been studied, it was evident that obtaining adequate amounts of blood to fill the capillary tubes from some participants was difficult. At this stage of recruitment 4/14 (29%) of participants had missing data. The primary outcome variable was therefore changed to $PtCO_2$ at 35 min, with $PcapCO_2$ at 35 min reverting to a secondary outcome variable. Other secondary outcomes were the individual $PtCO_2$ measurements at each time point; the proportion of participants who had a rise in $PtCO_2$ or $PcapCO_2$ of ≥4 and ≥ 8 mmHg; capillary pH at 35 min, and heart rate and SpO_2 measurements at each time point.

Sample size calculation and statistical analysis

A rise in $PtCO_2$ from baseline of ≥4 mmHg is considered a physiologically significant change and ≥ 8 mmHg a clinically significant change, based on previous criteria.[7,8] In our study of oxygen versus air-driven nebulisers in stable COPD patients, the standard deviation (SD) of baseline $PtCO_2$ was 5.5 mmHg.[3] With 90% power and alpha of 5%, 82 patients were required to detect a 4 mmHg difference. Assuming a drop-out rate of 10% our target recruitment was 90 patients.

The primary analysis used a mixed linear model with fixed effects of the baseline $PtCO_2$, time, the randomised intervention, and a time by intervention interaction term; to estimate the difference between randomised treatments at 35 min. A power exponential in time correlation structure was used for the repeated measurements. The secondary outcome variables of $PtCO_2$ at the other time points, SpO_2 and heart rate used

Table 2 $PtCO_2$ by time and randomised group

Action	Time	$PtCO_2$ Mean (SD) [*N* = 45 for each unless specified]		Oxygen minus air (95% CI)	*P*
		Oxygen	Air		
Baseline	0	38·0 (7·7)	37·2 (6·8)		
1st nebulisation	5	39·9 (8·3)	37·0 (7·1)	2·10 (1·49 to 2·71)	< 0·001
	6	40·1 (8·4)	37·0 (7·1)	2·24 (1·63 to 2·86)	< 0·001
	10	40·8 (8·6)	37·2 (6·9)	2·76 (2·15 to 3·37)	< 0·001
	15	41·1 (8·8)	37·3 (6·9)	2·97 (2·36 to 3·59)	< 0·001
	20	38·6 (7·8)	37·0 (6·4)[a]	0·86 (0·25 to 1·48)	0·006
2nd nebulisation	25	40·5 (8·3)	36·8 (6·8)[b]	2·77 (2·15 to 3·39)	< 0·001
	26	40·6 (8·4)	36·8 (6·8)[b]	2·88 (2·26 to 3·50)	< 0·001
	30	41·1 (8·5)	37·1 (6·6)[a]	3·20 (2·59 to 3·82)	< 0·001
	35	41·3 (8·6)	37·3 (6·5)[a]	3·31 (2·70 to 3·93)	< 0·001
Observation period	40	39·0 (8·1)[a]	37·0 (6·7)[a]	1·14 (0·52 to 1·76)	< 0·001
	45	38·1 (7·5)	36·7 (6·3)[a]	0·61 (– 0·01 to 1·22)	0·053
	50	37·9 (7·4)	36·6 (6·2)[a]	0·59 (– 0·02 to 1·21)	0·059
	55	37·9 (7·3)	36·6 (6·0)[a]	0·51 (– 0·10 to 1·13)	0·1
	60	37·9 (7·3)	36·7 (6·1)[a]	0·51 (– 0·10 to 1·13)	0·1
	65	38·1 (7·2)	36·7 (6·1)[a]	0·63 (0·01 to 1·25)	0·045
	70	37·5 (6·5)[a]	36·7 (6·1)[a]	0·60 (– 0·02 to 1·21)	0·059
	75	37·8 (6·8)	36·7 (6·1)[a]	0·42 (– 0·20 to 1·03)	0·18
	80	37·9 (6·9)	36·7 (6·3)[a]	0·40 (– 0·21 to 1·02)	0·2

Air Air-driven nebuliser group, *Oxygen* Oxygen-driven nebuliser group, *$PtCO_2$* Transcutaneous partial pressure of carbon dioxide
[a]*N* = 44
[b]*N* = 43

similar mixed linear models. $PcapCO_2$ and pH were compared by Analysis of Covariance with the baseline measurement as a continuous co-variate. As a post-hoc analysis we compared the difference in $PtCO_2$ between the 15 and 6 min, and the 35 and 26 min time points.

Comparison of categorical variables, $PtCO_2$ or $PcapCO_2$ change of ≥4 and 8 mmHg, was by estimation of a risk difference, and Fishers' exact test. As a post-hoc analysis we also compared the difference in paired proportions for those with $PtCO_2$ change of ≥4 mmHg in the oxygen arm only using McNemar's test and an appropriate estimate for the difference in paired proportions. The time for $PtCO_2$ to return to baseline during the observation period (defined as the time until the $PtCO_2$ was first equal to or below the baseline value, between 40 and 80 min), was compared using Kaplan-Meier survival curves and a Cox Proportional Hazards model. A simple t-test was used to compare the lowest value of the SpO_2 between 40 and 80 min, compared to baseline. SAS version 9.4 was used.

Results

Patients

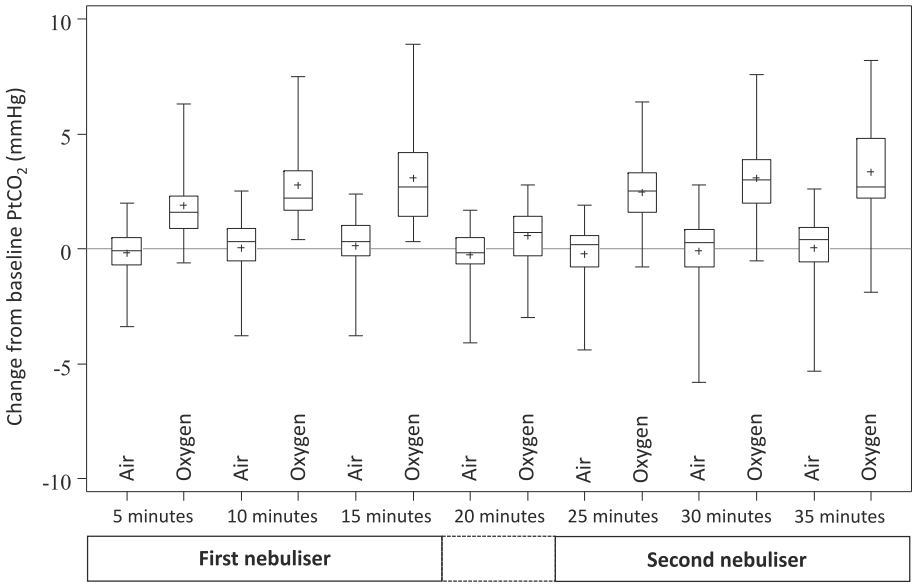
The trial recruited between May 14th 2015 and June 29th 2016. The CONSORT diagram of the flow of the 90 recruited participants through the trial is shown in Fig. 1. One participant withdrew after 18 min of air-driven nebulisation because of feeling flushed, and so complete data was available for $PtCO_2$ for 89 participants. The baseline $PtCO_2$ for this participant was 34.3 mmHg and at the time of withdrawal it was 34.6 mmHg. Oxygen-driven nebulisation was stopped in another participant at 27 min when the $PtCO_2$ rose by > 10 mmHg from baseline, a pre-defined safety criterion. The baseline $PtCO_2$ for this participant was 43.4 mmHg and at the time of withdrawal it was 54.1 mmHg. This participant had study measurements continued after this for the full duration of the study. No clinical adverse events were noted during the intervention periods.

A summary of baseline participant characteristics are shown in Table 1. Participants predominantly had severe airflow obstruction with a mean FEV_1 of 34.5% predicted. The mean (range) baseline $PtCO_2$ was 37.6 mmHg (24.3 to 58.5 mmHg), and mean SpO_2 was 93%. Patients randomised to the oxygen group were more likely to have required assisted ventilation previously. The mean (SD) time for the nebulised salbutamol to dissipate from the chamber was 5.2 (1.2) minutes.

$PtCO_2$

The mean (SD) change in $PtCO_2$ after 35 min was 3.4 (1.9) mmHg in the oxygen group (n = 45), compared to 0.1 (1.4) mmHg in the air group (n = 44). The difference (95% CI) in $PtCO_2$ for oxygen compared to air-driven nebulisations after 35 min was 3.3 mmHg (2.7 to 3.9), p < 0.001. (Table 2 and Fig. 2). After adjustment for baseline $PtCO_2$, a history of assisted ventilation, previous hypercapnia and baseline SpO_2, were not associated with the $PtCO_2$ at 35 min in either randomised group.

In 18/45 (40%) participants receiving oxygen-driven nebulisation, $PtCO_2$ increased from baseline by ≥4 mmHg at some stage during the intervention compared to none of the participants receiving air-driven nebulisation, risk difference (95% CI) 40% (25.7 to 54.3), p < 0.001. The full data description and comparisons at each time point are shown in the OLS. Two participants receiving



Air: Air-driven nebuliser group; Oxygen: Oxygen-driven nebuliser group;

$PtCO_2$: Transcutaneous carbon dioxide tension

Figure 2. $PtCO_2$ change from baseline (T = 0) to T = 35 min. Mean $PtCO_2$ with error bars showing one SD, by time and intervention

oxygen-driven nebulisation had a rise in $PtCO_2$ ≥ 8 mmHg, one of whom required intervention termination, exceeding the predefined safety criterion of a rise ≥10 mmHg from baseline.

The estimate (95% CI) of the time-related difference, 15 min minus six minutes, for oxygen compared to air, was 0.73 mmHg (0.11 to 1.35), P = 0.021; and for 35 min minus 26 min, 0.43 mmHg (– 0.19 to 1.06), P = 0.17. In the oxygen treatment arm the proportion of patients in whom the $PtCO_2$ increased from baseline by ≥4 mmHg at 6 min was less than the proportion at 15 min: 6/45 (13.3%) and 13/45 (28.9%) respectively, paired difference in proportions (95% CI) 15.6% (3.3 to 27.8), P = 0.013 (Additional file 1: Table S1). The proportion of patients in whom the $PtCO_2$ increased from baseline by ≥4 mmHg at 26 min (6 min into the second oxygen-driven nebulisation) was also less than the proportion at 35 min (completion of the second oxygen-driven nebulisation), although this difference was not statistically significant: 10/45 (22%) and 14/45 (31%) respectively, paired difference in proportions (95% CI) 8.9% (– 3.3 to 20.9), P = 0.15.

The median (25th to 75th percentile) time taken for $PtCO_2$ to return to baseline after cessation of the second nebulisation was 40 (40 to 45) minutes in the air group compared to 50 (45 to 50) minutes in the oxygen group, hazard ratio (95% CI) 1.59 (1.01 to 2.52), P = 0.047.

$PcapCO_2$ and pH

Data summaries for capillary blood gas sampling are shown in Table 3. The difference (95% CI) between oxygen and air for $PcapCO_2$ after 35 min was 2.0 mmHg (1.1 to 2.8), p < 0.001. Thirteen (31.7%) participants receiving oxygen had a rise in $PcapCO_2$ of ≥4 mmHg compared with three (7.7%) receiving air; risk difference (95% CI) 24% (7.5 to 40.5), p = 0.01. In addition to the two participants in whom the $PtCO_2$ increased by ≥8 mmHg, there were two additional participants with capillary data receiving oxygen who had a rise in $PcapCO_2$ of ≥8 mmHg and none from the air group. The mean (95% CI) difference in pH after 35 min was 0.015 units (0.008 to 0.024, p < 0.001) lower for oxygen nebulisation compared to air. One participant experienced a reduction in pH of 0.06 units (from 7.38 to 7.32) in association with a rise in $PcapCO_2$ of 9 mmHg (55 to 64 mmHg).

SpO_2 and heart rate

The SpO_2 was higher throughout both the nebulisation and initial washout periods in the oxygen compared with the air group (see Additional file 3: Table S2). Figure 3 shows the trend for the SpO_2 in the oxygen group to fall below that of the air group after cessation of the second nebulisation. At the end of the observation period (80 min), the SpO_2 was lower in the oxygen group (difference – 1.22%, 95% CI -2.04 to – 0.39, p = 0.004). The maximum reduction in SpO_2 from baseline was 0·8% (95% CI -0.2 to 1.7, P = 0.10) lower after oxygen compared with air nebulisation. The heart rate was slower in the oxygen group at 35 min by 3.3 bpm (95% CI 0.31 to 6.25), p = 0.031 (see Additional file 1: Table S3).

Methods of PCO_2 measurement

Due to the requirement to change the primary outcome measure, a post-hoc analysis was undertaken to compare the two methods of measuring $PaCO_2$. Based on data for 80 paired $PtCO_2$ and $PcapCO_2$ measurements at baseline and 35 min, the mean (SD) change in $PtCO_2$ was 1.7 mmHg (2.2) with a range of – 2.5 to 8.0 mmHg, and the mean (SD) change in $PcapCO_2$ was 1.7 mmHg (2.3), with a range – 3.0 to 9.0 mmHg. The estimate of bias for change in $PcapCO_2$ minus $PtCO_2$ was – 0.03 mmHg (95% CI -0.44 to 0.38), P = 0.89. The limits of agreement between $PtCO_2$ and $PcapCO_2$ were ±3.8 mmHg for each individual measurement obtained.

Discussion

In this study, oxygen-driven nebulisation increased the $PtCO_2$ in hospital in-patients with an AECOPD compared with air-driven nebulisation. Despite the small mean increase in $PtCO_2$ of 3.4

Table 3 Capillary blood gas measurements according to randomised treatment

Time (mins)	$P_{cap}CO_2$ Mean (SD)		Difference[a] (95% CI)	*P*
	Oxygen	Air		
0	40·2 (7·0) *N* = 43	38·5 (5·9) *N* = 41	–	–
35	42·6 (8·3) *N* = 41	39·0 (6·4) *N* = 39	2·0 (1.1 to 2·8)	< 0·001
Time (mins)	pH Mean (SD)		Difference[b] (95% CI)	*P*
	Oxygen	Air		
0	7·42 (0·04) *N* = 43	7·44 (0·03) *N* = 41	–	–
35	7·41 (0·04) *N* = 41	7·43 (0·04) *N* = 39	-0·015 (– 0·024 to – 0·008)	< 0·001

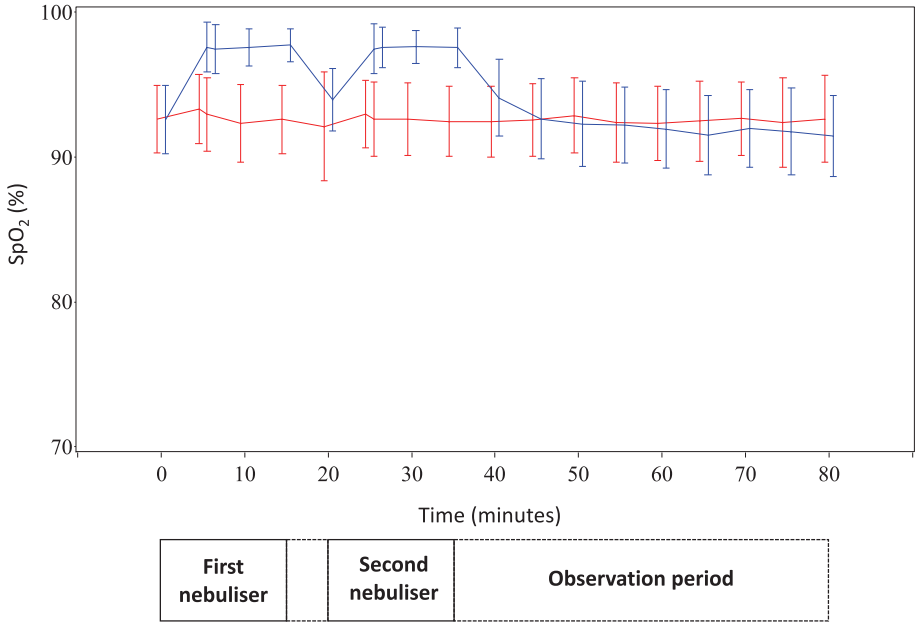
$P_{cap}CO_2$ Capillary partial pressure of carbon dioxide
[a]$P_{cap}CO_2$ at 35 min, adjusted for baseline
[b]pH at 35 min, adjusted for baseline

mmHg, the physiological relevance of this response is suggested by the increase in $PtCO_2$ of at least 4 mmHg in 18/45 (40%) of participants receiving oxygen-driven nebulisation, whereas no patient had an increase of 4 mmHg or more following air-driven nebulisation. The clinical relevance of this physiological response is suggested by the requirement to withdraw one participant during the second oxygen-driven nebulisation due to the $PtCO_2$ increasing by > 10 mmHg, and the increase of $PtCO_2$ or $PcapCO_2$ of at least 8 mmHg in 4/45 (9%) patients receiving oxygen-driven nebulisation, one of whom had a fall in pH of 0.06 into the acidotic range (7.32). These findings suggest that air-driven nebulised bronchodilator therapy represents an important component of the conservative titrated oxygen regimen which has been shown to reduce the risk of hypercapnia, acidosis and mortality in AECOPD.[1]

There are a number of methodological issues relevant to the interpretation of the study findings. Both the randomised controlled design and double-blinding of this study allow for robust and reliable data capture. The length of the nebuliser regimen was chosen to ensure adequate time for complete nebulisation to occur, and to replicate 'real-world' back to back treatments in the acute setting, by using two nebulisations separated by five minutes. It is possible that the magnitude of the differences in PCO_2 and pH may be even larger with continuous nebulisation which may occur in patients with severe exacerbations not responding to initial treatment or if the nebuliser is inadvertently left in place. The safety-based exclusion criteria of a baseline $PtCO_2 > 60$ mmHg and an oxygen requirement of ≥4 L/minute (to maintain target SpO_2 of 88 to 92%), effectively excluded patients with the most severe exacerbations of COPD.

Whilst respiratory rate and neurological symptoms were not formally assessed as outcome measures, no adverse events were identified during the interventions. However, we acknowledge that if changes in PCO_2 and pH of this magnitude occurred in more severe patients at the time of their presentation, they would have been at risk of symptoms of hypercapnia and respiratory acidosis, and the requirement to escalate treatment.

The original primary outcome measure and time of measurement was $PcapCO_2$ after 35 min. Following the first 14 study participants, it was evident that obtaining adequate amounts of blood to fill the capillary tubes from some participants was difficult or impossible to the extent that 4 out of 14 participants



SpO_2: Oxygen saturation measured by pulse oximeter

Figure 3. Time-course of SpO2 throughout study period (Blue = Oxygen-driven nebuliser group, Red = Air-driven nebuliser group)

had one or more missed samples. For this reason, the primary outcome was changed to $PtCO_2$ after 35 min. In other words, the method of capturing the change in PCO_2 was revised, rather than the outcome itself. $PtCO_2$ monitoring enabled continuous assessment to be undertaken, and is accurate in AECOPD,[9] and other acute settings.[10-12] The validity of this method was confirmed by the post hoc analysis of 80-paired samples, where each capillary blood gas sample obtained had a corresponding $PtCO_2$ measurement at the same time-point. This showed that the difference between the $PcapCO_2$ and $PtCO_2$ in the mean change from baseline was – 0·03 mmHg with 95% confidence intervals of – 0.44 to 0.38 mmHg. This data suggests that the use of $PtCO_2$ measurements did not adversely affect our ability to determine change in $PcapCO_2$ from baseline.

We did not investigate the potential mechanisms by which oxygen driven nebulisation increases $PtCO_2$. However as demonstrated in mechanistic studies of oxygen therapy in COPD, it is likely to be due to the combination of a reduction in respiratory drive, release of hypoxic pulmonary vasoconstriction, absorption atelectasis, and the Haldane effect.[13,14] Furthermore, the study was not designed to assess costs related to each regimen, however it is reasonable to assume that improved clinical outcomes seen by avoiding a rise in $PtCO_2$ and associated acidosis, would lead to a reduction in healthcare costs.

The findings from our study complement those of our previous randomised controlled trial of a similar design in stable COPD patients in the clinic setting, in which there was a mean $PtCO_2$ difference between the oxygen and air-driven nebulisation treatment arms of 3.1 mmHg (95% CI 1·6 to 4·5), $p < 0·001$, after 35 min.[3] In that study one of the 24 subjects was withdrawn due to an increase in $PtCO_2$ of 10 mmHg after 15 min of the first oxygen-driven nebulisation. As with the previous study, an increase in $PtCO_2$ occurred within 5 min, indicating the rapid time course of this physiological response. We had anticipated a greater effect in this current study as the patients had acute rather than stable COPD however the magnitude of the effect was similar, probably reflecting the similar severity of airflow obstruction, with a mean predicted FEV_1 of 35% and 27% in this and the previous study respectively.

The two previous open crossover studies of inpatients with AECOPD both showed oxygen-driven nebulisation worsened hypercapnia in patients with Type 2 respiratory failure.[4,5] Gunawardena et al[4] studied 16 patients with COPD and reported that only those with carbon dioxide retention at baseline (n = 9) demonstrated a rise in $PaCO_2$ after 15 min (mean of 7·7 mmHg), and one patient had a rise of 22 mmHg. Similarly, O'Donnell et al[5] reported that 6/10 patients, all with carbon dioxide retention at baseline, showed a rise in $PaCO_2$ after 10 min (mean of 12.5 mmHg).

The current BTS guidelines recommend air-driven nebulisation and, if this is not available in the ambulance service, the maximum use of 6 min for an oxygen-driven nebuliser. This is based on the rationale that most of the nebulised medication will have been delivered, and is categorised as grade D evidence.[6] We observed the mean time for dissipation of salbutamol solution from the nebuliser chamber of 5.2 min confirming that 6 min is adequate for salbutamol delivery. The proportion of participants with a $PtCO_2$ increase ≥4 mmHg was lower after 6 min than 15 min, suggesting some amelioration of risk with the shorter nebulisation treatment. Alternative methods of bronchodilator delivery include air-driven nebulisers or multiple metered dose inhaler actuations via a spacer.[15]

The potential for rebound hypoxia after abrupt cessation of oxygen therapy has been observed both in the treatment of asthma and COPD.[9,16,17] We identified some evidence consistent with this phenomenon which is a potentially important yet poorly recognised clinical issue.

Conclusions

In summary, air-driven nebulisation avoids the potential risk of increasing the $PaCO_2$ associated with oxygendriven bronchodilator administration in AECOPD. We propose that air-driven bronchodilator nebulisation is preferable to oxygen-driven nebulisation in AECOPD, and that when the use of oxygen-driven nebulisation is unavoidable, $PtCO_2$ is monitored if possible.

Authors' contributions

RB was the principal investigator for the study, is guarantor for the study, and affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. GB, JP, SM and JB were investigators on the study and collected the data. MW performed the statistical analysis. GB wrote the first draft of the manuscript. RB and PS conceived the study and wrote the first draft of the protocol with JP. GB, JP, SM, PS, JB, JF, MW and RB all contributed to study design, interpretation of results, manuscript writing, and reviewed the final manuscript prior to submission. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. No writing assistance was received. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the Health and Disability Ethics Committee, New Zealand (Reference 14/NTB/200). Written informed consent was obtained before any study-specific procedures.

Consent for publication

Not applicable.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. All authors have no competing interests to declare, other than the MRINZ receiving research funding from Health Research Council of New Zealand.

References

1 M a A, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ. 2010;341:c5462.

2 Murphy R, Driscoll P, O'Driscoll R. Emergency oxygen therapy for the COPD patient. Emerg Med J. 2001;18:333–9.

3 Edwards L, Perrin K, Williams M, et al. Randomised controlled crossover trial of the effect on PtCO2 of oxygen-driven versus air-driven nebulisers in severe chronic obstructive pulmonary disease. Emerg Med J. 2012;29:894–8.

4 Gunawardena KA, Patel B, Campbell IA, et al. Oxygen as a

driving gas for nebulisers: safe or dangerous? Br Med J (Clin Res Ed). 1984;288:272–4.
5 O'Donnell D, Kelly CP, Cotter P, Clancy L. Use of oxygen driven nebuliser delivery systems for beta-2 agonists in chronic bronchitis. Ir J Med Sci. 1985; 154:198–200.
6 British Thoracic Society Emergency Oxygen Guideline Group. BTS guidelines for oxygen use in adults in healthcare and emergency settings. Br Thorac Soc. 2017;72:1–214.
7 Wijesinghe M, Williams M, Perrin K, et al. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomised, crossover, clinical study. Chest. 2011;139:1018–24.
8 Perrin K, Wijesinghe M, Healy B, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax. 2011;66:937–41.
9 Rudolf M, Turner JA, Harrison BD, et al. Changes in arterial blood gases during and after a period of oxygen breathing in patients with chronic hypercapnic respiratory failure and in patients with asthma. Clin Sci. 1979; 57:389–96.
10 Senn O, Clarenbach CF, Kaplan V, et al. Monitoring carbon dioxide tension and arterial oxygen saturation by a single earlobe sensor in patients with critical illness or sleep apnea. Chest. 2005;128:1291–6.
11 Rodriguez P, Lellouche F, Aboab J, et al. Transcutaneous arterial carbon dioxide pressure monitoring in critically ill adult patients. Intensive Care Med. 2006;32:309–12.
12 McVicar J, Eager R. Validation study of a transcutaneous carbon dioxide monitor in patients in the emergency department. Emerg Med J. 2009;26:344–6.
13 Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administartion of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Resp Dis. 1980; 122:747–54.
14 Robinson TD, Freiberg DB, Regnis JA, Young IH. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161:1524–9.
15 van Geffen WH, Douma WR, Siebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for eaxcerbations of COPD. Cochrane Database Syst Rev 2016 (8): CD011826, Epub 2016 Aug 29.
16 Auerbach D, Hill C, Baughman R, et al. Routine nebulised ipratropium and albuterol together are better than either alone in COPD. Chest. 1997;112:1514–21.
17 Kane B, Turkington PM, Howard LS, et al. Rebound hypoxaemia after administration of oxygen in an acute exacerbation of chronic obstructive pulmonary disease. BMJ. 2011;342:d1557.
18 Bardsley G, McKinstry S, Pilcher J, et al. Oxygen compared to air driven nebulisers for acute exacerbations of COPD: a randomised controlled trial.ERJ. 2017;50:PA684.

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of adult chronic obstructive pulmonary disease and possible links with childhood wheezing. Paediatr Respir Rev. 2001;2:178–83.
29. Hwang YI, Park YB, Yoo KH. Recent trends in the prevalence of chronic obstructive pulmonary disease in Korea. Tuberc Respir Dis (Seoul). 2017;80:226–9.
30. Labonte LE, Tan WC, Li PZ, Mancino P, Aaron SD, Benedetti A, Chapman KR, Cowie R, FitzGerald JM, Hernandez P, et al. Undiagnosed chronic obstructive pulmonary disease contributes to the burden of health care use. Data from the CanCOLD study. Am J Respir Crit Care Med. 2016;194:285–98.
31. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, et al. Clinical and radiologic disease in smokers with Normal spirometry. JAMA Intern Med. 2015;175:1539–49.
32. Tan WC, Bourbeau J, Hernandez P, Chapman KR, Cowie R, FitzGerald JM, Marciniuk DD, Maltais F, Buist AS, O'Donnell DE, et al. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. Thorax. 2014;69:709–17.
33. van Durme Y, Verhamme KMC, Stijnen T, FJA v R, Van Pottelberge GR, Hofman A, Joos GF, Stricker BHC, Brusselle GG. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. Chest. 2009;135:368–77.
34. Afonso AS, Verhamme KM, Sturkenboom MC, Brusselle GG. COPD in the general population: prevalence, incidence and survival. Respir Med. 2011; 105:1872–84.
35. Garcia Rodriguez LA, Wallander MA, Tolosa LB, Johansson S. Chronic obstructive pulmonary disease in UK primary care: incidence and risk factors. COPD. 2009;6:369–79.

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