Volume 9 Number 3 June-July 2014

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The Journal of Pulmonary Technique

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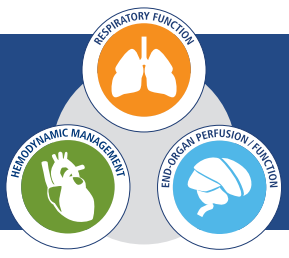

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Infringement Claims Dropped

BMC Medical Co., Ltd. and 3B Medical, Inc.—which specialize in the development, manufacturing and marketing of medical products for the treatment and management of sleep disordered breathing—have announced that ResMed (RMD) dropped one of the patents initially asserted against BMC and 3B, U.S. Patent No. 7,938,116 ("the '116 patent"), in the pending investigation before the US International Trade Commission under Section 337. Following a ruling by the ITC's Administrative Law Judge restricting the scope of the asserted claims of the '116 Patent, ResMed voluntarily withdrew the patent from the investigation. The ITC confirmed that the '116 Patent was dropped from the case in a Notice issued on March 11, 2014. In addition, ResMed has confirmed that a number of the product designs introduced by BMC and 3B in the ITC investigation are not alleged to infringe its patents.

Portable Device Introduced

CAIRE, which provides respiratory care products for the home healthcare industry, announced the release of the SeQual eQuinox portable oxygen concentrator (POC), featuring additional user enhancements from its other devices. The Multi-Language Voice Interface offers a new layer of comfort to users by providing verbal confirmation of flow rate settings, battery times and alarms. The user-friendly interface is adjustable to support a variety of patient languages. Weighing in at 14 pounds, the newly designed, easy-to-maneuver frame makes the SeQual eQuinox the lightest POC to offer 3.0 LPM continuous flow. This small package is still powerful enough to give patients the freedom to enjoy life on the go. The eQuinox is fully functional on AC Power in the home, DC Power in the car, and battery power everywhere else. With the option of a longer lasting 24-cell battery pack, the eQuinox can achieve 2.75 hours of operation at 2.0 LPM. Providing both continuous flow options from 0.5LPM to 3.0LPM and 9 pulse flow settings from 16mL to 192mL, the SeQual eQuinox can meet a patient's 24/7 needs. The comprehensive dosing selection allows a patient to be treated at rest, during sleep, at exercise, and at altitude.

Brand Refreshed

"Changing lives with every breath." That's the new tagline accompanying a ResMed's efforts to freshen up its brand to align with the company's appearance in the marketplace with its global focus on innovation that benefits patients' lives. ResMed's new logo includes an updated word-mark combined with a visually appealing "pulse" curve that shifts in color from bright blue to rich red, symbolizing the transition that deoxygenated blood makes to oxygenated blood with every breath, and every beat of the heart. The new brand transition starts with ResMed's US operations, and will roll out globally throughout the year. A key element will be a refreshed and user-friendly company website—ResMed.com—that helps people more easily find information to help them on their journey to better breathing. This is the first time in the company's 25-year history that it has unveiled a new brand.

No Extra CV Study Needed

Taking drugs for chronic obstructive pulmonary disease (COPD) down the same road as those for diabetes by requiring cardiovascular outcome safety trials is a mistake, a think tank panel has told the FDA. Both conditions carry a heavy burden of cardiovascular disease, but setting the bar too high for proof of safety in COPD could actually end up hurting patients, said Philip Sager, MD, a session chair at the meeting between the FDA and the Duke University-linked think tankCardiac Safety Research Consortium. Tiotropium (Spiriva) was an example of the scientific challenge cited by Peter Kowey, MD, of Jefferson Medical College in Philadelphia, who presented the industry and academic viewpoint. The UPLIFT trial showed

the drug to be a clear winner in COPD with a possible mortality advantage over placebo. But then questions about risk with the Respimat inhaler device keep coming up even after the large TIOSPIR outcomes trial to settle the issue. The main consensus between the FDA and the panel of academic and industry representatives was that outcomes trials are most warranted only when there has been a "meaningful" cardiovascular risk signal in the clinical development program. That differed from the stance taken with diabetes drugs, where the agency adopted stricter standards for proof of cardiovascular safety of drugs in 2008 following the rosiglitazone (Avandia) debacle. The COPD think tank did call, though, for extra care to be taken in collecting the underlying cardiovascular history on patients who have cardiovascular events in trials. While not a new concept, that strategy together with an adequate safety database and a trial population enriched with patients at extra risk due to comorbidities should often prevent the need for big, long, expensive outcomes trials, agreed Sally Seymour, MD, who spoke at the meeting as deputy director for safety of the FDA division tasked with evaluating pulmonary drugs.

Ready to Launch

Covidien has announced its Puritan Bennett 980 ventilator has received US Food and Drug Administration (FDA) 510(k) clearance. The new acute care ventilator from Covidien—designed to be simple, safe and smart—helps enable patients to breathe more naturally through innovative breath technology. The most critical goal of clinicians is to get patients off mechanical ventilation as soon as possible. The Puritan Bennett 980 ventilator can help with a range of software capabilities, including Proportional Assist, Ventilation Plus, and Leak Sync software. Proportional Assist Ventilation Plus has been shown to help reduce asynchrony, which studies have shown may reduce days on mechanical ventilation. Patients on mechanical ventilation are often sedated to ease agitation and help them tolerate breath support and other medical interventions. The Puritan Bennett 980 ventilator features advanced synchrony tools that help clinicians set the ventilator to adapt to their patients' unique needs and help provide the appropriate level of support throughout the breath. The Puritan Bennett 980 ventilator system is for patients ranging from neonatal to adult. The ventilator system was also approved for commercial distribution in Japan and Canada and will be available in those countries and the U.S. in the coming months.

Literary Work Funded

Medical technology maker Dräger has put its money where its mouth is when it comes to education and research, announcing that it has given the American Respiratory Care Foundation (ARCF) a $50,000 endowment to establish the Dräger Literary Award. In addition, Dräger has provided an unrestricted grant to the American Association of Respiratory Care (AARC) to help develop its new Leadership Program. Dräger is one of three companies in the respiratory industry to establish an endowment to the ARCF for the purpose of creating annual literary awards. The Dräger Literary Award recognizes the best paper focused on mechanical ventilation published in the science journal RESPIRATORY CARE. Each year, the Dräger Literary Award will be presented by the American Respiratory Care Foundation at the AARC's annual International Respiratory Congress. All papers published in the science journal RESPIRATORY CARE are judged automatically and the selection for awards is based on the decision of the Editorial Board of the journal. Since all papers are judged automatically, no application is required. The award consists of a certificate of recognition, registration to the AARC Congress, airfare to the Congress, and one night's lodging. Dräger also presented the AARC with an unrestricted grant to help develop its new Leadership Institute, which was established as a quality continuing education program for respiratory care practitioners. The Leadership Institute offers three educational tracks—research, education and management—and awards three scholarships in each track. The tracks have been developed by nationally respected leaders in the field of respiratory care, who will also provide mentoring to participants.

Enzyme Unlocks Treatment Puzzle

An enzyme called Src kinase may provide a new way to attack lymphangioleiomyomatosis (LAM), a rare lung disease that appears only in women either alone or in association with a genetic disorder known as tuberous sclerosis, said researchers from Baylor College of Medicine in a report that appears in the journal Cancer Research. Tuberous sclerosis complex (TSC) is

Respiratory Therapy
The Journal of Pulmonary Technique

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

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a rare genetic disease that affects many of the body's organ system, causing tumors in the brain, kidneys, heart, eyes, lung and skin. Because it also affects the central nervous system, those who have it suffer seizures, developmental delay, behavior problems, skin abnormalities and kidney disease. LAM, the major lung manifestation in TSC, is found in 35 percent of women with the disorder. The lung lesions that occur in women with LAM cause tumor-like growths with cells proliferating in and destroying lung tissue. LAM is a progressive cystic lung disease associated with collapsed lung (pneumothorax), leakage of a milky fluid made up of lymphatic fluid and lipids or fats into the chest cavity (chylous effusions), shortness of breath during exercise and respiratory failure. Sporadic LAM can develop in women who do not have TSC but have mutations in the gene associated with it. Dr N. Tony Eissa, professor of medicine–pulmonology, pathology and immunology and molecular and cell biology at Baylor, and his colleagues sought to find out where the errant cells in LAM were coming from and how they were activated to grow aberrantly. In studies of tissues from the lungs of normal people and people with LAM as well as in animals, Eissa and his colleagues made three new findings: Src kinase is activated in LAM cells; the enzyme contributes to the destruction brought by LAM cells by promoting the mesenchymal phenotype of cells and thus becoming more mobile and invasive; and inhibiting Src kinase can reduce the potential of LAM cells to migrate to the lung in animal model of LAM. There are drugs under development that can inhibit Src kinase in cells, said Eissa. He and his colleagues found the drugs can change the activity of LAM cells in tissue culture and in a mouse model of LAM. In the next few months, he and his colleagues will test such drugs in subjects with LAM. While there are treatments for LAM, there is no cure and some patients do not respond to existing treatments.

Viva Vivo

Breas Medical has announced the release of the Vivo 50, a homecare ventilator combining high-quality technology, robustness and premium design to provide excellent patient treatment in the United States. The Vivo 50 has been developed to meet the lifestyle demands of active patients with a focus on autonomy, durability and robustness. The Vivo 50 offers an extensive range of product features. The eSync technology is a highly responsive triggering technology that synchronizes smoothly with the patient's effort and empowers the clinical staff by providing a mechanism to customize patient treatment. The combination of the internal battery and click-on battery offers 12-hour autonomy for the patient. Additionally, the Hot Swap function provides the convenience of replacing the click-on battery while the device is running. The extensive monitoring capabilities of the Vivo 50 provide clinical staff with ample possibilities to define and control the patient's treatment plan. The Vivo 50 is equipped with SpO_2 and CO_2 monitoring solutions, which reduces the need for additional devices to an absolute minimum. The large full-color screen allows the clinical staff to easily read the set parameters, waveforms, numerical data and trends. One year of treatment data can be downloaded onto a memory card or read and analyzed online by an advanced PC software program.

Don't Ignore Sleep Apnea

If you are experiencing signs of sleep apnea it is extremely important to discuss the condition with your doctor. That's the message from Christy Hall, manager of Annie Penn Sleep Center and Respiratory Therapy, who has been a respiratory therapist for 24 years. According to Hall, sleep apnea is a sleep breathing disorder that restricts breathing patterns during sleep, disrupting the normal five stages of sleep, especially the important deep, REM sleep stage. Lately, more and more research has been surrounding sleep medicine, as medical professionals are finding sleep disorders and deprivation to be linked to serious health conditions such as heart disease. Untreated sleep apnea, in particular, has been shown to increase risk of cardiovascular disease morbidity and mortality, Hall said. Consistent snoring is a major indicator of sleep apnea. Individuals with sleep apnea may also have trouble sleeping in certain positions, experience daytime sleepiness or feel a sense that their sleep wasn't refreshing. The disorder is commonly seen in individuals who are overweight or obese and/or have a thick neck. Fortunately, sleep apnea is a completely treatable disorder, commonly treated with the use of a CPAP (continuous positive airway pressure) machine. While CPAP therapy remains the gold standard for sleep apnea treatment, individuals who have trouble complying with CPAP therapy can discuss treatment options, such as nasal valves and oral appliances, with their doctor. By detecting and treating sleep apnea early, a myriad of cardiovascular diseases and other serious health conditions can be prevented or decreased, Hall said.

Flow Indicated

Maxtec, based out of Salt Lake City, has announced the release of its new FLOCAP flow indicator. The FLOCAP is a single-use CO2 and flow-indication device designed for visualization of a patient's exhaled CO2 and expiratory flow. The CO2 indication will assist the caregiver in verifying proper ET Tube placement. The flow indicator helps the caregiver identify end of exhalation, which may help prevent breath stacking and its associated health issues during resuscitation. Maxtec is offering free samples for testing.

Alternatives to Consider

Acute respiratory failure is not uncommon and can occur from a variety of causes to people of all ages. Chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS) are just two of many reasons why a patient may experience respiratory failure and require invasive mechanical ventilation (IMV). Approximately 13.7 million people in the United States are living with COPD, and ARDS averages approximately 160,000 cases per year. While IMV has proven to be an indispensible therapy for persons undergoing such incidents, an increased understanding of further lung injury that can in fact be caused by the ventilator has led to a shift in the paradigms for providing respiratory support. A new device offers a minimally invasive option for respiratory support that may allow patients to either avoid IMV or mitigate its injurious side effects. The Hemolung Respiratory Assist System (ALung Technologies, Inc., Pittsburgh, PA) is a newcomer to the field that potentially addresses both the issue of CO2 removal as well as the highly invasive nature of traditional IMV and ECMO. Using techniques similar to renal dialysis, the Hemolung RAS provides extracorporeal CO2 removal (ECCO2R) in an effective and minimally invasive way. The Hemolung RAS uses an approach like ECMO, but with substantially lower blood flows (less than half a liter per minute) and only a single, much smaller catheter. Unlike ECMO, there is only one component in the circuit, and it is operated from a single, user-friendly control unit, making it the only fully integrated system on the market. The single circuit component of the Hemolung RAS is a cartridge, about the size and shape of a one quart can of paint, that contains both

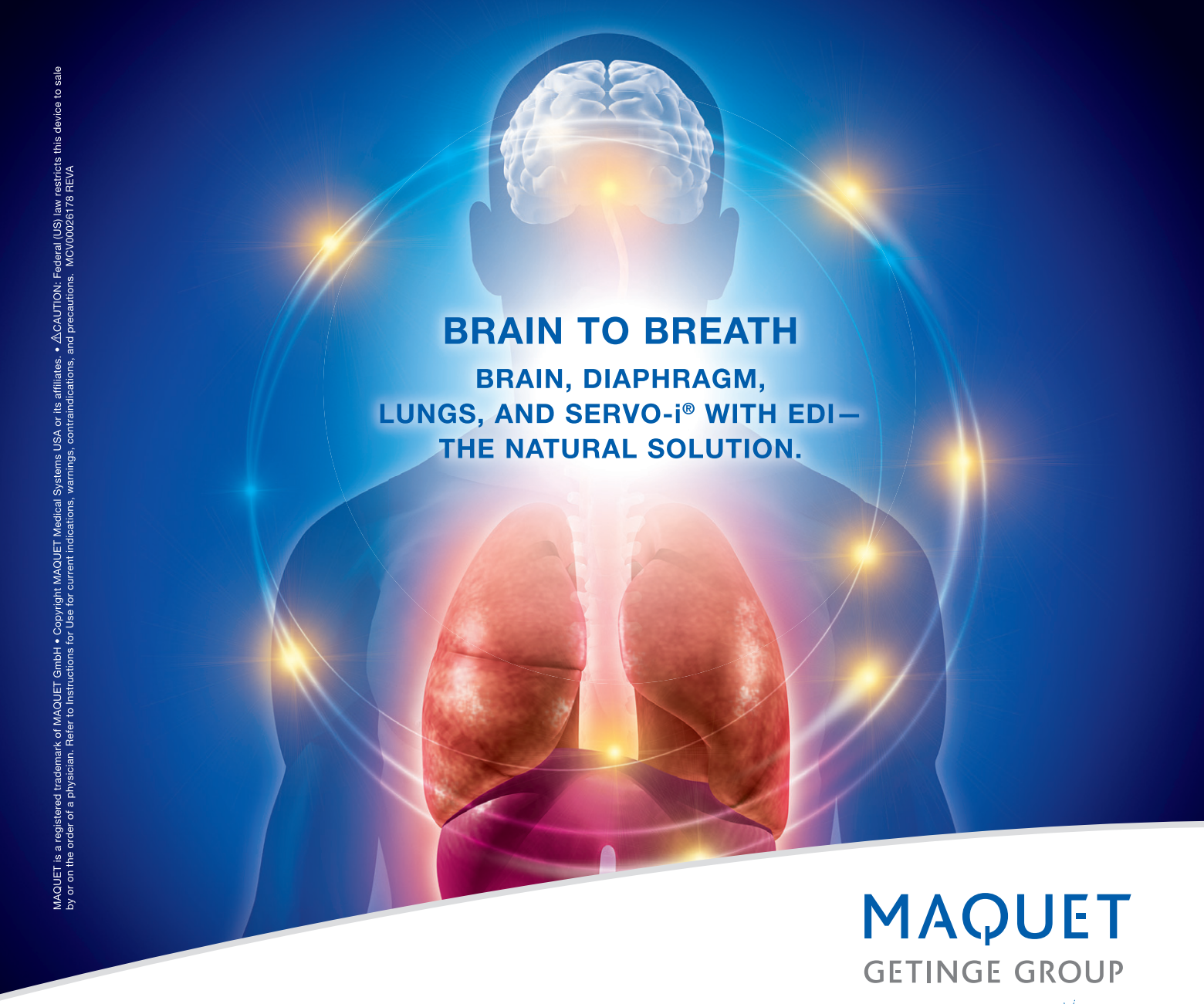
gas exchange membranes and a centrifugal pump. The unique design of this cartridge is based on a hollow, spinning, cylindrical core which both pumps the blood and creates enhanced mixing of blood flow near the membranes to maximize the efficiency of CO2 removal. The Hemolung RAS is the only gas exchange device to employ active mixing. The increased efficiency achieved with active mixing allows for a reduced membrane surface area necessary to achieve effective levels of CO2 removal without requiring dangerously high blood flows. The Hemolung RAS is the only device specifically designed for CO2 removal, a key differentiation among extracorporeal therapy techniques. It is possible to achieve clinically meaningful levels of CO2 removal at much lower blood flows than are necessary for meaningful oxygenation. The Hemolung RAS removes CO2 at a rate of 50 t o100 mL/min, using a blood flow rate of 350 to 500 mL/min. The active mixing technology enhances gas exchange 150% over passive diffusion devices, and the entire system is battery operated, allowing the patient to ambulate. The regulatory process in the US requires large, pivotal clinical trials, which are currently in the works. In the meantime, the device has been approved for use in the European Union, Canada, and in Australia on a limited basis. Its use in these countries is influencing the paradigm of care for patients with hypercapnic respiratory failure. There is a need for devices that are minimally invasive, that can be used earlier in the treatment paradigm, and that can be made available to a greater percentage of the population. The Hemolung RAS appears to offer all of these benefits. Information is from an article written by Dr Laura Lund, director of Scientific Affairs at ALung Technologies.

Nurses Forced to Be RTs

Recent layoffs at KentuckyOne Health mean that patients having difficulty breathing will no longer be cared for by respiratory therapists at three Louisville-area emergency rooms—even if it's from an asthma attack, drug overdose or cardiac arrest. Instead, nurses at the three facilities, Jewish Medical Centers South, Southwest and East, will take over respiratory care after getting a "refresher training," KentuckyOne spokeswoman Barbara Mackovic confirmed. While respiratory care is within nursing's legal scope of practice in Kentucky, some employees of the facilities are concerned the nurses don't have enough knowledge or practical experience performing functions like operating a ventilator, which sends oxygen into the lungs of patients who can't breathe on their own. In a statement to WDRB, Mackovic said safety is KentuckyOne's No. 1 priority and "any changes within our health care facilities will not place our patients at risk." She added that this model of care is "similar to the Saint Joseph Jessamine (in Nicholasville, Ky.) and ambulatory facilities across the region." In all, about 500 people were laid off and 200 open positions were cut.

Asthma Solutions

If you've ever tried to drink something through one of those little red coffee stirrers instead of a full-sized straw, you know what it's like to breathe with asthma. Twenty-five million Americans



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have been diagnosed with asthma. And for 10 percent of them, medications like inhaled corticosteroids and long-acting beta agonists aren't enough to keep them out of the hospital. In 2010, the FDA approved bronchial thermoplasty, the first nonpharmaceutical treatment for severe asthma. Inhaled drugs and other medications offer temporary relief for most asthma patients. Bronchial thermoplasty, on the other hand, is intended to reduce asthma symptoms permanently. The procedure attacks the problem at its very root—the muscles in the lungs' airways. During an asthma attack, muscle cells contract and restrict airflow. To keep the muscles from constricting, a catheter is used to deliver heated zaps of energy that essentially burn off the outer layer of smooth muscle cells. That way there's less muscle to contract. Studies of the procedure have not shown that it reduces airway hyperresponsiveness or the amount of air a person can exhale. But it does seem to improve people's quality of life. One study found that patients who underwent the procedure, which requires three sessions, saw the number of asthma attacks drop by a third, on average, and emergency room visits decline by 70 percent. They also lost far fewer days from work and school. The study was funded by Boston Scientific, the company that created bronchial thermoplasty and sells the machines. The biggest drawback to bronchial thermoplasty seems to be the immediate response to the treatment, which can temporarily make symptoms worse.

Strokes Can Cause Sleep Apnea

Stroke patients who have damage to their brain stem are more likely to have sleep apnea than those with damage in other parts of their brain, Michigan researchers report. Their study included 355 people in Texas, average age 65, who suffered an ischemic stroke, which is caused by blocked blood flow in the brain. Fifty-five percent of the patients were men, 59 percent were Hispanic, 35 percent were white, 4 percent were black and 1 percent were Native American. The researchers used CT and MRI brain scans to assess brain damage in the patients, who were assessed for sleep apnea about 13 days after their stroke. Of the 11 percent who had damage to the brain stem, 84 percent had sleep apnea. By comparison, only 59 percent of those without brain stem injury had sleep apnea. The study was scheduled for presentation at the American Stroke Association meeting in San Diego. Research presented at medical meetings should be viewed as preliminary until published in a peer-reviewed journal.

Zero Adds Up To a Lot

Nova Biomedical has launched a new blood gas analyzer that it says simplifies critical care testing by combining the micro-electronics of the consumer world with Nova's Zero maintenance cartridge technology for a smaller, faster, and less expensive analyzer. Stat Profile Prime's maintenance cartridge technology consists of individual cartridges for biosensors, calibrators, and liquid quality control. Each cartridge is maintenance-free, ready to use, and replaced in seconds. This design optimizes the life of each cartridge; improves analyzer uptime; and eliminates the waste, downtime, and higher costs of older combined calibrator/sensor cartridge systems. Nova's new technology MicroSensor Card contains biosensors for pH, PCO2, PO2, Na, K, iCa, Cl, Glu, and Lac. Credit card-sized, the MicroSensor Card is automatically calibrated and always ready to deliver a full 10-test profile in just 60 seconds. MicroSensor cards can be replaced in less than half the time of older cartridge systems, which can take more than one hour to calibrate and can remain unstable with drift, frequent re-calibrations, and reduced throughput for even longer periods of time. Stat Profile Prime's Clot Block sample flow path protects the MicroSensor Card from blockages and prolonged downtime caused by blood clots. Compact, lightweight, and simple to operate with a color touchscreen, Stat Profile Prime may be used in a fixed location virtually anywhere in the hospital or operated on a mobile cart with a battery back-up. Stat Profile Prime ensures the highest quality and lab accuracy with automated, true liquid quality control and continuous electronic self-monitoring, saving time and labor. Tests include: partial pressure of carbon dioxide and oxygen, acidity, sodium, potassium, chloride, ionized calcium, glucose, lactate, and hematocrit.

Bubbler Seals the Deal

B&B Medical Technologies has announced that the Bubbler Water Seal CPAP Valve is now FDA Approved. The company said that after working with focus groups and key opinion leaders, it had identified an enhanced feature set, which contributed to the design of a more convenient and versatile device for the clinical community. They designed the B&B Bubbler as they saw an increased demand for FDA-approved Bubble CPAP devices in the NICU. The B&B Bubbler can be used in neonatal critical care units, delivery rooms and special procedure units. A few of the top features and benefits include a dual-chambered design that allows fluid level to be observed without disrupting therapy, internal, drainable overflow chamber limits fluid to desired CPAP level, rotating CPAP dial and setting lock reduces risk of unintentional changes in pressure. Bubble CPAP has been around for over 30 years; however the first units were assembled by Respiratory Therapists in the hospital. Homegrown devices typically do not conform to today's regulatory environment. The first FDA-approved bubble CPAP units came onto the market less than 5 years ago. B&B Medical Technologies' goal is to develop innovative products that deliver positive outcomes, provide good patient care while addressing the need to control healthcare costs. The newest product solution is only the beginning—the company's development plan is to launch a new product each year.

Clearance Helps Save Lives

Breathe Technologies, Inc. has announced that the US Food and Drug Administration granted the fifth 510(k) clearance for its Non-Invasive Open Ventilation (NIOV) System, allowing its use with compressed air supply for non-oxygen dependent patients. The previous four FDA clearances cover the use of the Breathe NIOV System with compressed oxygen for home and institutional use, and include invasive and non-invasive patient circuits. The Breathe NIOV System is the first and only FDA-cleared, wearable, ventilation system for people with

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respiratory insufficiency. It provides augmented tidal volume and supplemental oxygen, which reduces the work of breathing for people with respiratory insufficiency caused by chronic obstructive pulmonary disease (COPD), including Alpha-1 Antitrypsin Deficiency. Patients who may receive similar benefits include those with pulmonary fibrosis, interstitial lung disease, cystic fibrosis and most respiratory conditions that result in activity-limiting shortness of breath. The new FDA clearance allows for the wearable ventilator to be used to assist patients with neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis. The new clearance also allows for use in patients with non-oxygen dependent respiratory diseases such as scoliosis. Over time, neuromuscular disorders can weaken the muscles that are essential for breathing, making it difficult for patients to move air in and out of the lungs effectively. Respiratory failure, often in association with an infection, is a frequent cause of death for people with neuromuscular diseases. The Breathe NIOV System reduces the work of breathing by unloading the ancillary respiratory muscles. Data from the seven studies that support the efficacy of the Breathe NIOV System demonstrate that the device reduces dyspnea (shortness of breath), increases oxygenation, enhances exercise endurance, and unloads respiratory muscle activity.

BLOOD GAS ROUNDTABLE

Roche

Tell us about the blood gas products you offer.
Roche Diagnostic's blood gas portfolio includes the cobas b 123 POC system, cobas b 221 system, and cobas bge link software for hospital point-of-care.

The cobas b 123 POC system is a mobile, near-patient blood gas analyzer with a broad assay menu including lactate. Blood clots are commonplace for most blood gas analyzers and it can be timeconsuming to return the analyzer to reliable performance. The cobas b 123 POC system features an unparalleled system of four levels of clot protection to help prevent pack failures. This next generation blood gas analyzer is designed to help provide optimal reliability, allowing you to spend more time providing quality care to your patients.

Analyzer downtime due to pack failure and blood clots and inability to control costs with existing devices are major user issues for Respiratory Managers requiring a near-patient blood gas analyzer. The cobas b 123 POC system reagent pack requires no refrigeration and offers excellent reliability. In addition, the cobas b 123 POC system has consumables with smart chips allowing them to be easily transferred between like devices which help customers control costs and spend more time providing quality care to their patients.

The cobas b 221 system was uniquely designed to help provide virtually uninterrupted performance. The analyzer has a powerful fluidic system that includes both peristaltic pump and vacuum pump mechanics that can remove the source of trouble and help minimize downtime. The cobas b 221 system configurable menu has options for blood gas (pO_2, pCO_2, and pH), electrolytes (Na^+, K^+, Cl^-, Ca^+, Hematocrit), metabolites (glucose, lactate, BUN), and Co-oximetry (O_2Hb, HHb, COHb, MetHb, tHb, Bilirubin). It was the first blood gas system FDA 510(k) cleared for testing pleural fluid pH. With the ability to trend patient data and automated acid-base mapping trending, the cobas b 221 system provides actionable information and simplifies regulatory compliance.

Both analyzers use cobas bge link software enabling the user to monitor and control multiple, decentralized units from one location. The cobas bge link software enhances operational efficiency of all connected systems through remote control and screen sharing to provide immediate real-time performance status, maintenance updates, and remote access for administrative management. The software allows you to manage patient orders through the web-based interface. Compliance documentation is simplified with event logs that can capture corrective actions and replace manual notes.

Describe the applications for your products?
The cobas b 123 POC system and cobas b 221 system analyzers can be used in a wide variety of hospital settings including the central laboratory, respiratory therapy department, intensive care units, emergency department, STAT Lab, operating room, NICU, Cath Lab and patient floor.

Both analyzers can use a variety of sample input devices including syringe, capillary, test tubes, and Microsampler PROTECT device. The cobas b 123 POC system is FDA approved for analysis of whole blood samples. The cobas b 221 system is FDA cleared for analysis of whole blood, serum plasma, dialysate solution and pleural fluid.

Discuss training and support for the use of your products.
Roche Diagnostics provides a variety of educational materials to help healthcare professionals operate the cobas b 221 POC system and cobas b 221 system properly and help maintain operator certification. These educational materials include:

- Onboard video tutorials and a customer-based training DVD along with instruction manuals that provide detailed descriptions to help operators avoid errors using the equipment.
- Roche offers on-site blood gas analyzer and cobas bge link software training at the customer facility. Roche also offers a three-day training program at its Indianapolis headquarters for two operators for the cobas b 221 system and the cobas bge link software.
- Roche offers extensive on-line support through https://usdiagnostics.roche.com, which gives users web-based access to all current documentation such as MSDS sheets, package inserts, customer bulletins and manuals.
- Roche's Indianapolis-based Tech Support team provides telephone support for immediate, real-time troubleshooting which may help reduce downtime and the need for a service visit.

Discuss point of care testing as it applies to your products.
The cobas b 123 POC system can help improve patient care testing by delivering accurate results for up to thirty patient tests per hour. The analyzer has a Micro Mode feature that uses only 37 µl sample for blood gas parameters, 55 µl for blood gas parameters and COOX, and 25 µl for COOX only. The cobas b 123 POC system has been designed with a mobile cart for ease of use in the OR, ER, ICU, RT area and Lab.

The cobas b 221 system can help improve point-of-care testing by

delivering accurate test results in 60 seconds for fast turnaround time and enhanced workflow efficiency. The speed to results combined with the low blood sample volume (88 µl), required by the cobas b 221 system, helps healthcare professionals get blood gas test results faster and reduces the time for physicians to make critical medical decisions that impact patient outcomes. In addition, the cobas b 221 system offers direct interfacing options to the hospital HIS/LIS which allows the respiratory therapist to run the sample and enable the physician to interpret the results in another part of the hospital or remotely.

The cobas bge link software provides remote instrument management and data management. Event logs, automated, scheduled email reports and user determined validation rules that allow you to manage your blood-gas testing environment with confidence and efficiency.

Siemens

Tell us about the blood gas products you offer.
Siemens Healthcare Diagnostics offers a comprehensive portfolio of blood gas solutions with our RAPIDSystems analyzers, designed to produce fast, accurate results so that clinicians can rapidly and confidently make critical treatment decisions. Further, with our breadth of products, we are able to provide solutions that meet a range of customer needs, both in low volume critical care settings and high-throughput environments.

Additionally, Siemens blood gas systems integrate with our RAPIDComm Data Management System, enabling point-of-care (POC) coordinators to manage and control testing quality over multiple analyzers on their network. The RAPIDComm system also provides the ability to manage operator access, set operator certification requirements, manage quality control (QC) results, and remotely troubleshoot devices on the network. Recently, Siemens released a major software upgrade for the RAPIDComm Data Management System that includes support for the RAPIDComm Web application, which enables management of blood gas testing from an iPad.

Describe the applications for your products.
Siemens blood gas analyzers are used to deliver fast, accurate results in many critical care environments, such as emergency rooms, intensive care units, respiratory therapy, and operating rooms, and, can be used to enhance blood gas testing efficiency in the clinical laboratory. Additionally, our blood gas analyzers feature comprehensive critical care testing menus.

Discuss training and support for the use of your products.
Siemens provides both live and virtual training for customers, as well as its Personalized Education Plan (PEP), a competency-based clinical laboratory educational tool conveniently available online. PEP allows healthcare professionals to easily plan a wide variety of product-specific, professional development, and job-relevant courses. The recent RAPIDComm System software upgrade also supports an interface to PEP Administrator, an extension to PEP that provides POC coordinators a way to simplify and streamline administration of education and training programs.

Discuss point-of-care testing as it applies to your products.
Siemens blood gas solutions help meet the growing demand for near-patient testing by providing clinicians with fast, reliable, laboratory-quality results.

In addition to blood gas results from Siemens RAPIDSystems, the Siemens RAPIDComm Data Management System also enables POC coordinators to remotely monitor and manage diabetes testing results via the DCA Vantage analyzer and urinalysis via the CLINITEK Status Connect System. This connectivity helps enhance oversight, improve results reliability, maximize instrument uptime, streamline workflow, and simplify compliance.

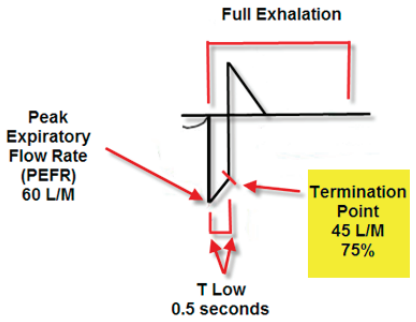
Airway Pressure Release Ventilation (APRV) Part II of II: Building a Better (Safer) Mechanical Breath

Kennard Chandler

The T Low Setting

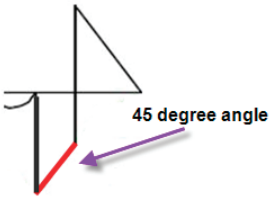
Setting and adjusting the T Low setting is the most challenging aspect of APRV. The setting for T Low is very brief (usually between 0.2 and 0.8 seconds). Normally the clinician takes 1/10 of the T High as a starting point. For example if the T High is 6.0 seconds, a good starting point for T Low would be 0.6 seconds. The T Low must be titrated to maintain the end-expiratory lung volume (FRC). This titration is accomplished by evaluating the expiratory flow rate curve (EFRC). The T Low sets the point at which the expiratory flow rate is terminated. This point of termination is called the Termination Point of the Expiratory Flow Rate (TP-EFC). If the expiratory flow rate is terminated too soon the exhaled release volume will be too small and the patient will retain CO2. If the expiratory flow rate is terminated too late the patient will lose end-expiratory lung volume (FRC) and alveolar derecruitment will occur. The ideal TP-EFC is 75% of the peak expiratory flow rate. Once you have a starting point, you must evaluate the expiratory flow rate curve and the release volumes to fine tune T Low.

Looking at the graphic below you can see that the termination point is at 75%.

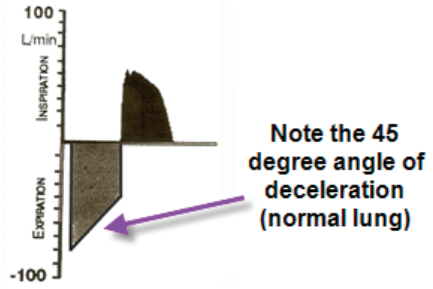


Angle of Deceleration

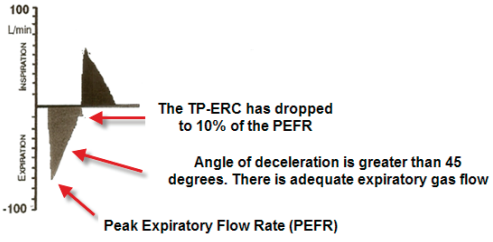
The expiratory flow curve also provides the respiratory therapist with information regarding the patient's lung mechanics. The angle of deceleration (the red line on the illustration below) represents the expiratory gas flow during the release phase. The steeper the angle, the faster the expiratory gas flow and vice versa. This angle will provide the clinician with valuable information regarding the patient's pulmonary mechanics. (See the illustration below.)



The normal lung has an angle of deceleration of 45 degrees. Do not confuse the angle deceleration with the TP-ERC as they are two very different concepts. The respiratory therapist should evaluate both the TP-ERC and the angle of deceleration. (See the illustration below.)

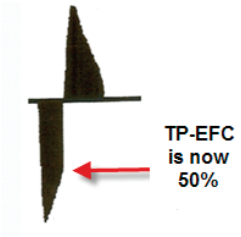


As compliance decreases, the T Low may need to be adjusted. In the illustration below the TP-EFC fell to 10%. This termination point allows for too much exhaled volume resulting in a loss of end-expiratory lung volume causing the loss of alveolar stability and derecruitment. T Low needs to be reduced or (tightened) to maintain adequate end expiratory volume, alveolar stability and re-gain alveolar recruitment. (See the illustration below.)



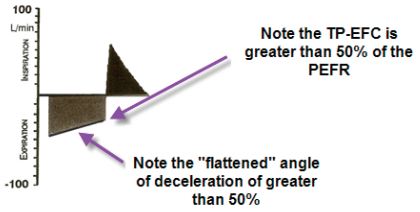
Shortening T Low from 0.8 sec. to 0.5 sec. resulted in increasing the TP-EFC from 10% to 50% of the PEFR.

This was written by Kennard Chandler, who is solely responsible for its content. This project would not have been possible without the suggestions of many of the respiratory therapy staff at Manatee Memorial. The author is indebted to ICON for their unwavering support and guidance. ICON also supplied and/or suggested many of the graphic ideas used in this paper.



This TP-EFC of 50% is far from the ideal TP-ERC of 75% discussed earlier. However, 50% may be the perfect TP-ERC due to this patient-increased pulmonary compliance. To determine the perfect TP-EFC, the respiratory therapist must evaluate the arterial blood gases, the release volumes and the patient's level of comfort.

When treating patients who have obstructive airway disease the angle of deceleration may flatten to greater than 50 degrees. The angle becomes greater as the expiratory gas flow decreases. (See the illustration below.)

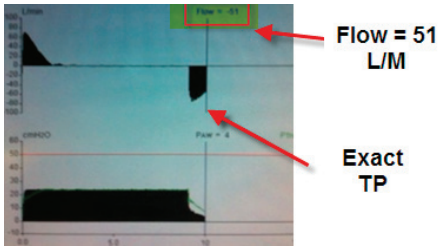


Note that the TP-EFC is less than 50% of the PEFR instead of the normal target of 75%. This extended expiratory time may be necessary due to the slow expiratory gas flow. Generally speaking, patients with obstructive airway disease already have increased end-expiratory alveolar volume (FRC) due to the high levels of auto-peep. Extending the T Low (expiratory time) in these patients may not result in loss of end-expiratory lung volume (FRC) and derecruitment. In these cases, a T Low setting of 0.8-1.2 seconds is typical, although times in excess of 2.0 seconds may be required in severe cases.

My hospital uses Drager ventilators and I will restrict my comments to these ventilators. Let's take a look at an actual screen shot taken from the Drager's display during APRV therapy. This screen shot is from an earlier model Drager and not the XL.

Note: As you can see from the screen shot below, determining the exact point or flow rate of flow termination (TP_EFC) can present a significant challenge for the respiratory therapist. It is vital that the respiratory therapist determine precise values for the PEFR and the TP-EFC. This is why I do not recommend using this ventilator when providing APRV therapy.

The Drager Evita XL ventilator's software is designed to locate and populate the exact termination point (TP) on the expiratory flow curve (EFC). I strongly recommend that you use a ventilator that is able to provide you with this precise information. Looking at the actual frozen screen shot below taken from the Drager Evita XL ventilator, you can see a green line which has been populated by the ventilator software showing the respiratory therapist the exact TP-EFC, along with the exact PEFR.



The green line that the Evita XL's software populates shows the respiratory therapist the exact point of termination on expiratory flow curve (lower red arrow) and the exact flow in L/M of termination (upper red arrow)

As shown above, the XL's micro processor will determine the PEFR termination point and freeze the display for you automatically. The Evita XL will accurately determine and freeze this TP-ERC and the PEFC on the screen in L/M. To arrive at the % of the termination point on the EFRC you simply divide these two values. This feature is an invaluable clinical tool to the respiratory therapist as it takes the "guess work" out of determining these key values. In a real clinical situation this screen is very easy to read.

Here is an easy way to think about adjusting the APRV settings:

- Optimizing oxygenation (PaO2 & SaO2)
  - * End-expiratory alveolar volume and therefore, alveolar stability and alveolar recruitment are optimized by adjusting T Low to achieve the perfect TP-EFC (usually 75%).
  - * P High must be set high enough to achieve a dynamic FRC that promotes alveolar stability and alveolar recruitment.
- The elimination of CO2 is accomplished through spontaneous breathing throughout the APRV cycle and the number and size of the release volumes. CO2 is also eliminated during T High as the dynamic FRC allows for greater alveolar recruitment and diffusion respiration
  - * The number of releases is controlled through the T High. The lower the T High the more releases per minute and vice versa.
  - * In contrast, lengthening the T High may increase alveolar recruitment, dynamic FRC allowing increased diffusion respiration further eliminating CO2.
  - * The P High will determine the size of the FRC, obviously the higher the P High the greater the volume of FRC.
  - * The T Low will determine the termination point during exhalation. This is an inverse relationship. The higher the termination percentage the less time for exhalation and therefore the lower the exhaled (release) volume and vice versa.

Additional notes regarding the settings used during APRV

Patients without the restrictive component to their hypoxemic respiratory failure may have near normal pulmonary compliance, such as in some presentations of COPD. Due to the difference

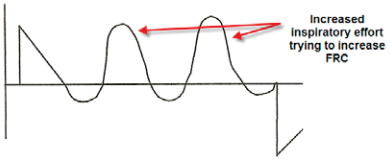
in pulmonary compliance, the delivered airway pressure or P High may result in much higher lung volumes resulting in much higher release volumes, resulting in mechanical alveolar hyperventilation and respiratory alkalosis. The P High and T Low settings for these patients will be much different. These patients may require a termination point percentage as high as 80-85% of EFR. The key variable will be the release volumes. If the release volume is too high, the P High may be too high. Also, the T Low may have to be tightened (higher percentage) to shorten the expiratory or release phase.

The initial starting point for setting the P High (as discussed on Page 20) is calculated by converting the plateau pressure of the conventional mode (CMV) and adding 2 cm of water pressure. During the initial set up the therapist must evaluate the release volumes to determine if they are appropriate for this patient. If they are too high the P High and T Low will have to be decreased.

If the patient is consistently inhaling forcefully with accessory muscles, he/she may need better optimization of the FRC for better alveolar recruitment. The options are:

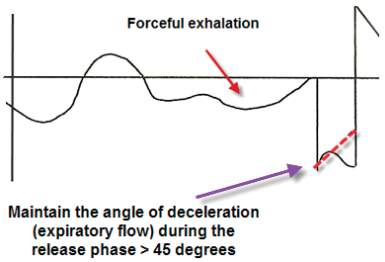
- Increase P High, this will elevate the mean airway pressure and the alveolar gas volume (FRC) and encourage alveolar recruitment (This is usually your best option).
- Decrease T Low (only if you are able to maintain a TP-ERC of 75% and the PaCO2 and pH are acceptable).

See the illustration below.



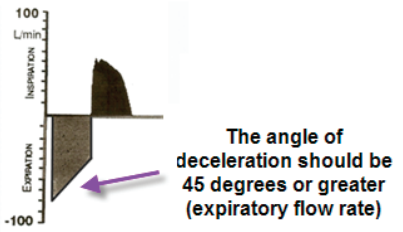
If the patient seems to be exhaling forcefully, alveolar over-inflation may be present. Options are:

- Drop the P High in increments of 1-2 cms of water pressure and stretch (increase) the T High (to maintain the mean airway pressure) and/or:
- Increase the T Low (allowing more time to exhale) only if you are able to maintain an optimal flow (angle of deceleration) during the release phase.



If Respiratory Acidemia presents, your options are:

- Increase P High (maximum of 40 cms of water pressure) to optimize end expiratory alveolar volume (FRC) and increase the release volumes.
- Increase T High (if spontaneous breathing is sufficient) in increments of 0.5 seconds up to 8 seconds in an attempt to optimize end-expiratory alveolar volume (FRC).
- Increase T Low to allow more time for alveolar emptying, but only if the expiratory flow of a release (angle of deceleration) does not drop below a 45-degree angle. See following image.



- If further increases in T High fail to decrease PaCO2 you may need to go in the opposite direction by decreasing T High to increase the number of releases per minute. Remember, this will decrease the mean airway pressure and may reduce the dynamic FRC adversely affecting oxygenation, therefore, an increase in P High may be needed to maintain the mean airway pressure.

If Respiratory Alkalemia presents, your options are:

- Decrease P High (oxygenation may suffer).
- Increase T High to decrease the number of releases per minute.

Patient Positioning

Patient positioning is very important during APRV. Sudden and dramatic changes in the patient's position usually result in dramatic changes in shunt. I have often seen stable patients on APRV become very unstable and experience worsening hypoxemia simply because the patient has been turned. Collaborate and educate your clinical team. "Kid gloves" must be incorporated when dealing with positioning the patient in APRV. Once the APRV patient is stable, the clinical team can carefully evaluate what the patient's positioning parameters should be.

Turbulent flow within the breathing circuit

Turbulent flow within the breathing circuit during APRV is a considerable problem, hence the reason for a "special ventilator circuit". Too much turbulence and the ventilator will report a "HIGH PEEP" alarm. You may have to remove the bacteria filter.

Never go back!

Once the decision has been made to transition from a conventional mode of ventilation to APRV, the goal is to remain in APRV, weaning to a pure CPAP. During APRV the high lung volume therapy is successful because it slowly de-wrinkles collapsed alveoli and opens more and more alveoli to participate in gas exchange. Changing to a traditional low lung volume strategy such as CMV or SIMV will result in immediate loss of recruitment, lung volume (FRC) and alveolar stability and therefore oxygenation. The loss of alveolar stability is immediate and alveolar collapse occurs. Unfortunately these alveolar surfaces are sticky, like plastic wrap and re-opening these alveolar units becomes difficult and in some cases impossible.

Weaning the patient during APRV therapy

Generally, weaning from APRV should not be considered until the PaO2 has improved and the FIO2 is ≤.40. Weaning consists of "dropping" the P High and "stretching" the T High. It is critical that you do both (drop and stretch) because APRV is a pressure/time product. In order to maintain mean airway pressure when you drop the P High you must also stretch T High. You will also have to adjust the T Low to ensure adequate "release volumes" while maintaining alveolar stability with a TP-EFC of 75%. This TP-EFC percentage may be higher depending on the pulmonary

compliance or lower as the lung injury improves. This process of "dropping and stretching" is continued until the patient is breathing spontaneously on pure CPAP.

Whenever the respiratory therapist "drops and stretches", the mean airway pressure will remain the same, however, a greater portion of the total mechanical minute volume is passed on to the patient. In other words, the patient becomes responsible for providing more of the total minute volume through their unassisted spontaneous breathing. This results in more "breathing work" being performed by the patient.

Before any weaning attempt, it is vital that the respiratory therapist assess the total minute volume and determine whether the patient will be able to sustain that minute volume through unassisted spontaneous breathing. For instance, if the total minute volume is 18 L/M, it is obvious that this high minute volume requirement is not sustainable and the patient will eventually tire and begin to develop hypercarbic respiratory failure.

As a rule of thumb the total minute volume should be less than 10 L/M. Some patients may be able to handle higher minute volumes. It is incumbent upon the respiratory therapist to make educated decisions regarding the patient's work of breathing and their ability to sustain the increased spontaneous minute volume. The respiratory therapist must also be sensitive to the patient's respiratory rate. Rapid shallow breathing remains a red flag as with any other weaning approach.

Indications/Inclusion Criteria for APRV

APRV may be used for any patient requiring ventilatory support. APRV may be particularly beneficial in the treatment of patients with acute lung injury (ALI) acute respiratory distress syndrome (ARDS) and other forms of acute restrictive disease that involves lung recruitment elements.

1. Trauma patients requiring ventilatory support within 48 hours of injury.

Contraindications/Exclusion Criteria for APRV

Patients with severe obstructive airway disease may be more complex to manage on APRV, but COPD is not an absolute contraindication. These patients may not have a restrictive component to their respiratory failure and will require a differ approach in terms of setting the P High and T Low.

1. Chronic heart disease may prohibit the use of APRV.
2. Contraindications to permissive hypercapnia; such as intracranial bleeding, brain tumor, fulminate hepatic failure, and hemodynamic instability.
3. Patients with significant bollous disease will require close observation for worsening of bullae.
4. Severe neurologic injury that may prevent the patient from having a reasonable opportunity for weaning.
5. Neuromuscular disease that impairs the patient's ability to breathe spontaneously; such as spinal cord injury at or above C5, ALS, Guillain-Barre Syndrome, Myasthenia Gravis.
6. Patients presenting with AMI as the cause of their ALI/ARDS may have difficulty maintaining their hemodynamic status.

Benefits of APRV

1. The ability to breathe spontaneously throughout the entire ventilatory cycle improves ventilation to poorly or non-ventilated lung regions reducing ventilation-perfusion mismatch. This is especially true of areas of dependent atelectasis.
2. During spontaneous, unassisted breathing, the posterior crura (posterior muscular) sections of the diaphragm will remain functional, minimizing posterior consolidation/ atelectasis, diaphragmatic weakness or atrophy. Maintenance of diaphragmatic tone or inspiratory effort will minimize dependent atelectasis.
3. During spontaneous breathing patients in the supine position will have improved ventilation of dependent lung regions, reduced pulmonary shunt and improved oxygenation.
4. Lower mean airway pressures than conventional modes of ventilation.
5. Providing a dynamic FRC which promotes greater alveolar ventilation. (enhancing alveolar recruitment), with resultant improvement in oxygenation.
6. Enhanced cardio-circulatory function.
7. Decreased need for patient sedation.
8. Eliminates the need for neuromuscular blocking agents.
9. Enhanced cephalad (towards the head) flow of secretions.

Potential Risks of APRV

1. There is a potential for changes in the delivered mechanical volume due to changes in lung compliance and resistance, as with any other pressure mode.
2. Patients with very compliant lungs, e.g. COPD, may experience more hemodynamic compromise and require a reduction in the airway pressure.
3. Hemodynamic instability, though not common, may occur in patients with intravascular volume depletion.
4. Clinical miscalculations and misunderstandings due to the learning curve associated with introduction of this new mode.

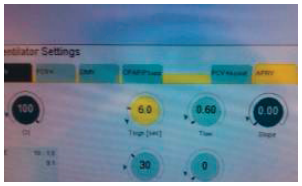
Initial Set-Up - General Guidelines for Adults

Transitioning a patient from conventional settings to APRV:

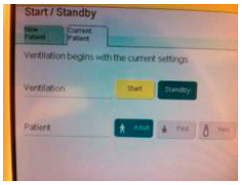
1. The Evita XL is the ventilator of choice for the delivery of APRV.
2. The breathing circuit must be changed to the special heated wire circuit.
3. Turn Automatic Tube Compensation (ATC) to 100%.
4. For information regarding the setting of P High, T High, P Low and T Low refer to pages 18-30 of this paper.
5. The practitioner should anticipate the expired minute ventilation to be less than on a conventional mode, such as CMV. This is due to the fact that there is less dead space ventilation with APRV.
6. Adjust settings based on the patient's arterial blood gas results and clinical status.

Setting up APRV using the Drager Evita XL Ventilator

1. Establish the "**Standby**" mode
2. Press the soft key "**Ventilator Settings**"
3. Press the "**More**" screen key
4. Touch the **ARPV** screen key (the LED will turn yellow)
5. Set the ventilation pattern for APRV following parameters:
   a. Inspiratory Pressure - P_{HIGH}
   b. Expiratory Pressure - P_{LOW}
   c. Inspiratory Time - T_{HIGH}
   d. Expiratory Time - T_{LOW}
   e. FIO_2
   f. Slope (pressure time rise) is set at zero
6. To set a specific parameter, touch the respective screen knob
7. Turn dial knob to set value
8. Press dial knob to confirm value (see figure)
9. Press the dial knob to activate mode of ventilation (see figure)



For #8



For #9

Monitoring

1. Respiratory care practitioners working with APRV, monitor the same parameters used for any patient undergoing mechanical ventilation. In addition, the RT must pay particular attention to the expiratory gas flow pattern.
2. Mean airway pressure has a linear relationship with oxygenation up to the point of alveolar over distention and creation of physiologic dead space.
3. Excessively high mean airway pressures may impair pulmonary perfusion, particularly in the presence of hypovolemia.
4. The exact point that P High may cause a significant reduction in cardiac output varies from patient to patient and is related to a number of factors, including
   - The total thoracic compliance
   - Ventricular function
   - Blood volume and fluid status
5. Low mean airway pressure is associated with alveolar collapse, de-recruiting and shunting, and therefore, hypoxemia and increased pulmonary vascular resistance.
6. Release volume (the exhaled gas volume during the brief release periods) as with any pressure-targeted mode of ventilation, will vary with changes in compliance and resistance.
7. Over time, increases in release volumes may represent an improvement in pulmonary compliance (recruitment of alveoli).
8. Respiratory rate may vary and require assistance for pain, anxiety, delirium, improvement or deterioration of lung function.

Weaning from APRV

The method to weaning the patient in APRV is simultaneous manipulation of P High and T High. This process is called "dropping and stretching" as discussed earlier.

1. P High is decreased by increments of 2 to 4 cms H_2O, and T High is simultaneously lengthened in 0.5-2.0 second increments, thus maintaining mean airway pressure. However, each time you drop and stretch, the patient will have to perform a greater percentage of the total minute volume. Careful monitoring of the minute volume, respiratory rate, work of breathing and patient comfort is essential to safe and successful weaning.
2. The time interval between changes in P High and T High is variable and patient dependent. Delaying the implementation of the weaning process or proceeding too slowly will unnecessarily lengthen the time the patient is on the ventilator and may increase the intensive care unit stay. Going too fast may result in a weaning failure that will lead to a loss of alveolar stability and promote alveolar collapse, leading to more ventilator and intensive care unit days.
3. The goal is to transition to a pure CPAP mode. The starting CPAP must be at least equal to the mean airway pressure in APRV. One the CPAP level has been reduced to 5-10 cms H_2O the patient may be evaluated for extubation.
4. Prior to switching to CPAP the P High is generally 10-15 cms H_2O and the T High is 10-15 seconds.
5. During the weaning period the RT must closely monitor the mean airway pressure, SPO2, exhaled minute volume, end title CO2 level or PaCO2 / pH and the patient's work of breathing and overall comfort.
6. Automatic tube compensation should remain on throughout the weaning process.

Case Study

Most of the patients who are receiving APRV therapy present with a restrictive component to their respiratory failure such as, ARDS and ALI. This restrictive component may be severe. These patients have very poor pulmonary compliance. Rarely, a patient with near normal pulmonary compliance will present with hypercarbic and/or hypoxemic respiratory failure requiring APRV therapy. Due to the significant difference in pulmonary compliance the P High and T Low setting will be much different. Unfortunately the respiratory therapist will not know that adjustments must be made until the APRV therapy is instituted.

This case study is based on an actual APRV patient. Some of the steps that were taken in the actual clinical course have been omitted for simplicity.

A 46-year-old male presented to the emergency department complaining of severe bilateral leg pain and non- healing sores. The patient gave no history. The patient has not seen a physician in some time. He is 69-inches tall and weighs 450 lbs. The clinical presentation was severe bilateral venous insufficiency, venous stasis dermatitis with large ulcerations and cellulitis. The patient was observed to be experiencing dyspnea at rest and an ABG was obtained:

pH 7.31 / PaCO2 79.7 mm Hg / PaO2 178 mm Hg / HCO3 39.6 mm Hg
on N. Cannula @ 3 L/M
Estimated A-a gradient = 136 mm Hq

Note: This is a rough estimate of the A-a gradient as inspiratory flow rate and tidal volume will influence the delivered FIO2 with a Nasal Cannula, however, the A-a gradient does not appear to be a clinical problem at this time.

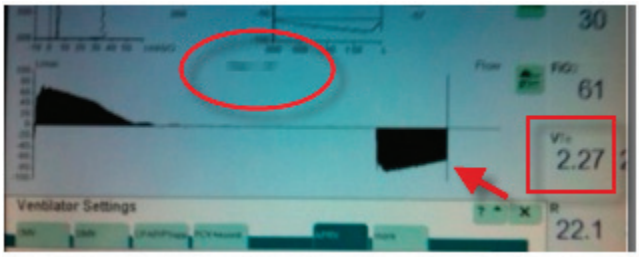
This patient continued to deteriorate while in the emergency room and attempts at non-invasive BiPAP therapy with the Vision were unsuccessful. He was intubated and place on CMV. Over the course of the next 48 hours, while on CMV, the patient developed worsening hypoxemic respiratory failure with his FIO2 requirements reaching 90%. The last ABG obtained on CMV was:

pH 7.46 / PaCO2 63.9 mm Hg / PaO2 77 mm Hg / HCO3 38.9 mEq/liter
A-a gradient = 485 mm Hg

Note the very high A-a gradient demonstrating severe hypoxemic respiratory failure.

The decision was made to transition to APRV. The respiratory therapist calculated the appropriate starting point for P High to be 28 cms H_2O (the plateau pressure adding 2 cms H_2O) the P Low was set at zero, the T High was 6.0 seconds and the T Low was 0.6 seconds. FIO2 was quickly weaned to 60% as per SpO2. The respiratory therapist then evaluated the termination point on the expiratory flow curve (EFC) and found it to be too high at 82%. The T Low was stretched until the TP-EFC was closer to

75%, in this case the TP-EFC = 54 L/M and the PEFR was 80 L/M (this is an unusually high PEFR) resulting in a TP-EFC of 67.5%. The T Low at this point was 1.2 seconds. Below is the actual screen shot of this patient while on these APRV settings. The red arrow shows the green line that shows the exact termination point of the expiratory gas flow and the EFC. The Evita XL has captured and frozen the EFC and the respiratory therapist can then find the exact point of the TP-EFC and the PEFR. The red oval shows the flow rate in L/M at the TP-EFC. This is not legible but we know that it was 54 L/M.



Next the respiratory therapist noted the release volume was 2.27 liters (red box above), much too high for this patient. To confirm this observation an ABG was drawn revealing:

pH 7.688 / PaCO2 31.9 mm Hg / PaO2 238 mm Hg / HCO3 38.3 mEq/liter
A-a gradient = 150 mm Hg

Notice that the APRV mode had already done it's magic by achieving alveolar recruitment and stability, as seen in the significant improvement of the A-a gradient, demonstrating a remarkable improvement in the degree of hypoxemic respiratory failure. The decision to change the mode of ventilation to APRV was brilliant. Now the respiratory therapist must fine tune the APRV setting to obtain release volumes that are appropriate for this patient while maintaining the gains made in alveolar recruitment and stability.

The respiratory therapist slowly shortened the T Low to 0.8 seconds and reduced the P High to 24 cms H_2O which resulted in release volumes of about 1 liter and a TP-EFC of 82 % or a TP-EFC of 59 L/M with a PEFR of 72 L/M. Ironically, this was the same TP-EFC (82%) as when the patient was initially set up on APRV. The FIO2 was weaned to 45%. ABG's revealed:

pH 7.472 / PaCO2 57.5 mm Hg / PaO2 90.7 mm Hg / HCO3 42.5 mEq/liter
A-a gradient = 158.3 mm Hg

The reduction in the P High from 28 cms water pressure to 24 cms water pressure reduced the release volumes and corrected the severe respiratory alkalemia. This move also caused a mild deterioration of the alveolar recruitment and stability as demonstrated by the A-a gradient increasing by 8.3 mm Hg. This is not a significant change but it does forewarn the respiratory therapist that if there is continued deterioration, the P High may need to be increased in increments of 2 cms water pressure to achieve the level of alveolar stability and recruitment as seen in the previous PaO2.

The respiratory therapist has a spectacular information source called ICON or Intensive Care Online; they are just a telephone call away. This resource has real time education solutions that will dramatically increase the respiratory therapist's confidence when managing APRV. In addition to the ICON academy and e-learning center, they are available 24/7 by telephone to assist you with the initial set up and management of APRV.

As a routine, whenever I set up APRV I call ICON and get them on board. I provide a history and the APRV initial settings along with a screen shot that I e-mail to them. After all, the folks at ICON have more experience with APRV than anyone on the planet. They will give you confirmation, education and offer suggestions. This input is invaluable. I encourage you to call them with each APRV application. With each ICON encounter you will become more knowledgeable and therefore more comfortable with teaching what you have learned. ICON also offers remote lectures with an ICON clinical education specialist. These interactive lectures cover a broad range pertinent to ICU and mechanical ventilation issues.

Utilization of the Pressure-Volume Tool To Maintain Lung Inflation During Extra Corporeal Membrane Oxygenation (ECMO)

Kenneth Miller, MEd, RRT-ACCS, NPS, AC-E

Minimizing ventilator-induced lung injury is a major concern when providing ventilation for patients with acute lung injury. The gold standard for lung protection is the ARDSNet Protocol.[1,2]

If the oxygenation end-point cannot be achieved, ECMO may be another interventional strategy.[3]

Recently, the utilization of ECMO in our facility has demonstrated a reduction in lung injury and improved outcomes. Gas exchange is managed by ECMO, while our strategy with the ventilator is to maintain lung inflation with the lowest pressures possible. The utilization of the Pressure-Volume Tool (P/V Tool, Hamilton Medical, Inc, Reno, Nevada) can help clinicians determine the lower inflection point (LIP), upper inflation point (UIP), and can be utilized to provide recruitment maneuvers if necessary.

The P/V Tool is a systematic ventilator application that allows the clinician to set lower and higher starting pressures, along with a sustained Phigh (PEEP), for a sustained time frame if desired for a recruitment maneuver.

After the maneuver, a pressure/volume graph is visualized to assess the inspiratory and expiratory limbs of the P/V loop.

In addition, a loop hysteresis can be visualized to determine if there is potential additional lung to be recruited. We perform a P/V tool every twelve hours for LIP/UIP assessment and recruitment maneuvers are performed if the static compliance is <20cm/H20 for all patients placed on ECMO.

We have utilized the P/V Tool on a daily basis to determine the LIP and UIP on 18 patients placed on Veno-Venous ECMO for Acute Lung Injury (ALI) management (see Fig. 1).

On seven of the patients whose lung compliance was <20cmH20, ranging from 8cmH20 to 14cmH20 (see Fig. 2), recruitment maneuvers were performed every six hours at a PEEP setting of 30cmH20 for 30 seconds to improve lung compliance (see Fig. 3).

All seven patients' lung compliance was improved and maintained >20cmH20 during the ECMO utilization by performing these sequential P/V tool assessments or recruitment maneuvers (see Fig. 4).

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Figure 1. PV Tool Assessment.

Figure 2. Continuous monitoring of Cstat (static compliance).

The utilization of the P/V Tool helped our clinical team maintain lung inflation during ECMO. The ability to assess and adjust ventilator settings or perform recruitment maneuvers, if indicated, helped to maintain lung compliance during ECMO management.

Figure 3. PV Tool recruitment maneuver with positive response, additional lung volume recruited.

Figure 4. Post PV Tool recruitment maneuver improvement in Cstat.

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Meta-Analysis to Compare the Accuracy of GeneXpert, MODS and the WHO 2007 Algorithm for Diagnosis of Smear-Negative Pulmonary Tuberculosis

Simon Walusimbi, Freddie Bwanga, Ayesha De Costa, Melles Haile, Moses Joloba, Sven Hoffner

Abstract

Background: Smear-negative pulmonary tuberculosis (SN-PTB), which is common in HIV-infected patients, is difficult to diagnose using smear microscopy alone. In 2007, the WHO developed an algorithm to improve the diagnosis and management of smear-negative tuberculosis in HIV prevalent and resource constrained settings. Implementation of the algorithm required individuals with presumptive TB to be initially evaluated using two sputum microscopy examinations followed by clinical diagnosis that may include chest X-ray and antibiotic treatment in smear-negative individuals. Since that time, the WHO has endorsed several new tests for diagnosis of tuberculosis. However, it is unclear how the new tests perform when compared to the WHO 2007 algorithm in diagnosis of SN-PTB. Using meta-analysis study design, we summarized and compared the accuracy of Xpert MTB/Rif assay (GeneXpert) and Microscopic Observation Drug Susceptibility assay (MODS), with the WHO 2007 algorithm in the diagnosis of SN-PTB.

Methods: A systematic review and meta-analysis of publications on GeneXpert, or MODS, or the WHO 2007 algorithm for diagnosis of SN-PTB, using culture as reference test was performed. Meta-Disc software was used to obtain pooled sensitivity and specificity of the diagnostic methods. Heterogeneity in the accuracy estimates was tested by reviewing the generated forest plots, sROC curves and the Spearman correlation coefficient of the logit of true positive rate versus the logit of false positive rate.

Results: Twenty-four publications on all three diagnostic methods were meta-analyzed. The pooled sensitivity and specificity for detection of smear-negative pulmonary tuberculosis were 67% and 98% for GeneXpert, 73% and 91% for MODS, and 61% and 69% for WHO 2007 algorithm, respectively. The sensitivity of GeneXpert reduced from 67% to 54% when subgroup analysis of studies with patient HIV prevalence ≥30% was performed.

Conclusion: The GeneXpert, MODS, and the WHO algorithm have moderate to high accuracy for the diagnosis of SN-PTB. However, the accuracy of the tests is extremely variable. The setting and context under which the tests are conducted in addition to several other factors could explain this variability. There is therefore need to investigate these factors further. The information from these studies would inform the adoption and placement of these new tests.

Background

The global burden of tuberculosis (TB) remains high with 8.7 million new TB cases estimated to have occurred in 2012 [1]. The majority of the new TB cases (80%) occurred in 22 countries and a substantial proportion (35%) were smear-negative pulmonary TB (SNPTB). In these countries, TB diagnosis relies mainly on smear microscopy which has a highly variable sensitivity ranging from 20% to 60% [2,3]. In sub Saharan, where the prevalence of HIV is relatively high and TB is a common opportunistic infection, TB/HIV co-infected patients frequently present with SN-PTB. This is because HIV patients usually form poor lung granulomas/cavities when infected with TB, resulting in lower concentrations of Mycobacterium tuberculosis (Mtb) in the lesions [4], which can pose diagnostic difficulties [5].

In 2007, the WHO issued an algorithm for the diagnosis of SN-PTB for use in resource-limited settings with high HIV infection rates [6]. Adoption of this algorithm (Figure 1), was expected to improve diagnosis and management of smear-negative tuberculosis. However, the diagnostic methods used when the algorithm was made, have since then been improved upon or entirely new tests have been developed. The WHO has also endorsed several of these new tests [7]. Further, the WHO 2007 algorithm outlines a lengthy diagnostic pathway which requires a patient to visit the clinic four times before a clinician decides whether to treat a patient as a case of smear-negative tuberculosis. In practice, few patients complete all the elements of the algorithm (see Figure 1) before a decision to treat or not is taken [8]. In addition, although the algorithm encourages sputum culture during the second clinic visit to assist the confirmation of diagnosis of smear-negative TB, this is often not practically possible. Reasons for this include firstly that the commonly available TB culture method in many of the focus settings is the Lowenstein-Jensen (LJ) method, a solid based medium that takes several weeks to detect bacterial growth. Secondly, in many of the countries for which the algorithm was developed, culture facilities are often limited to reference laboratories with insufficient capacity to meet the national demand for culture

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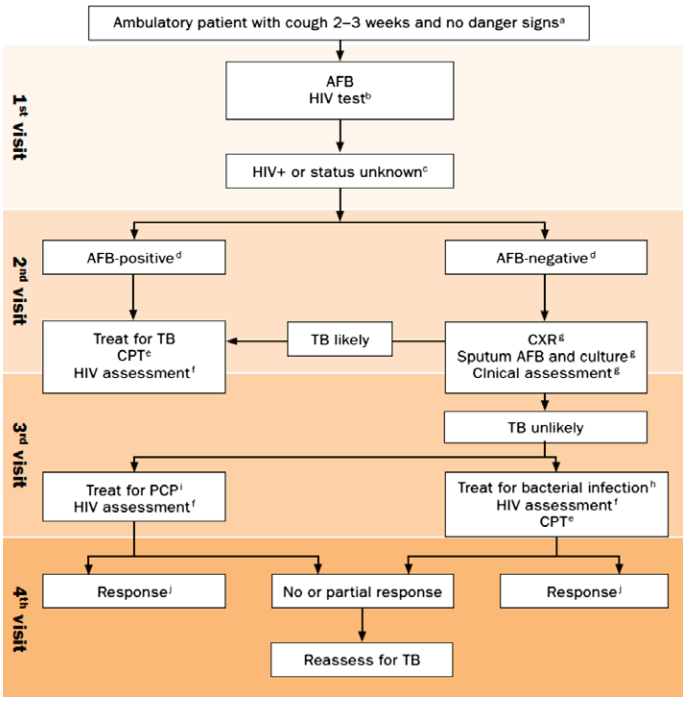

Figure 1. WHO 2007 algorithm for the diagnosis of TB in ambulatory HIV-positive patients. a) the danger signs include any one of: respiratory rate > 30/minute, fever > 39°C, pulse rate > 120/min and unable to walk unaided. b) for countries with adult HIV prevalence rate = 1% or prevalence rate of HIV among tuberculosis patients = 5%. c) In the absence of HIV testing, classifying HIV status unknown as HIV-positive depends on clinical assessment or national and/or local policy. d) AFB-positive is defined at least one positive and AFB-negative as two or more negative smears. e) CPT = Co-trimoxazole preventive therapy. f) HIV assessment includes HIV clinical staging, determination of CD count if available and referral for HIV care. g) the investigations within the box should be done at the same time wherever possible in order to decrease the number of visits and speed up the diagnosis. h) antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered. i) PCP: Pneumocystis carinii pneumonia, also known as Pneumocystis jirovecii pneumonia. j) advise to return for reassessment if symptoms recur.

confirmation [1]. Because of the reasons mentioned above among others, there has been limited success in improving diagnosis of smear-negative TB using the algorithm.

More recently, the WHO endorsed the Xpert MTB/Rif assay (GeneXpert) for the diagnosis of TB [9]. The GeneXpert relies on DNA-PCR technique for detection of TB and Rifampicin resistance related mutations simultaneously. It is the first molecular assay for TB detection to be fully automated and to integrate all the steps required for PCR-based DNA test. It gives results within 3 hours. The test has also been reported to be highly accurate for diagnosis of pulmonary TB [10]. Patients with presumptive HIV-associated TB who are negative on smear examination are the most likely to benefit from GeneXpert [11].

Another new test is the Microscopic Observation Drug Susceptibility assay (MODS). The WHO recently endorsed the test for rapid screening of multidrug-resistant TB [12]. The MODS relies on two well-known properties of M.tb i.e. (i) the rate of growth of M.tb in liquid medium is considerably quicker than on solid medium(ii) the morphology of M.tb in liquid culture is characteristic and recognizable, consisting of so called "cord" like structures [13]. Thus by using an inverted light microscope to examine tissue culture plates inoculated with sputum, M.tb growth can be detected within 7-10 days, compared to conventional solid culture that takes several weeks [14]. In settings where conventional culture services for diagnosis of TB are not readily available, the MODS could be an alternative for early diagnosis of SN-PTB since it is simple, rapid and cheap.

However, evidence on the performance of the GeneXpert, MODS assay, and the WHO 2007 algorithm for diagnosis of SN-PTB is scanty. In this study, we did a meta-analysis to summarize and compare the accuracy (sensitivity and specificity) of the GeneXpert (a molecular based assay), the MODS (a rapid culture method) and the WHO 2007 algorithm (an algorithm based method) for the diagnosis of SN-PTB. We considered all the elements of the WHO 2007 algorithm (its entirety) as one test.

Methods

Study design

A systematic review of publications on GeneXpert, MODS and the WHO 2007 algorithm for the diagnosis of SN-PTB was performed, followed by a meta-analysis.

Search strategy

Initially, we performed an electronic search in Pubmed without year restriction for articles in English for each test individually. The search terms used were 'GeneXpert', 'Microscopic observation drug susceptibility', and 'WHO TB algorithm'. We then reviewed the retrieved abstracts and selected publications for full text review. After fully reading the selected publications, their bibliographies were also reviewed and relevant additional publications were also retrieved for full text review. To ensure that no relevant publications were missed, we also performed a search in Google Scholar, but no additional publications were found.

Inclusion

We selected peer-reviewed articles published until 30th May 2012. The publications should have used the GeneXpert, or MODS, or WHO 2007 algorithm, for diagnosis of pulmonary TB. The inclusion criteria were: i) use of culture as the reference method (LJ, or 7H10 agar, or BACTEC 460, or BACTEC MGIT 960). ii) Publications should have reported data to allow first hand computation of sensitivity and specificity of the test for SN-PTB. In papers where this was not reported, we contacted the corresponding authors to request provision of the required data.

Data extraction

We created an excel spreadsheet and collected data on 20 variables per article, including: index test, author and year of publication, culture method, country of study, study HIV prevalence, sample size, specimen type, culture method, and numbers of true positive, true negative, false positive, and false negative. Numbers of the positive and negative values were extracted either directly or through calculation based on reported measures of accuracy. The obtained data were verified by a second investigator.

Assessment of quality of study publications

Publications included in the meta-analysis were assessed for quality using the QUADAS-2 tool [15]. The tool consists of four key domains that judge bias and applicability of the reviewed studies by reviewing how patients were selected, the index test, the reference standard, and the flow of patients through the study. These variables were also included in the main data excel spreadsheet.

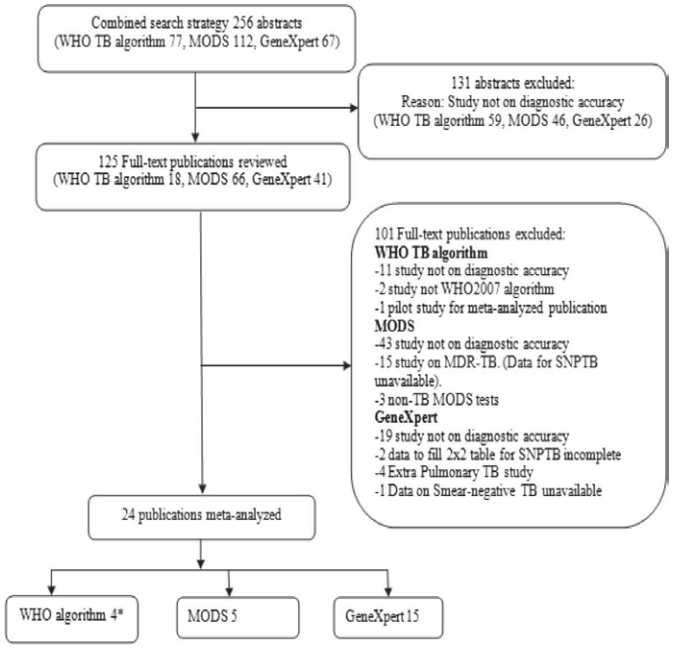

Figure 2. Flow chart for publication search. * One of the WHO publications provided separate diagnostic accuracy results for a rural and urban site. The results were therefore reported separately in Table 1. SNPTB = Smear-negative Pulmonary TB. Two landmark studies on GeneXpert were excluded [22,23]. We contacted the author but the data provided remained incomplete to fill 2x2 tables for smear-negative PTB (SNPTB).

Data analysis

From the main spreadsheet we created sub files for GeneXpert, MODS and the WHO 2007 algorithm. Each file was configured to fit into the Meta-Disc software v.1.4 for data analysis [16]. Using the random-effects model, the accuracy of each diagnostic method was analyzed and presented in form of forest plots. We used the forest plots to obtain a general overview of the accuracy estimates of each study before subsequent interpretation of the pooled summary estimates. Sensitivity was defined as the proportion of positive results obtained while specificity was defined as the proportion of negative results obtained, for each diagnostic method in reference to culture. For one of the publications on the WHO 2007 algorithm [8], we analyzed and reported the results separately. This is because the authors aimed to evaluate the effect of various patient and provider factors on the performance of the algorithm in a rural versus urban setting. They therefore reported the diagnostic performance of the algorithm at the two sites separately but in one publication.

Analysis for heterogeneity

As study results can be variable (heterogeneous), it is critical to explore this heterogeneity to understand the possible factors that influence the obtained accuracy estimates and whether it is appropriate to pool them. Heterogeneity can either be due to chance or due to differences in the threshold that is used to define positive and negative results of a test.

We explored for heterogeneity due to chance (other than threshold effect) for each diagnostic method by; i) visual inspection of the forest plots for deviation of sensitivity and specificity of each study from the vertical line corresponding to the pooled estimates. Large deviations from this line would indicate possibility of heterogeneity, (ii) Chi-square p-values,

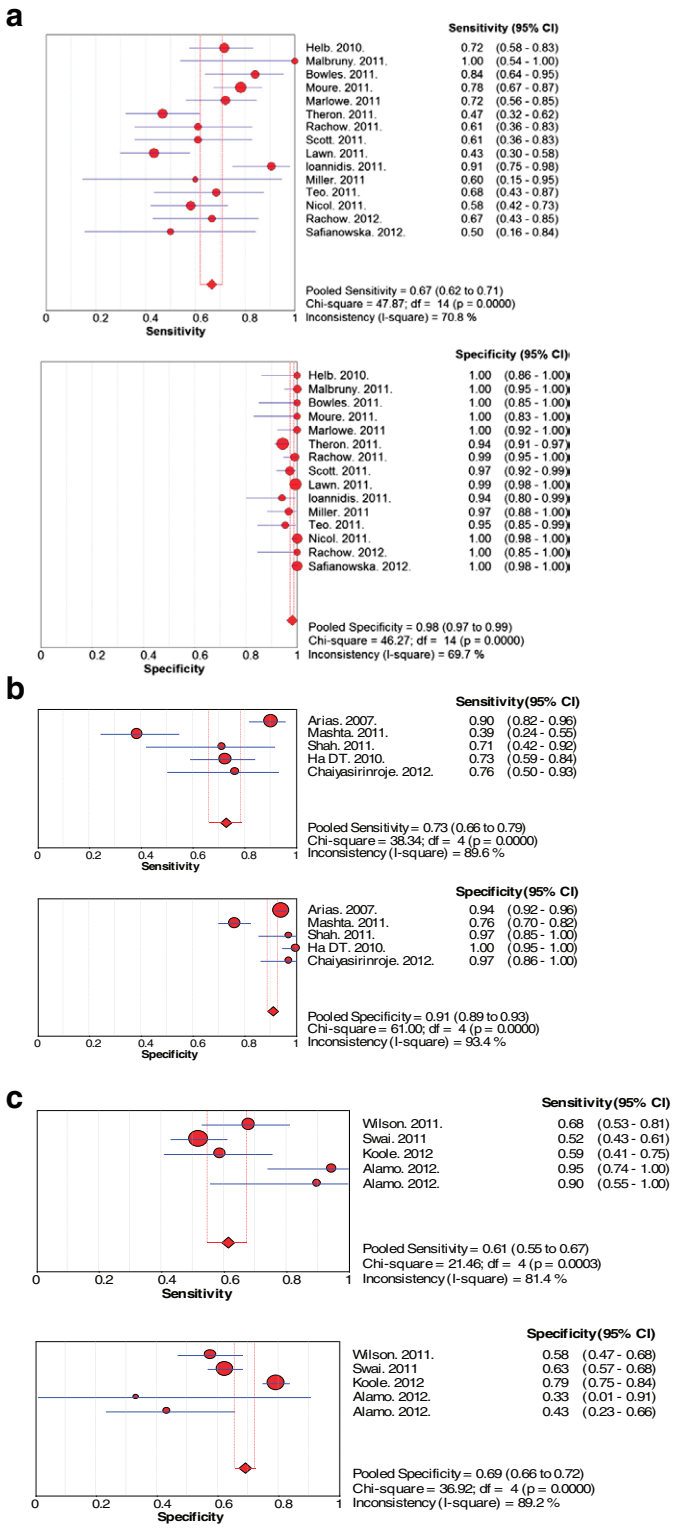

Figure 3. Forest plots of sensitivity and specificity for (a) GeneXpert test, (b) MODS test and (c) WHO 2007 Algorithm.

which are automatically computed by Meta-disc during analysis. A low Chi-square p-value would suggest presence of heterogeneity beyond what could be expected by chance alone and, (iii) the inconsistence index (I-square), which is also automatically computed by Meta-disc software. The inconsistence index is a quantitative measure of the amount of heterogeneity [17]. We interpreted the inconsistence index as follows: 0% to 40%: not important; 50% to 70%: represented

Table 1 Key characteristics of the meta-analyzed reports (n = 24)

Test	Author, (Year)	Ref	Country	Study HIV rate	Specimen type	Screen test	TP	FP	FN	TN
GeneXpert	Helb, 2010	[24]	Vietnam	1	Sputum frozen	Unclear	38	0	15	25
	Malbruny, 2011	[25]	France	3.4	Various	FM	6	0	0	73
	Bowles, 2011	[26]	Netherlands	NR	Sputum	ZN	21	0	4	23
	Moure, 2011	[27]	Spain	NR	Sputum frozen	FM + ZN	61	0	17	20
	Marlowe, 2011	[28]	USA	NR	Sputum sediment	Unclear	43	0	12	47
	Theron, 2011	[29]	S. Africa	27	Sputum	FM	22	19	25	319
	Rachow, 2011	[30]	Tanzania	59.9	Sputum frozen	ZN	11	1	7	102
	Scott, 2011	[31]	S. Africa	70*	Sputum sediment	FM	11	3	7	104
	Lawn, 2011	[32]	S. Africa	100	Sputum	FM	23	2	30	320
	Ioannidis, 2011	[33]	Greece	NR	Sputum	Unclear	29	2	3	32
	Miller, 2011	[34]	USA	NR	Sputum frozen	FM	3	2	2	58
	Teo, 2011	[35]	Singapore	NR	Various	ZN	13	2	6	42
	Nicol, 2011	[36]	S. Africa	24	Sputum-induced	FM	25	0	18	166
	Rachow, 2012	[37]	Tanzania	51.2	Sputum	ZN	14	0	7	22
	Safianowska, 2012	[38]	Poland	NR	Various	ZN	4	0	4	181
	Total						**324**	**31**	**157**	**1534**
MODS	Arias, 2007	[39]	Brazil / Honduras	12*	Various	ZN	75	28	8	469
	Mashta, 2011	[40]	India	NR	Sputum	ZN	17	45	27	146
	Shah, 2011	[41]	S. Africa	87	Sputum	Unclear	36	13	14	407
	Ha DT, 2010	[42]	Vietnam	100	Sputum	ZN	40	0	15	67
	Chaiyasirinroje, 2012	[43]	Thailand	NR	Sputum	Unclear	13	1	4	37
	Total						**181**	**87**	**68**	**1126**
WHO 2007 algorithm	Wilson, 2011	[44]	S. Africa	57*	Sputum-induced	FM	47	91	12	71
	Swai, 2011	[45]	Tanzania	68.1	Sputum	ZN	66	107	61	179
	Koole, 2012	[46]	Cambodia	26.5	Sputum	FM	20	70	14	270
	Alamo, 2012. Rural site	[8]	Uganda	100	Sputum	ZN	18	2	1	1
	Alamo, 2012. Urban site	[8]	Uganda	100	Sputum	ZN	9	13	1	10
	Total						**160**	**283**	**89**	**531**

Specimen type various included = bronchial aspirate, bronchial alveolar lavage.
ZN = Ziehl-Nielsen microscopy stain method.
FM = Fluorescent microscopy stain method.
TP = True positive (Individuals have disease and have positive test).
FP = False positive (Individuals do not have disease, but have positive test).
FN = False negative (Individuals have disease, but have negative test).
TN = True negative (Individuals do not have disease and have negative test).
NR = Not reported.
* = The rate reported was based on a denominator that included patients with undocumented HIV result.

moderate heterogeneity; >70% represented substantial heterogeneity [18].

Heterogeneity due to threshold effect was explored by plotting summary receiver operating curves (sROC) for each diagnostic method to assess if the points in the plots had a curvilinear (shoulder arm) pattern or not. A typical "shoulder arm" pattern would suggest presence of threshold effect [16,19,20]. The Meta-disc software automatically computes and shows the statistical analysis of the area under the sROC curve and the Cochrane indices (Q*). As a further assessment of threshold effect, we also calculated the Spearman correlation coefficient between sensitivity (logit of the true positive rate) and specificity (logit of the false positive rate) for each test. If threshold effect exists, an inverse correlation appears. We considered a positive Spearman correlation coefficient of >0.6 to be strong, and suggestive of threshold effect [21]. If the value was less than 0.6, the accuracy of the tests could be based on pooled estimates of sensitivity and specificity.

Results

Publications retrieved

The systematic review based on all the stated strategies retrieved a total of 256 abstracts. After reviewing the abstracts, 125 publications (WHO algorithm 18, MODS 66 and GeneXpert 41) were fully reviewed. Due to various reasons such as; a test not being evaluated for diagnostic accuracy or data to allow computation of sensitivity and specificity not reported (see Figure 2), 101 publications were excluded leaving twenty-four publications for final meta-analysis (GeneXpert-15, MODS-5, and WHO 2007 algorithm-4).

Description of meta-analyzed publications

Of the 24 publications that fulfilled the inclusion criteria for

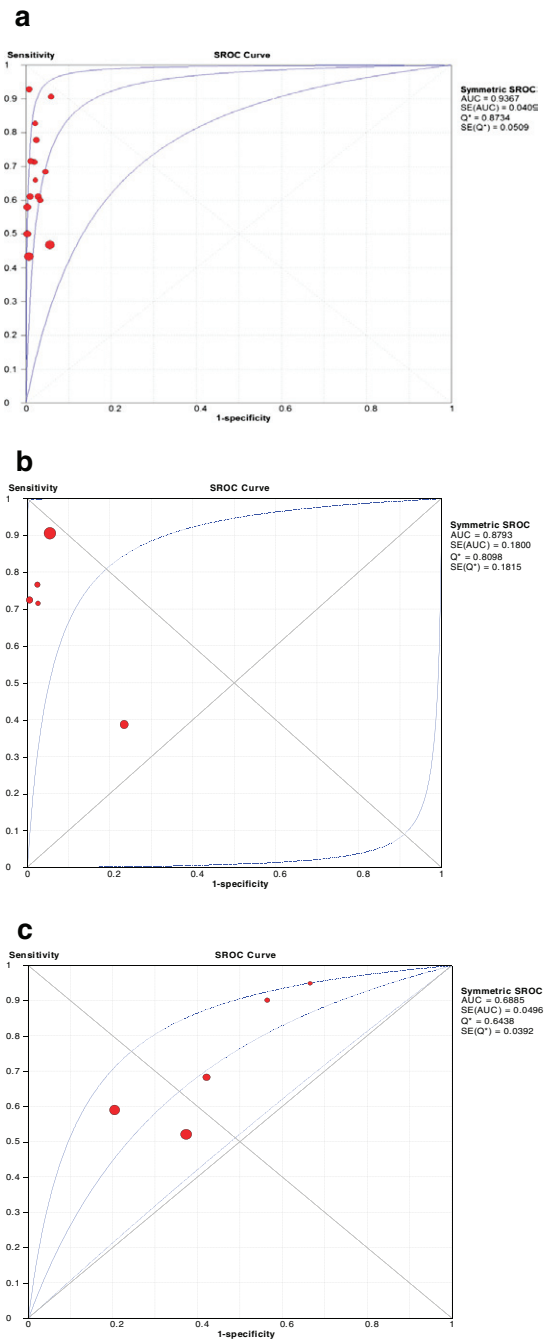

Figure 4. Summary receiver characteristics (sROC) (a) curve-GeneXpert, (b) curve-MODS and (c) curve-WHO 2007 algorithm. Note: sROC = summary receiver operating characteristic curve, which is a plot of the true positive rate (sensitivity) against the false positive rate (1-specificity) of a diagnostic test at different thresholds [47]. This generates a composite statistic (AUC or the Index Q*) that provides an overall evaluation of the accuracy of a test (perfect discriminating ability of true positivity from false positivity). The three curves of the sROC represent the estimate and the 95% upper and lower bounds of the estimate. AUC = Area under the curve of a constructed sROC curve. An AUC close to 1.0 signifies that the test has almost perfect discrimination while an AUC close to 0.5 suggests poor discrimination. An AUC significantly less than 0.5 would indicate that the criteria for "normal" and "abnormal" should be reversed. SE (AUC) = standard error of the area under curve Q* = An index which corresponds to the upper most point on the sROC curve at which sensitivity equals specificity. The closer this value is to 1, the closer the test to perfect accuracy (perfect discriminating ability of true positivity from false positivity). When the value of the Q* index is close to 0.5, it signifies that the test has poor discrimination. SE (Q*) = the standard error of the index Q*.

Table 2 Spearman correlation coefficient of the logit of TPR versus logit of FPR

Test	Spearman correlation coefficient	p- value
GeneXpert	0.232	0.405
MODS	0.4	0.600
WHO 2007 algorithm	0.9	0.037

Note: The logit of the true positive rate is the natural log of [true positive rate/(1-true positive rate)]. The logit of the false positive rate is the natural log of [false positive rate/(1-false positive rate)].

meta-analysis, the study HIV prevalence in 9 of them was ≥50% (GeneXpert-4, MODS-2, WHO 2007 algorithm-3). In addition, 10 of the 24 publications were conducted in countries from sub-Saharan Africa (GeneXpert-6, MODS-1, and WHO 2007 algorithm-3). Further, 6 out of 15 publications on GeneXpert used fluorescent microscopy (FM) as the screening test, while 3 out of 5 publications on MODS used Ziehl-Nielsen microscopy (ZN) as the screening test, and 2 out of 4 publications on the WHO 2007 algorithm used either FM or ZN. A summary of the description of the studies meta-analyzed is presented in Table 1.

Results on diagnostic accuracy

The results of the sensitivity and specificity of each test are shown in Figure 3. Overall, there was large deviation from the pooled estimates in the forest plots for all the three tests indicating the possibility of heterogeneity. However, the deviation was seen more with forest plots for sensitivity than specificity. The Chi-square p-values for heterogeneity for all three tests were low.

GeneXpert

The pooled sensitivity and the 95% confidence interval for GeneXpert was 67% (62% to 71%) while the pooled specificity was 98% (97% to 99%). On visualization of the forest plots, there was large deviation from the pooled estimate for sensitivity by several studies. For specificity, deviation from the pooled estimate was small. However, the I-square values for both sensitivity and specificity were above 40%.

MODS

The pooled sensitivity and the 95% confidence interval for the MODS test was73% (66% to 79%) while the pooled specificity was 91% (92% to 96%). On visualization of the forest plots, there was large deviation from the pooled estimate for sensitivity by two studies. For specificity, large deviation from the pooled estimate observed for one study. The I-square values for both sensitivity and specificity were above 70%.

WHO 2007 algorithm

The pooled sensitivity and the 95% confidence interval for the WHO 2007 algorithm was 61% (55% to 67%) while the pooled specificity was 69% (66% to 72%). On visualization of the forest plots, there was large deviation from the pooled estimate for both sensitivity and specificity by two studies. The I-square values for both sensitivity and specificity were also above 70%.

Analysis for threshold effect by summary receiver operating curves (sROC)

The patterns of the sROC curves are shown in Figure 4. The curves were consistent with each of the included reports of accuracy, with one outlier point (study) clearly detected in the sROC curve for MODS. The areas under the sROC curves

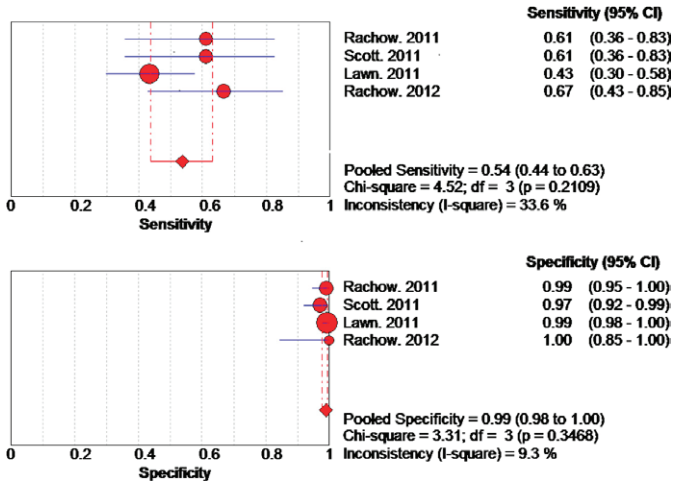

Figure 5. Forest plots of sub-analysis of sensitivity and specificity of GeneXpert.

and Cochrane (Q*) indices were 0.94 and 0.87 for GeneXpert, 0.87and 0.81 for MODS, 0.69 and 0.64 for WHO 2007 algorithm, respectively.

Spearman rank correlation for analysis of threshold effect

The Spearman rank correlations between the logistic transformations (logit) of the true positive rate (TPR) plotted against the logit of the false positive rate (FPR) for each method is presented in Table 2. Only the WHO 2007 algorithm had a significant and strong positive correlation coefficient of threshold effect.

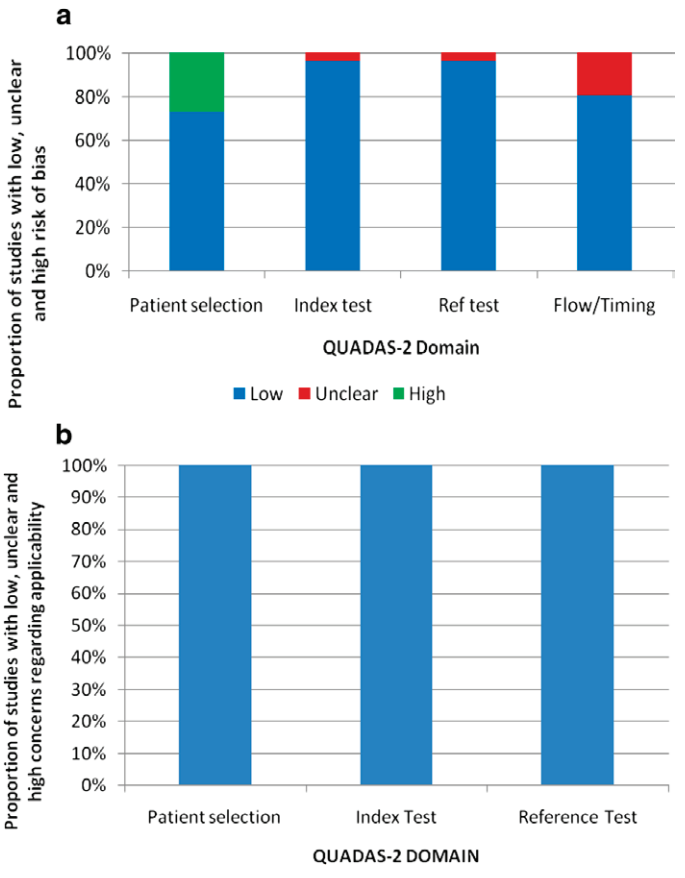

Figure 6. QUADAS-2 Results of (a) risk of bias and (b) concerns on applicability.

Sub-group analysis

Having found indication of possible heterogeneity, we performed the following sub-group analyses.

Based on HIV prevalence

For the GeneXpert, we focused on publications of studies in settings with HIV prevalence ≥ 30%, a typical value for TB patients from sub-Saharan Africa, where the GeneXpert is expected to be of much benefit due to the high levels of HIV-associated TB [9]. There were four publications, from such high HIV prevalence settings; two from South Africa and two from Tanzania, which we sub-analyzed. The pooled sensitivity of the GeneXpert from these settings was reduced from 67% to 54%, while the specificity remained 99%. These results are presented in Figure 5. For the WHO algorithm, a similar sub-group analysis gave a sensitivity of 65% and a specificity of 55%. We did not perform a similar sub-analysis for the MODS because the publications were inadequate for the analysis. Instead, we performed a sub-group analysis, excluding the outlier study which had reported what the authors decsribed as " unexplained observed disturbing inconsistencies in results", when they used the MODS for diagnosis of smear-negative TB [40]. Pooled sensitivity of MODS increased from 73% to 82%, and specificity increased from 91% to 95%.

Based on screening tests used

Since FM microscopy is increasingly becoming an alternative to ZN microscopy for diagnosis of TB in several settings [48], we also performed subgroup analysis for studies that used FM versus ZN as screening tests. The sensitivity for GeneXpert for studies that used FM as screening test was 52% and specificity was 98%. For studies that used ZN the sensitivity for GeneXpert was 69% and specificity was 99%. None of the studies evaluating MODS used FM as a screening test, thus a similar sub-analysis was not possible. However, the sensitivity for studies that evaluated MODS using ZN as screening test was 73%, while the specificity was 90%. There were an inadequate number of studies that evaluated WHO 2007 algorithm using FM as a screening test. However, for those studies that used ZN as the screen test, the sensitivity was 60% and the specificity was 61%.

Based on patients not completing all elements of the WHO 2007 algorithm

Lastly, since the WHO 2007 algorithm is widely used for diagnosis of smear-negative TB, but in practice few patients complete all the elements of the algorithm before clinicians exclude or initiate treatment for smear-negative TB, we performed a sub-group analysis of the WHO algorithm, excluding the publication that reported performance of the algorithm based on data of those patients that completed all the elements of the algorithm before clinicians decided if to treat or not [8]. The pooled sensitivity of the WHO algorithm reduced from 61% to 57%, while specificity increased marginally from 69% to 70% (data not shown).

QUADAS results of meta-analyzed publications

Seventeen out of the 24 meta-analyzed publications (70%) had a low risk of bias. Of the publications at risk of bias, six were on GeneXpert, while one was on WHO 2007 algorithm. The source of risk in these publications arose principally from unclear and flow of patients. However, all the publications

Table 3 QUADAS-2 results of risk of bias and concerns on applicability for each study included in the meta-analysis (n = 24)

Test	Author, Year	Risk of bias				Applicability concerns		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Genexpert	Helb [24]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Malbruny [25]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Bowles [26]	(-)	(?)	(?)	(?)	(+)	(+)	(+)
Genexpert	Moure [27]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Marlowe [28]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Theron [29]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Rachow [30]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Scott [31]	(-)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Lawn [32]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Ioannidis [33]	(-)	(+)	(+)	(?)	(+)	(+)	(+)
Genexpert	Miller [34]	(-)	(+)	(+)	(?)	(+)	(+)	(+)
Genexpert	Teo [35]	(-)	(+)	(+)	(?)	(+)	(+)	(+)
Genexpert	Nicol [36]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Rachow [37]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Genexpert	Safianowska [38]	(-)	(+)	(+)	(?)	(+)	(+)	(+)
MODS	Arias [39]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
MODS	Mashta [40]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
MODS	Shah [41]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
MODS	Ha DT [42]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
MODS	Chaiyasirinroje [43]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
WHO2007	Wilson [44]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
WHO2007	Swai [45]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
WHO2007	Koole [46]	(+)	(+)	(+)	(+)	(-)	(+)	(+)
WHO2007	Alamo [8] Rural site	(-)	(+)	(+)	(+)	(-)	(+)	(+)
WHO2007	Alamo [8] Urban site	(-)	(+)	(+)	(+)	(+)	(+)	(+)

(+) = low. (-) = High. (?) = Unclear.

matched the review questions, and therefore had low concern for applicability. The overall quality of the 24 publications is shown in Figure 6, while the quality of for the individual studies are shown in Table 1.

Discussion

We set out to compare the accuracy of GeneXpert, MODS and the WHO 2007 algorithm, for diagnosis of SN-PTB by doing a meta-analysis of the published literature. To our knowledge, this is the first study done to compare the accuracy of the three methods for the diagnosis of SN-PTB.

Overall, the MODS had the highest pooled sensitivity of 73%, followed by the GeneXpert with sensitivity of 67% and the WHO 2007 algorithm with sensitivity of 61%. GeneXpert had the highest pooled specificity of 98%, followed by MODS with 91% and the WHO 2007 algorithm with 69%.

There was substantial heterogeneity in the accuracy estimates for all the three tests that we evaluated, with the inconsistence indices (I^2) ranging from 71% to 90% for sensitivity, and 70% to 93% for specificity. Considering the sROC curves in view of the substantial heterogeneity, the GeneXpert had the highest accuracy for detection of SN-PTB with an area under the curve of a constructed sROC curve (AUC) value of 0.94, followed by MODS with 0.88 and the WHO algorithm with 0.69.

Several reasons can explain the heterogeneity that we observed. These include; variations in the HIV prevalence among study patients and the corresponding variation in the severity of TB disease. Additionally use of either FM or ZN as the screening test including operator/technician performance, type of specimen tested, and differences in the culture methods used as reference test can explain the variability.

Thus, the observed heterogeneity for the GeneXpert could be due to differences in the severity of HIV and the co-morbidities among the patients evaluated, since the test is fully automated after sample processing, requiring no technician involvement. On the other hand, technician performance could be a major factor in the heterogeneity observed for MODS, since inexperienced technicians could confuse artefacts for M.tb cords.

With regard to heterogeneity observed for the WHO 2007 algorithm, few clinicians fully adhere to the algorithm in practice, due to operational difficulties. Therefore, the decision by clinicians if to treat or not for SN-PTB is made variably. For example, of the 4 studies on the WHO 2007 algorithm in our review, only 1 reported results based on full adherence to all the elements of the algorithm [8]. However, full adherence to the algorithm in this study was quite low, ranging from 13% for the rural site to 19% for the urban site. Based on this report, in a best case scenario, the sensitivity of the algorithm is 95% (95% CI; 74%-100%) while specificity is 33% (95% CI; 23%-68%). On the other hand, based on the 3 other reports on the WHO 2007 algorithm, the sensitivity of the algorithm in a real world scenario is 57% (95% CI; 50%-64%,) while specificity is 70% (95% CI; 66%-73%). The variable access to some of the tests in the algorithm such as chest X-ray could explain the heterogeneity observed for the WHO 2007 algorithm.

Our results of the GeneXpert for diagnosis of SN-PTB are similar

to those recently reported by the Cochrane Collaboration [49]. Both our findings and those by the Cochrane group are however lower than what was reported in another publication, where the authors found sensitivity of GeneXpert for smear-negative PTB to be 75% and specificity 98% [50]. However, it was not clear whether they used the random-effects model for this subgroup analysis in their report. The random-effects model is the recommended analytical approach for meta-analysis since it incorporates heterogeneity among studies as opposed to the fixed-effects model which ignores heterogeneity [51].

Unlike in the report by the Cochrane group, where meta-analysis for the effect of HIV on the diagnostic accuracy of GeneXpert for SN-PTB could not be done, due to the small numbers of publications, in our study we found that the sensitivity of GeneXpert reduced from 67% to 54% while specificity remained unchanged. This finding was based on four studies with HIV prevalence ≥30%, an HIV rate which is commonly seen in six of the nine TB high burden countries from sub-Sahara Africa [1].

We used a comprehensive search and selection strategy which has been used before [52]. Further, most information (70%) was from publications which had low risk of bias, while all (100%), had low concerns regarding applicability (Figure 6a and b and Table 3). This implies good internal and external validity of the results in the primary studies. We therefore believe that our findings are robust. In addition any plausible bias is unlikely to alter the results as the confidence intervals for all the tests was narrow.

Limitations

Our study had the following limitations: There were few publications on MODS and the WHO2007 algorithm on diagnosis of SN-PTB. Moreover a substantial number of the publications on these two tests had to be excluded due to lack of reported data to compute sensitivity and specificity of the tests for diagnosis of SN-PTB. This included 2 large landmark studies on GeneXpert for the same reason [22,23]. The negative or positive influence of these studies on the pooled accuracy of the tests could therefore not be established. Further, although there was substantial heterogeneity across all studies for the three diagnostic methods, we did not perform a meta-regression analysis to investigate the effects of the various characteristics associated with the observed heterogeneity. However, our primary aim was not to explore the factors that may be accountable for the differences among studies. Besides, to achieve reliable conclusions from such an investigation, one would need to pre-specify the protocol of the review since explorations of heterogeneity that are devised after heterogeneity is identified cannot be conclusive. We did not also assess publication bias of the studies which we meta-analyzed. This was because there were few studies on MODS and the WHO algorithm for such analysis [53]. In addition, despite its cited advantages (such as being free and user friendly), the meta-disc software which we used in our analysis is limited in some statistical tests including the Egger's test and Begg's tests that are recommended for assessing publication bias.

Conclusions

The GeneXpert, MODS, and the WHO algorithm have moderate to high accuracy for the diagnosis of SN-PTB. However, the accuracy of the tests is extremely variable. The setting and context under which the tests are conducted in addition to several other factors could explain this variability. There is therefore need to investigate these factors further. The information from these studies would inform the adoption and placement of these new tests.

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Cardiovascular Risk And Mortality In End-Stage Renal Disease Patients Undergoing Dialysis: Sleep Study, Pulmonary Function, Respiratory Mechanics, Upper Airway Collapsibility, Autonomic Nervous Activity, Depression, Anxiety, Stress And Quality Of Life: A Prospective, Double Blind, Randomized Controlled Clinical Trial

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Abstract

Background: Chronic kidney disease (CKD) is one of the most serious public health problems. The increasing prevalence of CKD in developed and developing countries has led to a global epidemic. The hypothesis proposed is that patients undergoing dialysis would experience a marked negative influence on physiological variables of sleep and autonomic nervous system activity, compromising quality of life.

Methods/Design: A prospective, consecutive, double blind, randomized controlled clinical trial is proposed to address the effect of dialysis on sleep, pulmonary function, respiratory mechanics, upper airway collapsibility, autonomic nervous activity, depression, anxiety, stress and quality of life in patients with CKD. The measurement protocol will include body weight (kg); height (cm); body mass index calculated as weight/height^2; circumferences (cm) of the neck, waist, and hip; heart and respiratory rates; blood pressures; Mallampati index; tonsil index; heart rate variability; maximum ventilatory pressures; negative expiratory pressure test, and polysomnography (sleep study), as well as the administration of specific questionnaires addressing sleep apnea, excessive daytime sleepiness, depression, anxiety, stress, and quality of life.

Discussion: CKD is a major public health problem worldwide, and its incidence has increased in part by the increased life expectancy and increasing number of cases of diabetes mellitus and hypertension. Sleep disorders are common in patients with renal insufficiency. Our hypothesis is that the weather weight gain due to volume overload observed during interdialytic period will influence the degree of collapsibility of the upper airway due to narrowing and predispose to upper airway occlusion during sleep, and to investigate the negative influences of haemodialysis in the physiological variables of sleep, and autonomic nervous system, and respiratory mechanics and thereby compromise the quality of life of patients.

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Background: Chronic kidney disease (CKD) is one of the most serious public health problems. The increasing prevalence of this disease in developed and developing countries has led to a global epidemic. Current epidemiological surveys suggest that approximately 1 million individuals with terminal CKD have undergone kidney replacement therapy worldwide. A large part of this epidemic may be explained by the increase in the number of diabetes mellitus cases and the increase in life expectancy. Diabetic nephropathy is expected to affect approximately 5.4% of the world population by 2015.[1]

CKD is defined as the presence of kidney damage or reduced kidney function for ≥3 months, regardless of the diagnosis. The advanced stage of this condition is known as terminal CKD or end-stage kidney disease, with progressive and irreversible loss of kidney function.[2]

CKD is classified on the basis of the glomerular filtration rate (GFR), as recommended by the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative, which provides the basis for the management of this disease. CKD is classified into 5 stages: stage 1, kidney damage with normal or increased GFR ≥ 90 mL/(min·1.73 m^2); stage 2, kidney damage with mildly decreased GFR of 60 to 89 mL/(min·1.73 m^2); stage 3, moderately decreased GFR of 30 to 59 mL/(min·1.73 m^2); stage 4, severely decreased GFR of 15 to 29 mL/(min·1.73 m^2); and stage 5, kidney failure with a GFR < 15 mL/(min·1.73 m^2). Evidence of kidney damage for ≥3 months is required for the diagnosis of stage 1 and 2 CKD, as manifested by pathological kidney abnormalities or abnormal urine composition (such as haematuria or proteinuria) or abnormalities on imaging tests.[3]

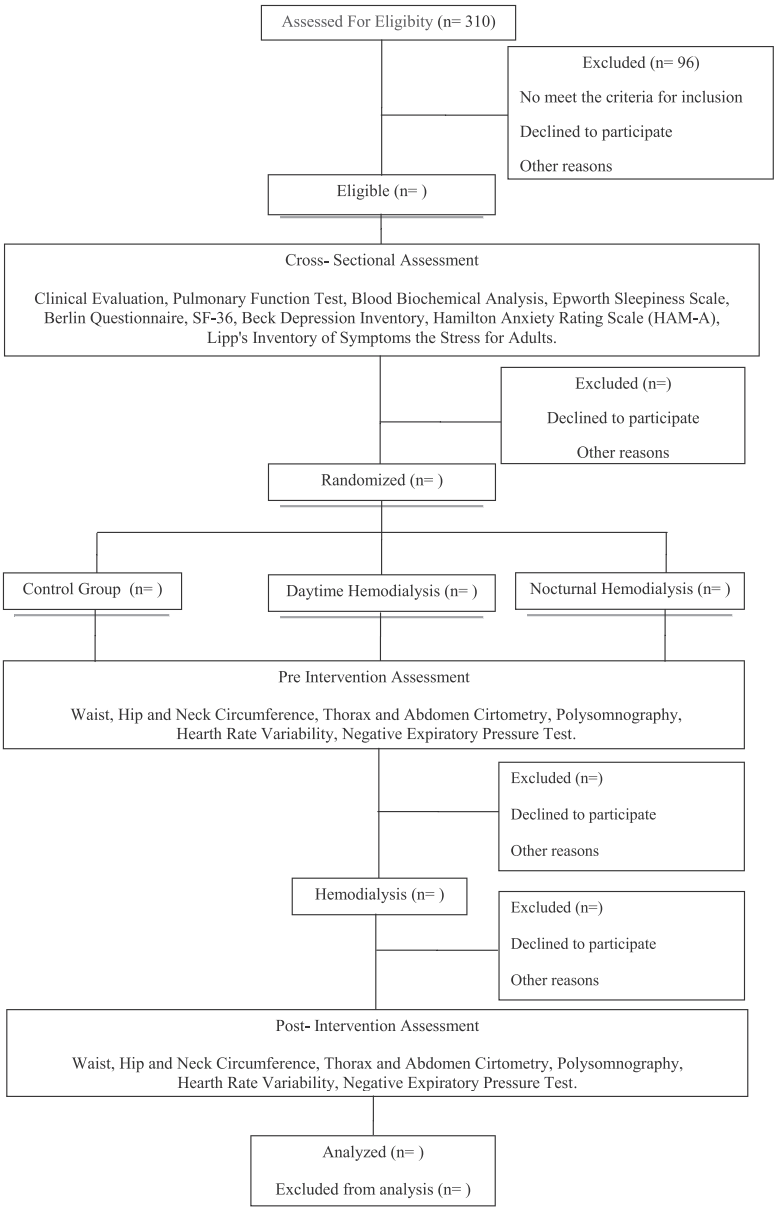

Figure 1 Flowchart of the study protocol.

The prevalence rate of sleep disorders in patients with CKD ranges from 40% to 80%, which is higher than those in the general population.[4] The most frequent comorbidities include diabetes mellitus type 2,[1] periodic leg movements during sleep,[4] obstructive sleep apnea (OSA) and nocturnal hypoxemia,[5] dyslipidaemia, coronary disease, heart failure,[6,7] systemic arterial hypertension,[8,9] respiratory disorders,[10,11] stress,[12] depression,[12-14] anxiety.[15]

OSA is a respiratory disease characterized by the collapse of the upper airways during sleep in predisposed subjects. After chronic obstructive pulmonary disease and asthma, OSA is the most important and widespread respiratory disease, affecting 3% to 7% of the male population and 2% to 5% of the female population between 40 and 65 years of age in the Western world.[16] In Brazil, the prevalence of OSA is even higher at 24.8% in men and 9.6% in women, according to a recent epidemiological study conducted in the city of São Paulo.[17]

The causal association between OSA and CKD or whether the 2 diseases result from a common pathophysiologic process has not yet been clarified. Uremic milieu has been implicated as a cause of OSA in patients with CKD. Altered ventilatory drive and chemoreceptors can lead to decreased respiration via a blunted response to ventilatory stimuli, such as hypoxia or acidaemia. Upper airway obstruction can occur from localised oedema or the collapse of the dilator muscles, leading to an increased risk of OSA. Suppression of the respiratory musculature due to metabolic acidaemia/acidosis, osmotic disequilibrium, and a reduction in middle molecule clearance could potentially cause or contribute to OSA.[18]

Aims and hypotheses

The present study involving patients with CKD was designed with 4 main objectives: (1) to assess the effects of dialysis on sleep parameters and determine the prevalence and severity of sleep disorders; (2) to determine the behaviour of sympathetic and parasympathetic autonomic nervous system activity through an analysis of heart rate variability; (3) to detect upper airway collapsibility as a risk indicator for OSA; and (4) to evaluate levels of depression, anxiety, stress and quality of life. Our hypothesis is that the weather weight gain due to volume

overload observed during interdialytic period will influence the degree of collapsibility of the upper airway due to narrowing and predispose to upper airway occlusion during sleep, and to investigate the effects of nocturnal hemodialysis compared to daytime hemodialysis and the influences in the physiological variables of sleep, autonomic nervous system (ANS), and respiratory mechanics and thereby compromise the quality of life in chronic kidney diseases and end-stage renal disease patients undergoing dialysis.

Methods/Design

Study design

A prospective, consecutive, double-blind, randomized controlled clinical trial is proposed to investigate the effect of dialysis on sleep, pulmonary function, respiratory mechanics, upper airway collapsibility, ANS, depression, anxiety, stress and quality of life in end-stage renal disease patients, as summarized in Figure 1.

Subjects

The participants will be recruited from the Centro de Nefrologia Zona Norte (São Paulo, Brazil) and sent to the Sleep Laboratory of the Universidade Nove de Julho (São Paulo, Brazil). Patients will be recruited consecutively and screened for eligibility using a standardised protocol. The following will be used as the inclusion criteria: male or female patients aged 18 to 80 years; chronic kidney failure; candidate for kidney transplant with indication for dialysis; cognitive level sufficient for understanding the procedures and following the instructions; and agreement to participate by signing a statement of informed consent. Meanwhile, the following will used as the exclusion criteria: craniofacial abnormalities; undergoing active treatment of sleep apnea; active malignancy; active alcohol and/or drug abuse; and dementia or treatment-refractory psychiatric diseases leading to an inability to provide informed consent.

Randomization

After the initial assessment and compliance with eligibility criteria, participants will be randomized into two intervention group [patients achieving diurnal hemodialysis and nocturnal hemodialysis] and the control group [CKD not submitted to dialysis]. Randomization numbers will be generated using a randomization table at a central office. A series of numbered, sealed, opaque envelopes will be used to ensure confidentiality. Each envelope will contain a card stipulating to which group the subject will be allocated.All patients underwent randomization protocol that will meet the eligibility criteria and be clinically stable.

Blinding

Baseline data will be collected prior to randomisation so that trial investigators, assessors, research co-ordinators and trial participants will be blinded to allocation while the data is being collected. Blinding will be maintained in all steps of the research.

Sample size calculation and statistical analysis

According to the findings of a previously published epidemiological study[17] that the proportion of adults with an apnea/hypopnoea index (AHI) ≥ 15 corresponds to 16.9% of the Brazilian population and that of a previous study[18] that AHI ≥ 15 had an approximately 50% prevalence rate in patients with CKD undergoing conventional dialysis (3 times a week, 4 h per session),[19] the sample size was calculated as 57 patients, with an $\alpha = 0.05$ and $\beta = 90\%$ (test power).

The Kolmogorov-Smirnov normality test will first be performed to determine whether a normal distribution sample is present. A descriptive analysis will be performed, with the data expressed as either mean and standard deviation or median values and 95% confidence intervals, as appropriate. One-way analysis of variance will be used for comparisons between work shifts once the samples have a normal distribution. $V_{0.2}$ and ΔV (%) values will be linearly correlated with the AHI, for which either the Pearson or Spearman correlation test will be used, depending on the sample distribution. Either the non-paired Student *t* test or Mann-Whitney test will be used for comparisons between individuals with and those without OSA.

In addition, a logistic regression analysis of continuous factors with categorical responses will be performed. Receiver operating characteristic (ROC) curves will be constructed to determine the sensitivity (true-positive rate) versus 100% specificity (false-positive rate) at various levels of the measured $\dot{V}$ (%) and $V_{0.2}$ (%) to identify the cut-off value yielding the largest number of correctly classified patients. The statistical analysis will be

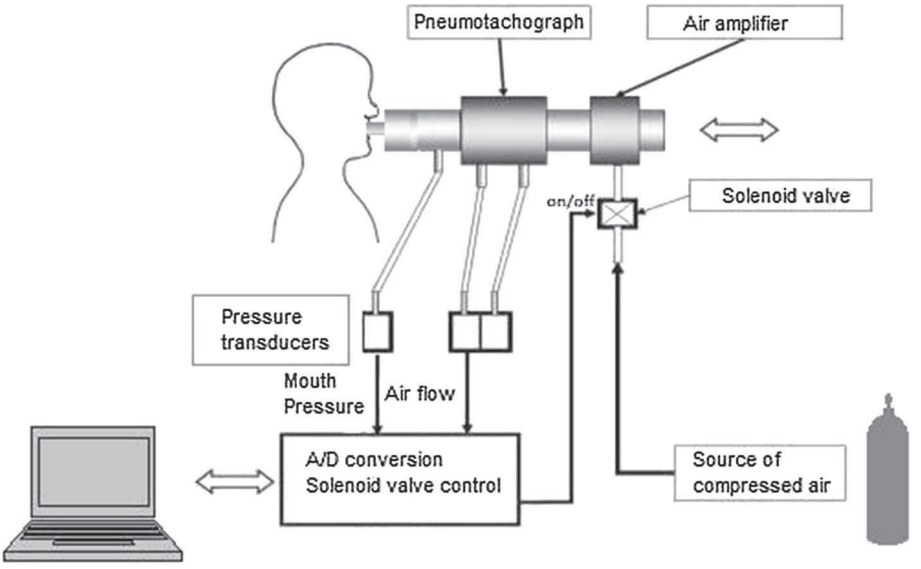

Figure 2 Schematic representation of the negative expiratory pressure.

performed by an experienced statistician using the JMP version 8.0 (SAS/STAT Software, SAS Institute Inc., Cary, NC, USA) and SPSS version 16.0 programs (Somers NY). A 5% level of significance and 95% confidence interval will be applied.

Ethical considerations

The study will be conducted in accordance with the ethical standards established in the 1961 Declaration of Helsinki (as revised in Hong Kong in 1989 and Edinburgh, Scotland, in 2000) and is in compliance with the Regulatory Guidelines and Norms for Research Involving Human Subjects of the National Health Board of the Brazilian Health Ministry issued in October 1996. This protocol received approval from the Human Research Ethics Committee of Universidade Nove de Julho (Brazil) under process no. 368856/2010 and is registered with the World Health Organization under Universal Trial Number (UTN) U1111-1127-9390 and the Brazilian Registry of Clinical Trials (REBEC no. RBR-7YHR4W). All participants will be required to sign a statement of informed consent and will be allowed to withdraw from the study at any time with no negative consequences. All the procedures of the study will be confidential.

Evaluation protocol

Clinical evaluation

Patients with chronic kidney diseases and end-stage renal disease undergoing dialysis, based on recommended procedures, will be submitted to general physical measurements performed by a well-trained physician and physical therapist before and after the dialysis session using precise instruments. The measurement protocol will include body weight (kg); height (cm); body mass index (BMI) calculated using the formula weight/height;[2,15] circumferences (cm) of the neck, waist, and hip;[20] heart and respiratory rates; blood pressures; Mallampati index;[21] tonsil index;[22] heart rate variability;[23] maximum ventilatory pressure; negative expiratory pressure (NEP) test; and polysomnography (PSG; sleep study), as well as the administration of specific questionnaires addressing sleep apnea, excessive daytime sleepiness,[24,25] symptoms of stress,[12] and depression,[12-14] anxiety,[15] and quality of life.[26,27]

The following data will be obtained from medical charts: biochemical values, associated pathological conditions, laboratory values (iron, intact-parathyroid hormone, haemoglobin, calcium, phosphorus, and creatinine), duration of dialysis therapy, comorbidities, and aetiology of kidney disease.

Physical examination

Weight and height determinations will be performed using an electronic scale (model 200/5; Welmy Industria e Comercio Ltda, São Paulo, Brazil), and the BMI will be calculated.[16] For the assessment of the tonsils and Mallampati index scoring, each subject will be in the sitting position and instructed to open the mouth as wide as possible.[21,22]

Waist and neck circumferences

Measurements of waist and neck circumferences will be performed with a metric tape (7 mm in width). The sites for the measurements will be standardised. Waist circumference will be measured at the midpoint between the lower edge of the last rib and the iliac crest. Neck circumference will be measured horizontally over the cricoid cartilage.[28]

Thorax and abdomen cirtometry

Cervical-thoracic abdominal cirtometry will be performed to assess thorax and abdomen mobility and define the diaphragm index. The measurement will be performed by fixing the zero point on the metric tape to the anterior region of the thorax at the level that is being measured (axillary, xiphoid, or abdominal), with the tape encircling the entire circumference of the thorax or abdomen with maximal possible pressure and the other extremity of the tape placed over the same fixed point. The aim of applying the maximal possible pressure of the tape on the body is to avoid the interference of soft structures in the measurements. Mobility and range of motion will be provided by maximal inspiration and expiration.[29]

Lung function tests

Spirometry

Lung function tests will be performed during the day, with the patient seated in a comfortable position. For such, the KoKo PFT Spirometer System version 4.11 (nSpire Health, Inc, Louisville, CO, USA) will be used in accordance with the guidelines for the execution of lung function tests established by the Brazilian Society of Pneumology[30] and European Respiratory Society.[31] The subjects will perform the test in a comfortable position, with the body erect and upper limbs unsupported. All the examinations will be performed by a competent technician trained in obtaining the necessary cooperation from the subjects and appropriately operating the equipment to ensure accurate, reproducible results. The spirometer will be calibrated before each exam using a 3-L syringe.[30]

Analysis of respiratory mechanics

Maximal inspiratory pressure and maximal expiratory pressure physiologically constitute the most adequate test for the determination of ventilatory muscle strength. Maximal inspiratory pressure is an indicator of ventilatory capacity and the development of respiratory failure, the measurement of which is indicated for the assessment of the degree of abnormality and monitoring of the weakening of individual inspiratory muscles in disease progression.[32] The tests will be performed on the same day on which the patients will undergo spirometry. The tests will be performed in a quiet setting. The patients will be seated comfortably, breathing calmly and at rest, with the trunk at a 90-degree angle in relation to the thighs.[30]

Sleep evaluation

Berlin questionnaire

The Berlin questionnaire is used to identify patients at high risk of respiratory sleep disorders in a variety of populations. This clinical history questionnaire has recognised efficacy in distinguishing individuals at high risk of OSA, with 10 items organised into 3 categories as follows: snoring and apnea (5 items), daytime sleepiness (4 items), and systemic arterial hypertension and obesity (1 item). All marked responses are considered positive. The score is divided into the following categories: category 1 is considered positive in the occurrence of 2 or more positive responses to items 1 to 5; category 2, in the occurrence of 2 or more positive responses to items 6 to 8; and category 3, when the response to item 9 is "yes" or when the BMI ≥ 30 kg/m^2. Two or more positive categories indicate a high risk of OSA.[24]

Epworth Sleepiness Scale

The Epworth Sleepiness Scale is a simple, self-administered questionnaire with items addressing situations involving activities of daily living and the occurrence of daytime sleepiness in adults. The subjects will be instructed to classify their

likelihood of feeling the desire to nap or sleep in 8 situations on a scale of 0 to 3 (0, no chance of napping; 1, small chance of napping; 2, moderate chance of napping; and 3, strong chance of napping).[25,33]

Polysomnography

All the patients will undergo a standard overnight PSG (Embla, A10 version 3.1.2 Flaga, Hs. Medical Devices, Reykjavik, Iceland) at the Sleep Laboratory of Nove de Julho University. Polysomnography exams will be held the night before the haemodialysis and approximately 12 hours after this dialysis. All recording sensors will be attached to the patient in a non-invasive manner using tape or elastic bands. The following physiological variables will be monitored simultaneously and continuously: 4 channels for the electroencephalogram (C3-A2, C4-A1, O1-A2, and O2-A1), 2 channels for the electrooculogram (EOG-Left-A2 and EOG-Right-A1), 4 channels for the surface electromyogram (muscles of the submentonian region, anterior tibialis muscle, masseter region, and seventh intercostal space), electrocardiogram (derivation V1 modified), airflow detection via 2 channels through a thermocouple and nasal pressure cannula, respiratory effort of the thorax and abdomen via x-trace belts, snoring and body position sensors, and arterial oxygen saturation and pulse rate via an oximeter.

All the subjects will be monitored by a technician experienced in PSG. Sleep stages will be visually scored in 30-s epochs, and each PSG recording will be analysed manually under blinded conditions by the same examiner with experience in scoring PSG recordings in accordance with international standards established by the Academy of Sleep Medicine Manual for Scoring Sleep and Associated Events. The patients will be instructed to remain as relaxed as possible and sleep naturally, as if at home. All signals will be recorded continuously.[34,35]

NEP test

The NEP test will be conducted before and after hemodialysis sessions, performed through the administration of a negative pressure at the mouth during expiration. This is a practical test performed while awake and requires little cooperation from the subject. In the absence of expiratory flow limitation, the increase in the 8 pressure gradients between the alveoli and the open upper airway caused by NEP results in an increase in expiratory flow.

NEP will be generated by the Super Air Amplifier (Exair model 120021, Cincinnati, OH, USA) coupled to a tank of compressed air via an electrically operated solenoid valve (model 95004, Norgren Ltd; Vimercate, MI, Italy) automatically activated in early expiration and kept open for 2 s by software control (Figure 2). A pneumotachograph (Hans Rudolph model 3830; Kansas, MO, USA) will be connected to the air amplifier and the mouthpiece to measure airflow ($\dot{V}$) with pressure transducers (PCLA02X5; Sensortechnics GmbH, Puchheim, Germany). Mouth pressure will be measured by pressure transducers (PCLA0050; Sensortechnics GmbH, Puchheim, Germany). NEP of 10-cm H_2O will be set by occluding the pneumotachograph with a stopper and adjusting the flow of compressed air-to-air amplifier (Figure 2).

Each NEP manoeuvre will be performed each after at least 4 breaths to normalise the breathing pattern. The tests will be performed once with the subject seated comfortably and again in supine position on a cot. In both positions, care will be taken to maintain the comfort of the subjects, with the neck in a neutral position, as it has been documented that the position of the head exerts an influence on upper airway collapsibility.[36]

All manoeuvres will be performed with the subjects awake and wearing a nose clip. The airflow and mouth pressure signals will be low-pass filtered and sampled at 200 Hz. Both digital signals will be displayed in real time on the monitor and stored on the computer for subsequent analysis. Signal analysis and solenoid valve control will be performed using software written in 9 LabVIEW 8.2 (National Instruments) developed by the Italian National Research Council, Institute of Biomedicine and Molecular Immunology "A. Monroy."

NEP application during tidal expiration produces an immediate peak flow followed by a sudden drop of a variable degree. Upper airway collapsibility is to be evaluated by measuring flow limitation as flow drop ($\Delta\dot{V}$) expressed as the percentage of peak flow immediately after NEP administration. To avoid reflex and voluntary reactions to the NEP stimulus, the minimum flow will be identified in the first 200 ms of NEP administration.[37]

Upper airway collapsibility will also evaluated by measuring V0.2 immediately after NEP administration. These values will be expressed as the percentage of mean inspiratory volume of the 3 breaths preceding NEP administration. Measured volumes will be accepted only when differences between inspiration and expiration for each of the 3 previous breaths are less than 10%. Values of $V_{0.2}$ and $\Delta\dot{V}$ (%) are calculated as the mean of 4 measurements. Measurements of upper airway collapsibility will be evaluated as expiratory volume in 0.2 s (percentage of the mean inspiratory volume of the 3 breaths preceding NEP application) and as flow drop (ΔV), expressed as the percentage of peak flow.

Assessment of ANS

Nerve-Express is a fully automatic, non-invasive computer-based system designed for the quantitative assessment of the ANS on the basis of the analysis of heart rate variability. This system is based on a method of clusterisation of the relationship between sympathetic and parasympathetic nervous system statuses.

This technological breakthrough is achieved by using proprietary algorithms and a new approach based on a leading theory of artificial intelligence, the Marvin Minsky's Frame Theory. Nerve-Express provides an objective and reliable real-time evaluation of the ANS state during the orthostatic test and Valsalva manoeuvre combined with deep breathing.

A signal sensor is attached to the thorax by an elastic strap and is coupled to the Nerve-Express software program, which collects and stores the data. The modality of the exam is the orthostatic test, in which the patient goes from the supine to the orthostatic position.[38,39]

Inventory of symptoms of stress for adults

The Inventory of Symptoms of Stress for Adults (LIPP) is based on a 4-phase model of stress and its manifestations in the somatic and cognitive domains. In the initial stress phase, which is called the alert phase, the body makes greater efforts to prepare itself to cope with a stressor. This phase is considered a positive phase of stress because it is important for adjustments to environmental demands.

The second phase is called resistance and occurs when a chronic stressor demands coping for a long period of time. This phase is associated with fatigue, perception of burnout, and cognitive loss. The next phases, referred to as almost exhaustion and exhaustion, are consequences of the breakdown of resistance and loss of capacity for adjustment. During these phases, one can observe important changes in sleep, work, and libido in addition to symptoms of anxiety and depression.[12]

Hamilton anxiety rating scale (HAM-A)

The term depression is used to describe a clinical syndrome, where there are several particular signs and symptoms. Depression can occur as a primary manifestation of mood, associated with systemic medical illnesses, other psychiatric disorders or disorders arising from the use of psychoactive substances. With regard to the study of depression, has not, to date, the biological or physiological parameters to evaluate its clinical manifestations in a definitive or conclusive. So the depression scales emerge as useful tools for assessing the severity of depressive, serving to translate clinical phenomenon in objective and quantitative information. In addition to characterizing the intensity of depression, these scales would serve to evaluate the response to treatment when applied before, during and after therapeutic intervention.

Within this context, the rating scales of depression severity, whose first date from the end of the last century can be divided into ranges: a) self-assessment, b) hetero c) mixed, involving self and observer.[15]

The first scale of hetero-evaluation, that is, applied by an observer, was the Hamilton Rating Scale for Depression (HAM-D), designed and developed by Hamilton in the late 50s. Currently, it is the most widely used depression scale worldwide and is probably the most important being regarded as "standard gold" in assessing the severity of depression compared with new and used rating scales in order to check the reliability of these.

Rating Scale Hamilton Anxiety is one of the most atualemnte used to assess anxiety in patients and is composed of 14 items (6 items - Humor anxious and 8 items - Physical symptoms) that pertain to the observed behavior. The patient will respond from their own experience the classification of symptoms present in Likert scale where 0 = absent, 1 = mild, 2 = medium intensity, 3 = 4 = strong intensity and moderate intensity.

The total score reflects the general state of the patient's anxiety, the aspects considered by the scale for the assessment are: mood, cognition, behavior, alertness and somatic symptoms, and in addition to other symptoms, scores between 0 and 17 are considered normal, between 18:25 26 moderate and 30 severe, over 30 are uncommon, but show a severe state of anxiety.[40,41]

Beck depression inventory

The Beck Depression Inventory (BDI) has 21 items, including attitude, depressive symptoms, and suicidal ideation, scored on a scale ranging from 0 to 3. The cut-off scores are as follows: <11, minimal depression; 12 to 19, mild to moderate depression; 20 to 35, moderate depression; and 36 to 63, severe depression.[12]

Quality of life

Patients with CKD may develop eating disorders due to the diet and water intake restrictions during treatment, which may also result in dysfunctional behaviour and treatment noncompliance. Thus, stress, anxiety, and depression are common among such patients and imply a reduction in quality of life. The Short Form 36 (SF-36) will be used for the assessment of quality of life. This measure has 36 questions grouped into 8 domains or scales of physical functioning, role limitations due to physical health, bodily pain, general health perception, social functioning, and role limitations due to emotional problems, vitality, and mental health.[26,27]

Study interventions

Haemodialysis

Regular daytime or nocturnal haemodialysis was standardised during the trial. It was performed 3 times per week, with a 4-h session duration, 250-mL/min blood flow, and 500-mL/min dialysate flow, using bicarbonate-buffered dialysate with 1.25 mmol/L ionised calcium concentration, dialysate temperature of 36.5°C, and Polyflux 17-L dialyser.[42]

The ultrafiltration amount for each haemodialysis session was decided by individual dry weight, which was fixed during the trial. In addition, during the trial, the patients were not permitted to change their medication or start new drugs, especially antiplatelet agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, and β-blockers.

The patients who required a change in medication for medical reasons were subsequently excluded from the study. Use of N-acetylcysteine was also prohibited in view of its potential influence on ischemia-reperfusion injury.

Quality control

To ensure the quality of the data, the physiotherapists and physicians in charge of data collection will receive specific training. Periodic external monitoring will be performed to verify the adequate application of methodology in performing examinations and data collection.

Discussion

CKD is a major public health problem worldwide, and its incidence has increased in part by the increased life expectancy and increasing number of cases of diabetes mellitus and hypertension. Sleep disorders are common in patients with renal insufficiency and is much more prevalent in patients with end-stage renal disease than in the general population.[4]

Symptomatic obstructive sleep apnoea syndrome has been related to be a risk factor for hypertension, heart failure and vascular dysfunction, and has been proposed to be causally related to both non-fatal and fatal coronary and cerebrovascular events.[43] Moreover, renal chronic patients frequently presented restless legs syndrome that also is associated with higher mortality and elevated incidence of cardiovascular events.[44] Thus, once presence of OSA also seems to reduce quality of haemodialysis[45] it's incorrectly identification among CKD patients may lead to worst outcomes or fail of hypertension control.[46]

Our hypothesis is that the weather weight gain due to volume overload observed during interdialytic period will influence the degree of collapsibility of the upper airway due to narrowing and predispose to upper airway occlusion during sleep, and to investigate the influences of different shifts haemodialysis in the physiological variables of sleep and ANS activity, and respiratory

mechanics, and depression, anxiety, stress and quality of life in end-stage renal disease patients. With our proposed study, we intend to identify the main factors that cause sleep disorders in patients with CKD that lead to the identification of the best treatment to reduce mortality and improve the quality of life of these patients.

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Exploring the Impact of Elevated Depressive Symptoms on the Ability of a Tailored Asthma Intervention to Improve Medication Adherence Among Urban Adolescents with Asthma

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Abstract

Background: In patients with asthma, medication adherence is a voluntary behavior that can be affected by numerous factors. Depression is an important co-morbidity in adolescents with asthma that may significantly impact their controller medication adherence and other asthma-related outcomes. The modifying effect of depressive symptoms on an asthma intervention's ability to improve asthma controller medication adherence among urban adolescents with asthma has not yet been reported.

Objective: To assess self-reported symptoms of depression as an effect modifier of the relationship between randomization group and controller medication adherence at 6-month follow-up.

Methods: These analyses use data from a randomized controlled trial (RCT) conducted in Detroit high schools to evaluate a tailored asthma management program. The intervention included referrals to school or community resources for students reporting symptoms of depression and other issues. Elevated depressive symptoms were defined as a positive answer to ≥5 of 7 questions from a validated tool included on the baseline questionnaire. Self-reported adherence to controller medication was collected at intervention onset (session 1) and at 6month follow up. Analyses were restricted to students with report of a controller medication at baseline. Logistic regression was used to assess elevated depressive symptoms as an effect modifier of the relationship between randomization group and 6-month adherence.

Results: Of the 422 students enrolled in the RCT, a controller medication was reported at intervention onset by n=123 adolescents (29%). Analyzing this group, we observed an interaction between elevated depressive symptoms and adherence (p=0.073). Stratified analysis showed improved adherence in treatment group adolescents meeting criteria for elevated depressive symptoms at baseline as compared to the control group (adjusted Odds Ratio [aOR]=9.50; p=0.024). For adolescents without elevated depressive symptoms at baseline, improvements in adherence did not reach statistical significance (aOR 1.40, p=0.49).

Conclusions: In this sample of students reporting controller medications at baseline, report of elevated depressive symptoms at baseline and randomization to the intervention group was associated with significantly better adherence at 6-month follow up when compared to that of a control group. Larger studies are needed to evaluate the impact of depression on the relationship between adherence and asthma intervention effectiveness.

Background

There is a significantly higher prevalence of asthma in urban African American and Latino adolescents and these groups are known to have worse asthma-related outcomes than their White counterparts [1]. Asthma control is impacted by a number of factors, including adherence to prescribed regimens. Adherence, as per its definition, is an "active, voluntary and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result". Adherence is influenced by a number of internal and external factors including patient beliefs and attitudes, disease and therapy-related factors, health system characteristics, and socioeconomic factors [2]. According to the literature, urban adolescents with asthma in general have poor adherence to asthma controller medications [3]. Studies using electronic monitoring of controller medication adherence in adolescents [4,5] have shown 40-50% adherence, with significantly lower rates of adherence in African American adolescents [6].

Depression is a known co-morbidity of asthma; however, few studies provide estimates of depression as co-morbidity in adolescents with asthma. Existing reports suggest the prevalence of depression among adolescents with asthma ranges from 7.2 to 16.3% [7-9]. Depression may impact quality of life in adolescents with asthma. In a previous analysis of Puff City data, we have shown that depressive symptoms significantly impact emotional quality of life [10]. Depression has been associated with medication adherence in adults and in diseases other than asthma [11-13], but the impact of depression on asthma intervention effectiveness with regard to controller medication adherence has not been explored in urban adolescents.

The present analyses explore the impact of elevated depressive symptoms at baseline on the ability of an asthma intervention to improve adherence to controller medications at 6-month follow-up, among urban teens with asthma. The intervention upon

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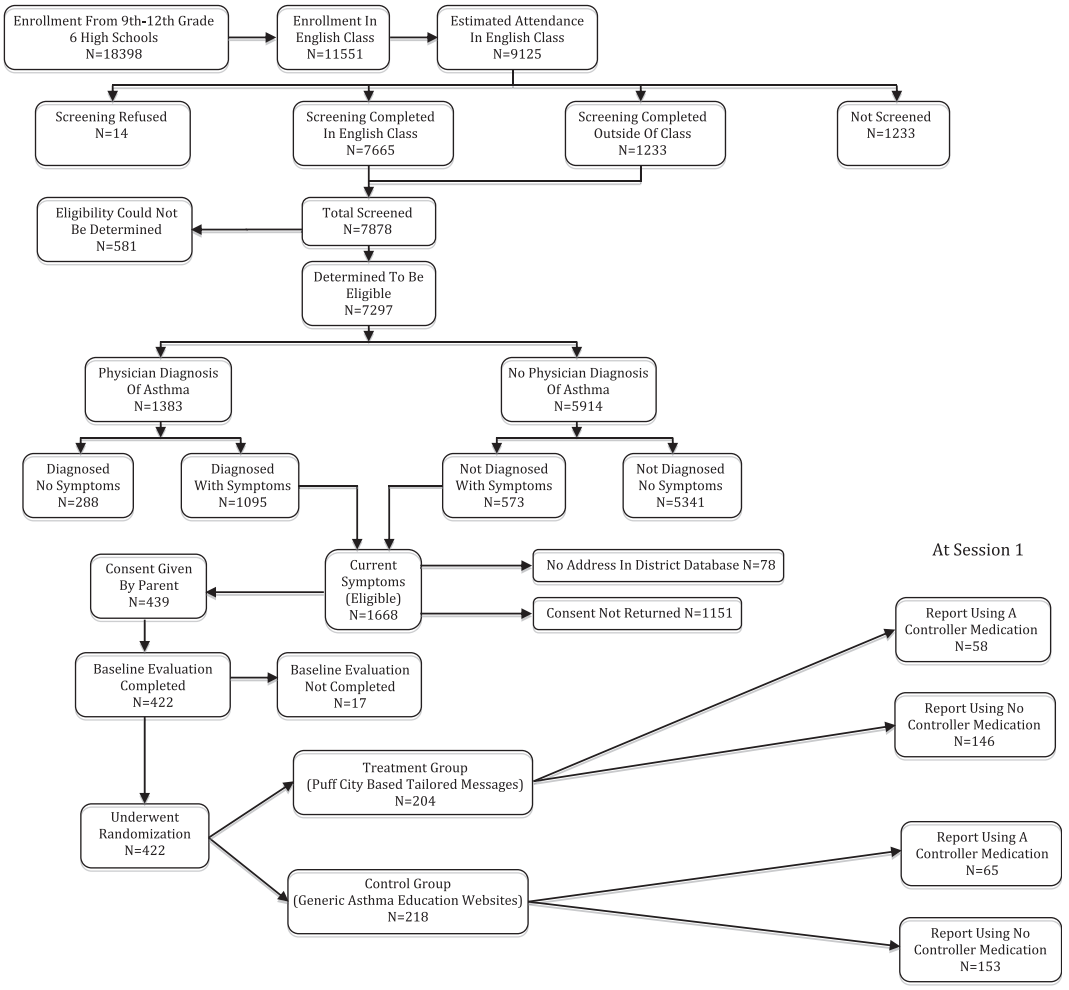

Figure 1 CONSORT Flow diagram for the school-based Puff City randomized controlled trial showing the screening of participants and breakdown of treatment and control groups.

which these analyses are based is Puff City, a computer-tailored, web-based program for urban teens with asthma, originally developed and tested in 2001 [14]. An enhanced version was evaluated in Detroit high schools using a randomized controlled trial conducted from 2007-2011 [15]. The subgroup analyses reported here include urban teenagers that were enrolled in the 2007-2011 RCT of Puff City, and reported controller medication(s) at intervention onset.

Methods

The details of the Puff City randomized controlled trial have been published previously [1416]. Briefly, to identify students with asthma or asthma symptoms, caregivers of all 9th through 12th grade students of six Detroit public high schools were notified by mail of a Lung Health Questionnaire (LHQ) to be administered during an English class. Parents could opt out of having their student complete the LHQ by signing and returning the letter to the school or by contacting the school. Eligibility to participate in the RCT was based on LHQ responses. To be eligible, the students had to have a physician diagnosis of asthma accompanied by one or more of the following: presence of daytime and/or nighttime symptoms in the last 30 days, medication use for asthma symptoms in the last 30 days, and ≥1 refill(s) of beta-agonists in the last 1 year. Adolescents without a physician diagnosis of asthma were also eligible to participate if they had positive responses to items selected from International Study of Asthma and Allergies in Childhood (ISAAC) [17], and had symptom frequencies similar to those used in EPR 2 and 3 (e.g., for "mild persistent asthma" criteria from EPR3 include "symptoms ≥ 2 days/week, nighttime awakening ≥ 3-4x/month, and interference with normal activities = minor limitation") [18,19]. Students identified as eligible for the RCT based on the above criteria were mailed an invitation to participate in the RCT, along with forms for parental written consent and student written assent. Once consent and assent were obtained, a study ID was assigned and entered into the study database. In this way, no student data was shared with investigators until appropriate informed consent was obtained [15]. After a baseline assessment, consenting students were randomized into a treatment or control group (Figure 1). The treatment group underwent a total of 4 computer-based tailored online asthma management sessions that featured topics such as asthma management behaviors (including asthma medication use and adherence, having a rescue inhaler nearby, and smoking cessation and/or reduction), trigger avoidance and basic asthma physiology. The control group was provided access to existing, generic asthma education websites during 4 computer sessions of duration similar to that of the treatment group. Asthma controller medications that were prescribed by a physician were requested from both treatment and control students at the onset of intervention session 1 using a medication selection module designed for this purpose. The module displayed pictures of medications listed in the Health plan Employer Data and Information Set (HEDIS) measure for asthma called Use of Appropriate Medications for People with Asthma [20], and included corticosteroids, inhaled steroid combinations, leukotriene receptor antagonists, mast cell stabilizers, and antibody inhibitors. Participants were asked to select the asthma medications they were currently taking, if any. All medications reported by the participant were categorized as "controller" or "rescue".

A referral coordinator was also part of the intervention. The referral coordinator's task was to assess, refer, and follow-up with students in the intervention group identified to be at-risk of a serious event through a risk assessment report generated by the data management system [16]. Students were contacted if they reported sharing asthma medication, severe asthma symptoms, lack of physician or health insurance, and/or depressive symptoms. Treatment students with depressive symptoms were usually referred to school-based resources (e.g.,

Table 1 Prevalence of elevated depressive symptoms and controller medication adherence at intervention onset (Session 1) for teens in the treatment and control groups

	Treatment N = 58		Control N = 65		Odds ratio (95% CI)	*p* value
% of teens with elevated depressive symptoms at baseline (n)	20.7	(12)	24.6	(16)	0.80 (0.34, 1.87)	0.60
Core behavior and report of medication at session 1						
Controller medication, adherent ≥ 5 of last 7 days	24.1	(14)	27.7	(18)	0.83 (0.37, 1.87)	0.65
Controller medication, not adherent < 5 of last 7 days	75.9	(44)	72.3	(47)		

school counselor, school social worker, or school-based clinic); and to community-based resources when school resources were not available.

As part of the study protocol, participants received mail and telephone reminders to login to the program and complete a follow-up survey scheduled for 6 months post-baseline. Survey questions collected information on asthma outcomes (e.g., symptom-days, symptom-nights, days of restricted activity), as well as information on controller medication adherence. Follow-up questions were the same for treatment and control students, although treatment students could receive additional "booster" messages based on responses to the 6-month survey questions. This study was approved by the Institutional Review Boards of the participating institutions (IRB Protocol #4579) and by the Detroit Public Schools Office of Research, Evaluation and Assessment.

Study definitions

Depressive symptoms were reported at baseline using 7 questions from the Diagnostic Predictive Scale (DPS) that enquires about symptoms typically associated with depression in the preceding 6 months [21]. The DPS is a result of adaptations to the Diagnostic Interview Schedule for Children (DISC), which is a structured diagnostic instrument specifically designed for use by non-clinicians [22]. The fourth version (DISC-IV) was further adapted to create several shorter scales (including the Diagnostic Predictive Scale used in this study) for use as screening tools for various psychiatric diagnoses, including depression [21]. The DPS has been tested in various populations and has been reported to be an efficient and reliable screening tool [23,24] for children between the ages of 8 to 18 years. Using published cutoff scores established by Lucas et al. [21], elevated depressive symptoms was defined as a positive response to 5 or more questions on the DPS. Adherence to asthma controller medication was defined as self-reported use of the medication on 5 or more days out of last 7 days. Controller medication adherence collected at the 6-month follow-up was the primary outcome of these analyses.

Statistical analysis

Since the goal of these analyses was to assess the effect of depression on the ability of the intervention to improve controller medication adherence, analyses were restricted to the group of adolescents reporting asthma controller medications at baseline. Logistic regression was used to assess elevated depressive symptoms as an effect modifier of the relationship between randomization group and controller medication adherence at 6 months using the p value of <0.10 as indicating the presence of effect modification and the need to present stratum-specific results. [25]. Baseline controller medication adherence was included as a covariate in all logistic regression models. Adjusted odds ratios (aOR) and corresponding 95% confidence intervals were calculated to describe the association between randomization group and controller medication adherence at 6 months.

Results

The breakdown of the study population is shown in Figure 1. Baseline assessment was completed by 422 adolescents. A total of 58 adolescents in the treatment group (28.4%) and 65 in the control group (29.8%) reported a controller medication at the start of the intervention (Table 1). Among those reporting use of a controller medication at intervention onset, the percentage of adolescents in the treatment and control groups meeting criteria for elevated depressive symptoms was 20.7% (n=12) and 24.6% (n=16), respectively, p=0.60. Controller medication adherence for treatment and control group students at intervention onset was 24.1% (n=14) and 27.7% (n=18) respectively.

At the 6-month follow up, after adjusting for baseline adherence, 22 adolescents in the treatment group (37.9%) reported controller medication adherence, as compared to 17 adolescents in the control group (26.2%) (Table 2). The relationship between elevated depressive symptoms at baseline and controller medication adherence met criterion for the presence of an interaction (p=0.073) [16,25]. Stratified analysis is presented in Table 3. For adolescents that reported elevated depressive symptoms at baseline, 7/12 (58.3%) in the treatment group reported being adherent to their controller medication at the 6-month follow-up, while 2/16 (12.5%) were adherent in the control group, aOR=9.5; p=0.024. For adolescents that did not report depressive symptoms at baseline, medication adherence at 6month follow-up was only slightly higher among students randomized to the treatment group (32.6%) compared to the controls (30.6%) at the 6-month follow up, aOR=1.4; p=0.49.

Discussion

The Puff City program uses tailoring to promote positive behaviors such as regular use of controller medications by providing personalized health messages to help address the adolescents' beliefs, attitudes and barriers to behavior change in addition to referrals from an asthma referral coordinator. Results of these subgroup analyses suggest that the effectiveness of a program to improve adherence to controller medications in urban adolescents with asthma may be significantly impacted by the presence of depressive symptoms. For this reason, it may be worthwhile to address depressive symptoms when treating asthma in order to improve asthma-related outcomes. We did note a modicum of improvement in medication adherence among treatment students who did not meet criteria for elevated depression at baseline, but a comparison to the control group did not reach statistical significance. Therefore, interventions to improve controller medication adherence in adolescents with and without depressive symptoms may still be needed. Our results may have important implications for designing future interventions specifically targeting improvements in controller medication adherence in urban adolescents with asthma.

Table 2 Comparison of controller medication adherence at 6 month follow-up for by randomization group for students included in the analysis sample*

	Treatment N = 58		Control N = 65		Adjusted** odds ratio (95% CI)	*p* value
Core behavior at 6 months**						
Controller medication, adherent ≥ 5 of last 7 days	37.9	(22)	26.2	(17)	2.10 (0.89, 4.92)	0.089
Controller medication, not adherent < 5 of last 7 days	62.1	(36)	73.8	(48)		

**Students enrolled in Puff City and reporting a controller medication at baseline assessment. **Adjusted for controller medication adherence at start of intervention.*

Table 3 Comparison of controller medication adherence at 6 month follow-up by randomization group and by baseline elevated depressive symptoms, for students included in the analysis sample*

	Treatment		Control		Adjusted** odds ratio (95% CI)	*p* value
Meet criteria for elevated depressive symptoms at baseline:						
Core behavior at 6 months**						
Controller medication, adherent ≥ 5 of last 7 days	58.3	(7)	12.5	(2)	9.50 (1.35, 67.0)	0.024
Controller medication, not adherent < 5 of last 7 days	41.7	(5)	87.5	(14)		
Do not meet criteria for elevated depressive symptoms at baseline:						
Core behavior at 6 months*						
Controller medication, adherent ≥ 5 of last 7 days	32.6	(15)	30.6	(15)	1.40 (0.53, 3.67)	0.49
Controller medication, not adherent < 5 of last 7 days	67.4	(31)	69.4	(34)		

**Students enrolled in Puff City and reporting a controller medication at baseline assessment. **Adjusted for controller medication adherence at start of intervention.*

Other investigators have also found depression to be a significant determinant of medication adherence in several disorders other than asthma. A recent meta-analysis of 31 studies (18,425 participants) of adults with various chronic conditions reported a 1.76 times greater odds for non-adherence in depressed patients [26]. Another report suggests that approximately 20 to 30 percent of prescriptions are never filled (primary non-adherence) and 50% of medications prescribed for chronic diseases are not taken as prescribed [2]. Medication non-adherence is associated with higher downstream health care costs [27], and can be reduced by improved self-management of chronic disorders such as asthma. We are unaware of any other study that has reported the effectiveness of asthma interventions on controller medication adherence among adolescents with depressive symptoms.

Other co-morbidities have been observed in asthma. Besides depressive symptoms, adolescents with asthma have also been found to have a higher prevalence of anxiety disorder [28] and internalizing behaviors [29]. These are linked through several psychological and biological factors such as the stress of asthma management, medication regimens, and avoidance of allergic triggers; or through cognitive responses to asthma symptoms such as learned helplessness or fear of bodily sensations. In the case of adolescents, having asthma symptoms may induce social anxiety (due to concern for negative evaluation by peers) that can significantly impact asthma-related outcomes [30].

The overall rate of controller medication use in this study was low (29% at baseline) resulting in a small sample available for analyses. There are additional limitations to this study. First, we used self-reported measures of asthma controller medication adherence, which can have questionable validity and reliability [31,32]. We note that self-report of asthma controller medication adherence has been used in national surveys such as National Health and Nutrition Examination Survey (NHANES) [33], and National Asthma Survey (NAS) [34]. Second, we cannot determine which component of the intervention was instrumental in motivating participants to be more adherent, i.e., depressed students received tailored messages about controller medication through the online program in addition to referrals made by the asthma referral coordinator for their depressive symptoms. Moreover, we cannot confirm that students followed up on referrals from the asthma referral coordinator and cannot report on the therapies or advice these students may or may not have received from these referrals. Consequently, we cannot speculate on the mechanism by which controller medication adherence was improved among students reporting depressive symptoms at baseline. Third, a sustained intervention effect for controller medication adherence post 6month follow-up is unknown. Finally, because this study was done in urban adolescents with asthma, the results may only be applicable to other populations with characteristics similar to that of our study population. Given the limitations of this study, additional analyses in larger study samples are needed.

Conclusions

In these subgroup analyses of data from a RCT to evaluate an online asthma management program for urban adolescents with asthma, students who were randomized to the treatment group and met criteria for elevated depressive symptoms had better controller medication adherence when compared to a control group at 6-month follow up. Adolescents without depressive symptoms at baseline did not show statistically significant improvement in controller medication adherence. Interventions aimed at improving controller medication adherence as part of asthma self-management programs may need to be tailored for participants with depressive symptoms.

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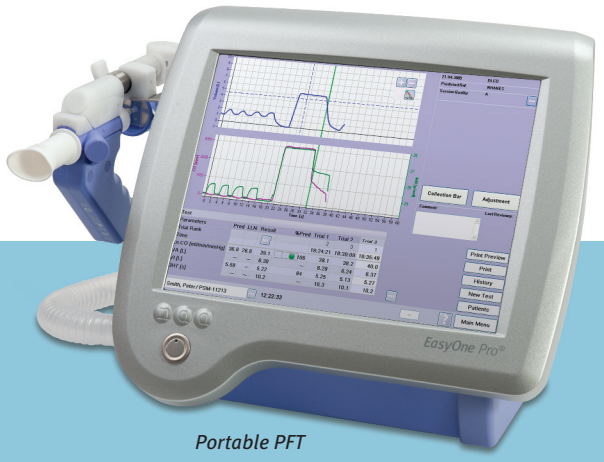

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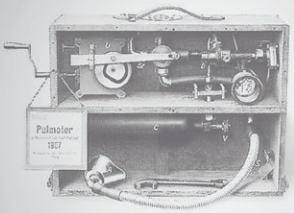

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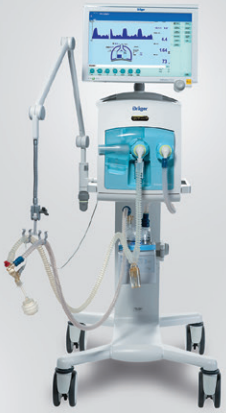

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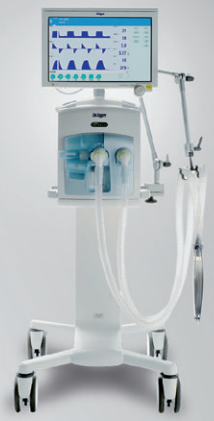

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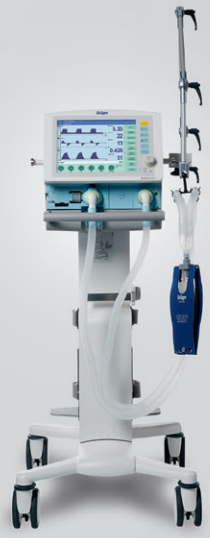

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