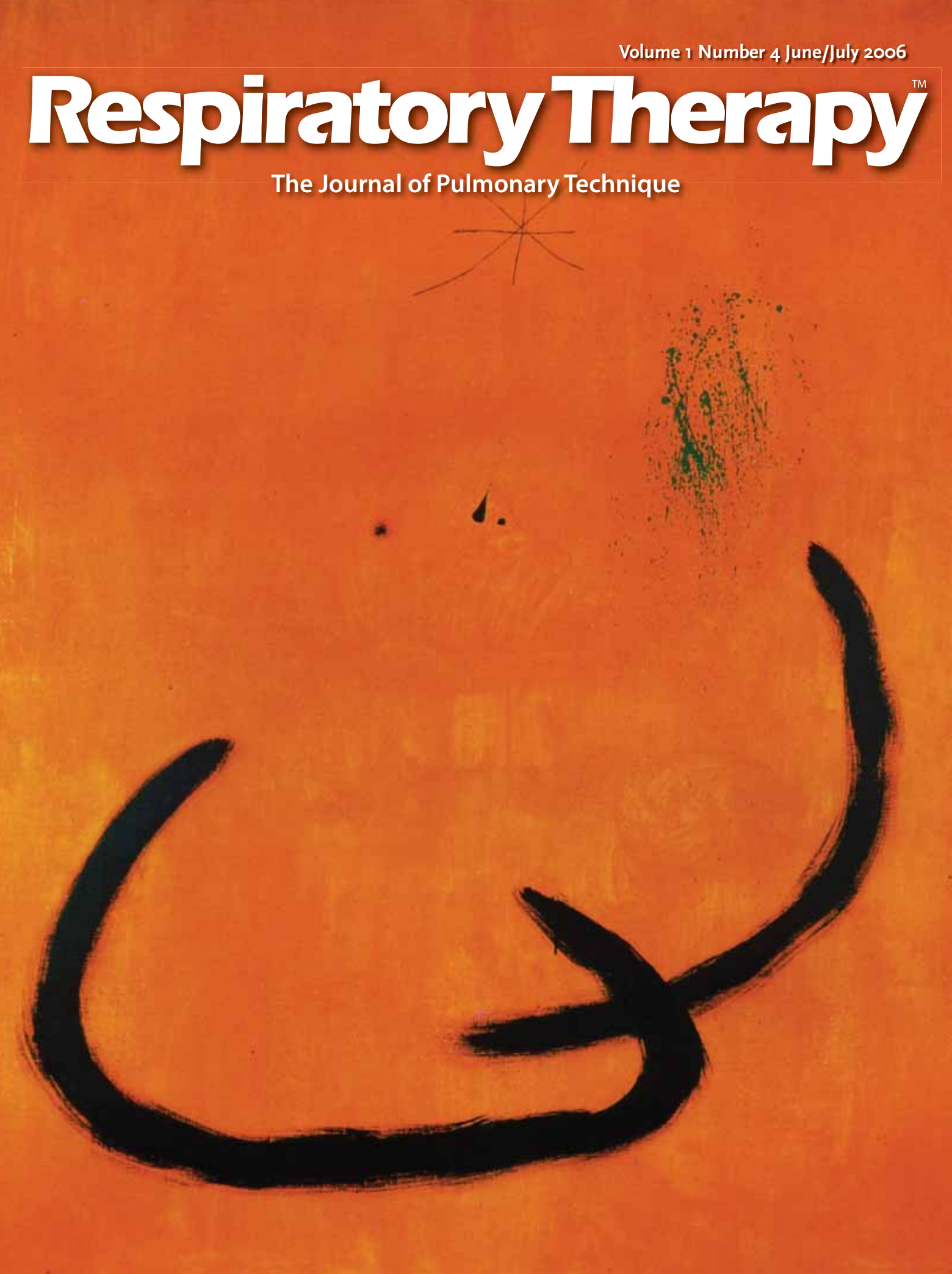
Volume 1 Number 4 June/July 2006

Respiratory Therapy™

The Journal of Pulmonary Technique



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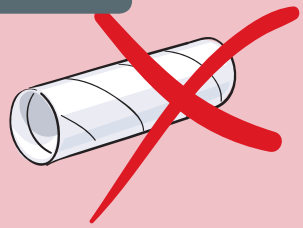

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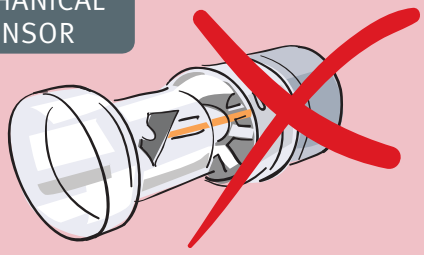

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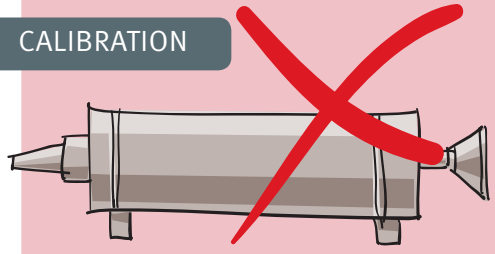

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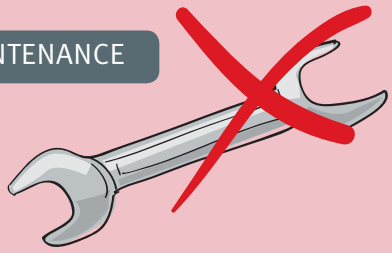

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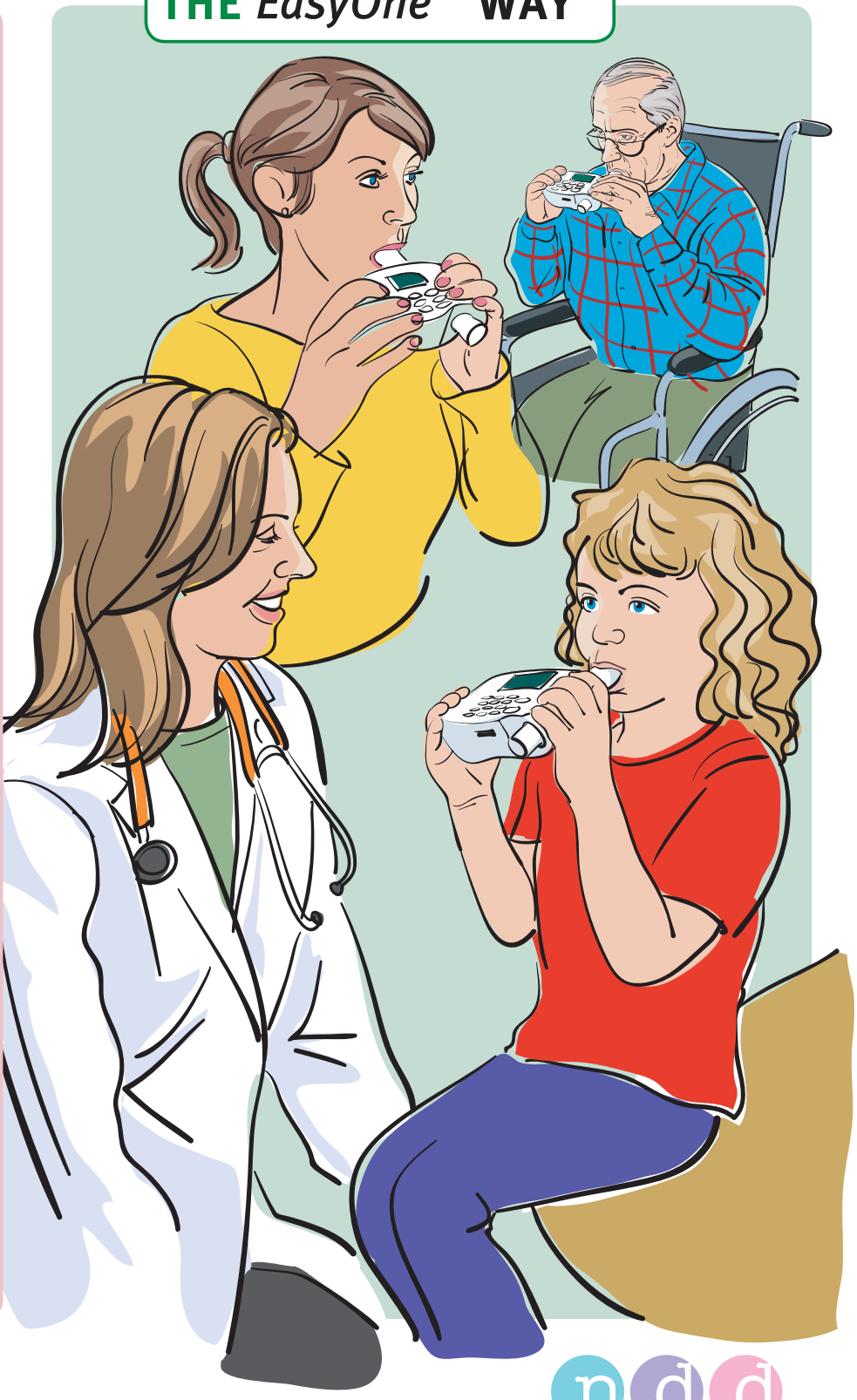

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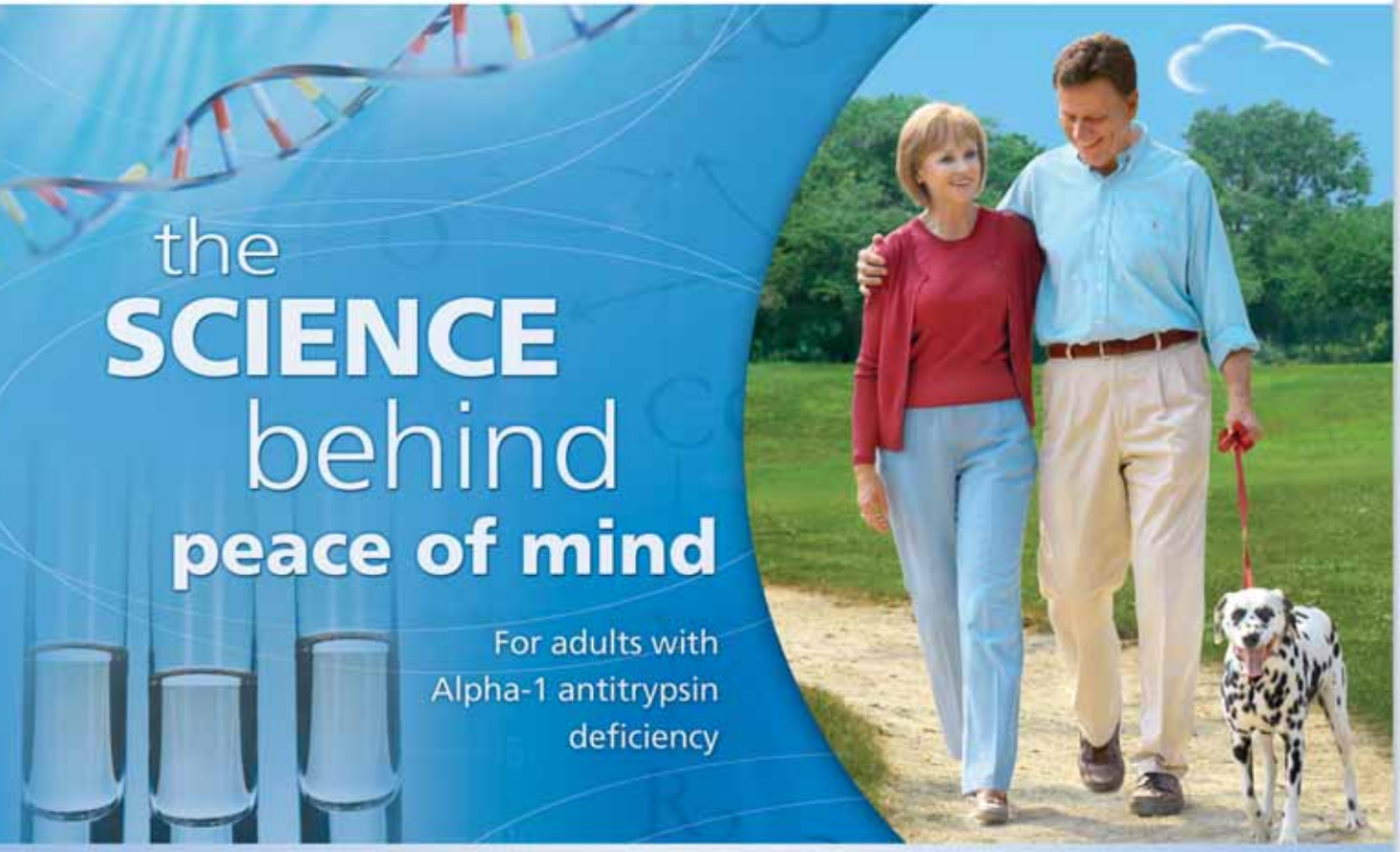

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Zemaira® is indicated for chronic augmentation and maintenance therapy in adults with alpha$_1$-proteinase inhibitor (A_1-PI) deficiency and clinical evidence of emphysema. Clinical data demonstrating the long-term effects of chronic augmentation therapy with Zemaira® are not available.

As with other Alpha-1 therapies, Zemaira® may not be appropriate for the following adult individuals as they may experience severe reactions, including anaphylaxis: individuals with a known hypersensitivity and/or history of anaphylaxis or severe systemic reaction to A_1-PI products or their components and individuals with selective IgA deficiencies who have known antibodies against IgA. In clinical studies, the following treatment-related adverse reactions were reported in 1% of subjects: asthenia, injection-site pain, dizziness, headache, paresthesia, and pruritus. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

For more information, call **1-866-ZEMAIRA (1-866-936-2472),** or visit **www.Zemaira.com.**

Please see brief summary of full prescribing information on following page.

* Shelf life purity specification is ≥90%

† In a retrospective analysis in the pivotal clinical trial, Zemaira® patients were three times less likely to experience exacerbations of their COPD than Prolastin® patients

‡ No clinically significant differences were detected between the treatment groups

§ Based on recommended dosage as stated in the product package inserts of 60 mg/kg body weight at the infusion rate of 0.08 mL/kg/min

Prolastin is a registered trademark of Talecris Biotherapeutics, Inc.

References: 1. Prolastin® Alpha$_1$-Proteinase Inhibitor (Human), Full Prescribing Information, January 2005. **2.** Aralast™ Alpha$_1$-Proteinase Inhibitor (Human), Full Prescribing Information, January 2003. **3.** Data on file, ZLB Behring LLC.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Alpha$_1$-Proteinase Inhibitor (Human) Zemaira®

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Kankakee, IL 60901 USA
US License No. 1709

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INDICATIONS AND USAGE

Alpha$_1$-Proteinase Inhibitor (Human), Zemaira®, is indicated for chronic augmentation and maintenance therapy in individuals with alpha$_1$-proteinase inhibitor (A_1-PI) deficiency and clinical evidence of emphysema.

Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A_1-PI.

Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.

Safety and effectiveness in pediatric patients have not been established.

Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A_1-PI deficiency has not been established.

CONTRAINDICATIONS

Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A_1-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

WARNINGS

Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See **DESCRIPTION** section of full prescribing information for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to ZLB Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).

During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

PRECAUTIONS

General – Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.

Information For Patients – Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.

Pregnancy Category C – Animal reproduction studies have not been conducted with Alpha$_1$-Proteinase Inhibitor (Human), Zemaira®. It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.

Nursing Mothers – It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.

Pediatric Use – Safety and effectiveness in the pediatric population have not been established.

Geriatric Use – Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS

Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated. In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild.

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.

Table 3 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prolastin®. No clinically significant differences were detected between the two treatment groups.

Table 3: Summary of Adverse Events

	Zemaira®	Prolastin®
No. of subjects treated	89	32
No. of subjects with adverse events regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).

The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia.

Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.

In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prolastin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

HOW SUPPLIED

Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A_1-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), one vented transfer device, and one large volume 5 micron conical filter.

STORAGE

When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

Prolastin® is a registered trademark of Bayer Corporation.

Adapted from 19131-03
Revised: August 2004

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Editorial

PARADIGM SHIFT?

Here's an interesting piece from our news section: According to Basque Research, liquid ventilation could help save the lives of premature babies and adults suffering from ARDS, but the patent-owning company will not market it, because there's not enough money in it. The news item is somewhat vague on the details, so it's hard to tell just who is refusing to finance what, but the notion of medicine being driven solely by profit is one that I'm sure all our readers have contemplated in the last decade. Healthcare – and I might as well just say it plainly – like everything else, is driven by the movement of capital. Who could argue with that?

What you don't get much argument or discussion about is just why this is so. We just assume that this is the way it is in the world (and also assume, wrongly, that it has always been so). It's sort of like thinking inside the box, except that the world within the box has become so pervasive that we don't even notice that we're *in* a box.

According to the historical analyst Fredric Jameson, "Every position in culture – whether apologia or stigmatization – is also implicitly and explicitly a political stance" within what he perceives as the impenetrable fog machine of a historical inevitability powered by the movement of multinational capital. Says Jameson, "No theory of culture or politics has been able to do without the possibility of positioning [itself] outside the massive Being of capital… We are henceforth submerged in its filled and suffused volumes to the point where our now postmodern bodies are incapable of distantiation." The prodigious expansion of multinational capital, currently under the rubric of globalization, Jameson says, has wound up penetrating and colonizing all aspects of life, to where we cannot even conceive that there might be another paradigm to work from.

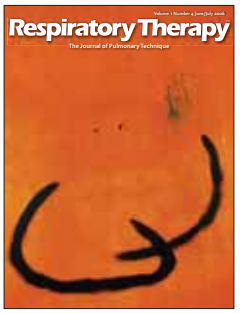
What Jameson is saying is that the way we picture the world determines our choices and possibilities, and looking through our current economic lens is specifically what leads to the conundrum of good healthcare products and technologies not reaching the market.

In fact, the problem is thinking in terms such as "the market," and my using the expression is only further evidence of the invidiousness of the current modes of ideological totalization health care providers are up against. And isn't "the market" after all, merely an abstraction? Is this the way really the best way to picture the world and our place in it? Compare the cool, indeed icy, abstraction of the "flow of capital" or words like "increasing the viability of health maintenance organizations" to a "I have a sick patient who can't breathe."

Even our vocabularies of ethical justice have been tainted with the reductionism of economic abstractions. The social philosopher Alain Badiou argues that the vast majority of our empirical orientations, that is, the guiding principles on which we make our decisions, have nothing to do with actual living truths, but "merely organize a repulsive mixture of power and opinions. The subjectivity that animates them is that of the tribe and the lobby." We must re-learn to make value judgments not on the basis of abstract values, he says, but "according to the real situation of the moment." Like that woman who can't breathe, who would be helped by a new therapy, for instance. Ethics and justice and how they are applied to healthcare should not be a sentiment or an ideology, but a practice.

Les Plesko, Editor

PS: I'll be following up on liquid ventilation, the ostensible jumping off point for this editorial, in our next issue. If you wish to contribute your thoughts to the subject, please contact me directly at lplesko@ucla.edu. As you may have noticed, we are constantly expanding the breadth and depth of our news and commentaries sections. All our readers are always welcome to offer news, comments, letters and opinions. We will publish all information relevant to respiratory therapy and related subjects.



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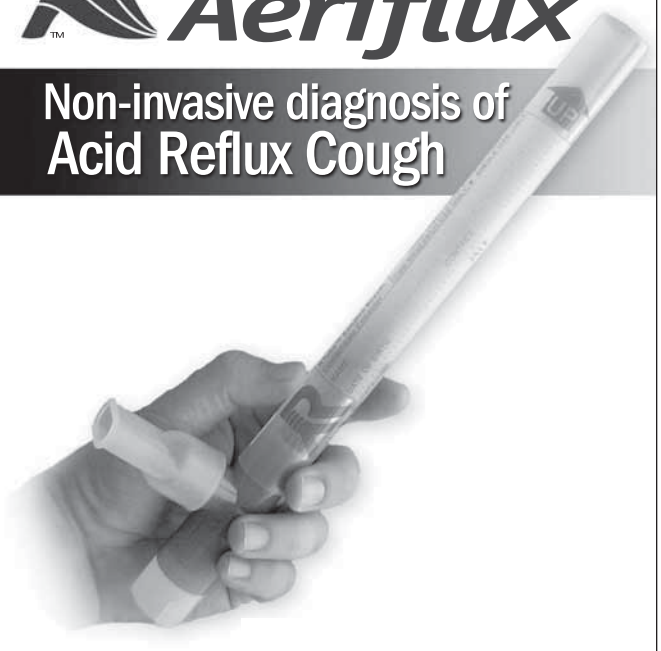
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News

☐ June-July 2006

MERGE MANIA

The healthcare industry recorded 964 mergers and acquisitions in 2005, the most the industry has seen in five years, according to a report by Irving Levin Associates, a health care research firm based in Norwalk, CT. Merger and acquisition volume was valued at $158.7 billion, placing it second over the last five years in terms of dollar amount to the $164.4 billion committed in 2004, according to the report. The majority of mergers and acquisitions occurred in the pharmaceutical, medical device and biotechnology industries, with 34 deals involving physician medical groups and 30 involving managed care companies. The hospital sector recorded 53 deals.

OBLIVIOUS

A majority of Americans are unaware of the disparities that exist in healthcare, according to a new poll from the Harvard School of Public Health and the Robert Wood Johnson Foundation. This lack of awareness was greatest among whites, with only 25% believing healthcare is worse for racial and ethnic minorities. In comparison, 44% of blacks and 56% of Hispanic Americans said racial and ethnic minorities received worse care than whites. Although most Americans are unaware of the disparities, they did say that everyone deserves equal care.

IT WAS 20 YEARS AGO TODAY

John R. Goodman, BS, RRT
John Goodman is with Transtracheal Systems Inc, Englewood, CO.

January 2006 marked the 20th year that SCOOP transtracheal oxygen therapy (TTOT) has been available as an alternative to oxygen delivered via standard nasal cannula. Dr. Henry Heimlich first published on the safety and efficacy of TTOT in 1982. In 1986, Drs Bryan Spofford and Kent Christopher dramatically advanced the concept of TTOT by improving the design of the catheter itself, and enhancing the product with a full program of supportive education and care. The SCOOP program was designed to be maintained within the respiratory therapy department of the participating hospital. This is a common sense model based on the respiratory therapist's inherent expertise with the airway, as well as normally providing coverage on a 24/7 basis.

Well over 600 physicians, respiratory therapists, and nurses came to Denver for training during those early formulative years. It was an exciting time for all involved, with a great deal of speculation that the elimination of the nasal cannula could not be too far beyond the horizon.

Those early predictions have never fully materialized. There are a number of reasons for this. First, there is little or no reimbursement, both to the physician and the home oxygen company. Secondly, TTOT can be labor intense and time consuming for busy physicians, respiratory therapists, and nurses. Finally, it is viewed (rightfully so) as an "invasive"

procedure. An attempt to minimize these problems has been quite successful with the development of the Fast Tract procedure. The Fast Tract is a true surgical approach that has streamlined the SCOOP program of care and made it much less labor and time intense.

However, even after 20 years, the number of TTOT patients is still pretty small compared to the total number of patients on oxygen. If indeed there are somewhere around 1,000,000 patients on continuous supplemental oxygen in the United States, then TTOT patients make up less than 1% of this total. The single biggest explanation for this seems to be that in many (if not most) cases, the patient is simply unaware that TTOT exists as an option. Certainly the patient must assume *some* of the responsibility for this lack of knowledge in the information driven society we all live in today. However, much of the responsibility must also reside with the patient's family practice physician and their pulmonologist as well. If the physician doesn't have a good understanding of TTOT and what it can do for their patient, it is highly unlikely they will be strong advocates of TTOT in general.

In order for a hospital based TTOT program to be successful, it requires a commitment from the hospital to make sure all components of the transtracheal team are organized, integrated, and most importantly, communicating with one another. This insures the highest possible chance of success.

The clinical benefits of TTOT are very well documented. There are over 160 references in the medical literature extolling the advantages of TTOT over any comparative form of oxygen delivery. There is more and more evidence proving that TTOT does much more than simply oxygenate our patients.

Scientific evidence gathered over the past 10 years suggests that *flow* of oxygen (and other gas mixtures as well) through a transtracheal catheter can help reduce a patient's shortness of breath, both at rest and with activity. This concept is called Transtracheal Augmented Ventilation (TTAV). TTAV has been used to treat patients with Obstructive Sleep Apnea, and has proven to be a new mode of weaning patients from long-term mechanical ventilation. New and innovative applications for TTOT are being developed in hospitals around the USA and indeed around the world. In addition to the United States, there are transtracheal oxygen patients in England, Germany, Switzerland, Norway, Italy, Belgium, the Netherlands and Australia.

If you have patients who might be interested in getting rid of their nasal cannula for good, and becoming a TTOT patient, they should speak with their pulmonologist. The pulmonologist is best able to evaluate a prospective patient regarding their candidacy for TTOT. There is a very short list of absolute contraindications, and a very long list of reasons why a patient currently receiving oxygen via nasal cannula might want to consider TTOT for true 24/7 oxygen delivery.

One of the most important things a potential TTOT patient can do is speak with a current TTOT patient. A current patient can tell you what it is actually like living with a transtracheal catheter in their neck. Cleaning routines, problems with mucus management and cough can all be discussed with someone who has already "learned the ropes."

If a patient is considering having a transtracheal catheter placed, make sure there is a TTOT center in the area of the country where they live. This makes it easier for the patient to be seen, and insures a properly educated TTOT team will be available should the patient need them on short notice.

TTOT is not for every patient. By most estimates perhaps it is indicated for 3 out of 10 oxygen dependent patients. But in those patients, TTOT can be a life changing therapy. There are many patients who are well beyond their 10th year on SCOOP oxygen therapy. Compared to patients using a nasal cannula, TTOT patients live longer, spend less time in the hospital, sleep better, have better exercise capacity, reduced shortness of breath, and improved self-image. Probably the single greatest benefit a TTOT patient receives is the fact that a TTOT patient is truly getting their oxygen every minute of every day. We call this *compliance* and being compliant is very hard to do wearing an uncomfortable, unsightly nasal cannula. It is this improved compliance that probably explains the increased survival of TTOT patients over their nasal cannula counterparts. Remember; oxygen is a drug, and probably the most important *drug* our patients with chronic lung disease are taking. It is the only drug ever shown to improve survival. Simply stated, patients who are most compliant with their oxygen therapy live longer than those who can't/don't/won't wear their oxygen 24 hours per day.

If you would like more information on TTOT, you can access the SCOOP website at www.tto2.com. You can get many of your questions answered there. If a patient goes to their physician already prepared with questions, it will increase the likelihood that the physician will be more willing to assist the patient in determining if they are a good candidate for TTOT.

HYPOCRITICAL OATH

Only one medical school in the US uses the classic version of the Hippocratic Oath, according to a report by Kevin O'Reilly in AM News. In the eight years since Antonio Gotto took over as dean of the Weill Medical College of Cornell University in New York, he has met with graduating students the day before commencement to get down the proper pronunciation of their names and run through a recitation of Cornell's version of the Hippocratic Oath. Some of the language was said to be so archaic that students, who had little prior exposure to the oath, found it humorous. "They would laugh at certain parts," Dr Gotto said. "Then I'd give them dire threats that I wouldn't graduate them the next day if they laughed during the ceremony." Student reaction prompted Gotto to form a 20-member committee of faculty and students to rewrite the oath. June 2005 marked Cornell's first commencement in which students recited the new version, still dubbed the Hippocratic Oath. No one laughed during the ceremony. But along with the laughter, some of the precepts Hippocrates laid down 2,500 years ago also went missing. In fact, the State University of New York Upstate Medical School in Syracuse is the only medical school that still administers the classical Hippocratic Oath. As such, the vast majority of graduating medical students don't swear to avoid performing abortions, assisting suicides or having sex with patients as a part of their oath.

An *Academic Medicine* study of the 141 allopathic and osteopathic school oaths in use in 2000 found that one explicitly prohibited abortion, four urged physicians to avoid sexual relationships with patients, and 25 explicitly prohibited physician-assisted suicide. Among those, 19 were schools using the Osteopathic Oath.

"The practice of giving an oath to graduating medical students has increased dramatically in the last 100 years," said Robert D. Orr, MD, who co-authored the article and is director of clinical ethics at the University of Vermont College of Medicine. "At the same time, the content has been diluted. We're sort of at cross-purposes." It has also been argued that what are read today as prohibitions of assisted suicide and abortion were actually injunctions against providing poisons to assassins and a

particular type of abortive suppository known even then to do irreparable damage to women. Among the things that are pledged in many oaths are protecting patient confidentiality, loyalty to colleagues, and acting with beneficience. Only 18% of the oaths pledge fledgling physicians to "do no harm," while 18% make oath-takers swear to God.

SLEEP ON IT

New practice parameters published by the American Academy of Sleep Medicine in the March 1 issue of the journal Sleep validate continuous positive airway pressure, CPAP, as the standard of care for treating adults with moderate to severe obstructive sleep apnea, OSA. "CPAP is the most effective therapy we have for treating patients with sleep apnea, a disorder that can contribute to the development of hypertension and heart disease," said Lawrence J. Epstein, MD, president of the American Academy of Sleep Medicine. "It is immediately effective, relatively noninvasive and usually well tolerated." OSA afflicts 15 million to 20 million Americans, the majority of whom remain undiagnosed and untreated. Men are twice as likely as women to develop sleep apnea, with excessive weight being the primary risk factor. OSA is much more common in women as they enter menopause. The practice parameters indicate that in addition to preventing pauses in breathing and restoring oxygen levels, CPAP improves self-reported sleepiness in patients with OSA and may also improve their overall quality of life. The parameters, which were based on an accompanying review of the evidence found in the scientific literature, suggest that physicians may choose to use CPAP as a part of their patient-care strategy to lower blood pressure in hypertensive patients with OSA. CPAP is also presented as a treatment option that clinicians may recommend for patients with mild cases of OSA. According to the parameters, a trained sleep physician plays a critical role in the initiation and maintenance of a patient's CPAP treatment. Treatment with CPAP must be based on both a prior diagnosis of OSA and a systematic process of titration that determines the optimal level of air pressure for the individual patient's needs. An overnight sleep study, or "polysomnogram," conducted in a sleep center or laboratory is essential for both of these requirements. In order to establish and maintain a long-term adherence to CPAP, the parameters also recommend that trained health care providers conduct follow-up of patients, especially during the first few weeks of treatment. Patients should also schedule annual follow-up appointments with a sleep specialist who can troubleshoot problems and make any necessary adjustments to their air pressure level.

Here are the warning signs to give to patients to see if they candidates for CPAP treatment:

1 You are overweight with a body mass index (BMI) of 25 or more
2 You are a man with a neck size of 17 inches or more
3 You are a woman with a neck size of 16 inches or more
4 You have high blood pressure
5 You are a menopausal or postmenopausal woman
6 You snore loudly and frequently
7 You make choking or snorting sounds during sleep
8 You stop breathing during sleep
9 You normally feel tired even after a full night of sleep
10 You fall asleep while driving or during periods of daytime inactivity
11 You have a family member who has sleep apnea.

For more information go to journsalsleep.org or sleepeducation.com.

ASK ME ANYTHING

Here's what Dr David Carley, PhD, a neuroscientist with the University of Illinois at Chicago Center for Sleep and Ventilatory Disorders says about treatment for sleep apnea: Sleep apnea is the most common form of a larger group that we call sleep related breathing disorders. Sleep apnea is estimated to affect 3 percent to 5 percent of the United States population with similar percentages in westernized countries. The most common sign is snoring. That's certainly not to say that everyone who snores has sleep apnea syndrome but nearly everyone with sleep apnea, in fact, snores in a very prominent fashion. Another characteristic of the disease is significant obesity, which is more common in men than in women for reasons we don't fully understand. When we see a patient who reports loud snoring, is obese, middle-aged, and they tell us they are very sleepy all day long, we have a portrait of the classic sleep-apnea patient. What drives most patients to come and seek medical attention [for sleep apnea is] their overwhelming daytime sleepiness, which accumulates over a period of years. The patient compensates but eventually they can't overcome the sleepiness anymore. They have accidents while driving or fall asleep at inappropriate times on the job.

There appear to be a variety of risk factors for developing sleep apnea. There's at least a small genetic component because sleep apnea tends to run in families. Other factors include, gender, males are more at risk, obesity, along with other disorders that increase a person's risk such as high blood pressure or diabetes. Having sleep apnea places a person at risk for a variety of other disorders, including high blood pressure and a variety of organ dysfunctions.

Treatments for sleep apnea are amazingly effective in the laboratory. The patient can come to a center and receive a mechanical treatment, which involves placing a mask over the nose and actually blowing air into the nose all night long. It's amazingly effective at maintaining regular breathing for the individual. The downside of course is it's cumbersome, awkward, inconvenient and uncomfortable. Also, in the long run our best guess is that less than half of our patients can tolerate using this device every night. CPAP is not the only form of treatment, but it's by far the most common. In very mild cases orthodontic devices can be worn and attached to the teeth and reposition the jaw, trying to make the back of the throat stay open and be larger. There are a variety of surgeries such as very aggressive tonsillectomies that take out extra tissue in the back of the throat, trying to open the air passage and allow air to flow more easily during sleep. These are very effective in a minority of patients, but for the majority of patients, the first line treatment is the airway pressure devices that use a mask.

[A study we are doing] involves a manipulation of serotonin. Using the early stage research tools we've gained evidence suggesting interference with serotonin is an effective way to maintain regular breathing during sleep. This is a new idea and we've only just begun to test it in patients, but it's showing more promise than any of the earlier tests with drugs. There is a whole family of drugs that act to interfere with serotonin as a natural molecule in the brain. We are looking at the anti-depressant mirtazapine. Some anti-depressants, however, promote serotonin. So we are trying to find the right drug that has the right pharmacological properties.

We enrolled a group of patients newly diagnosed with sleep apnea in the study. We used mirtazapine and a placebo. We've found every single patient we tested improved when taking the mirtazapine as opposed to the placebo. On average, half reduced the number of times they stopped breathing during a

night of sleep. We're hoping to frame larger studies and consider additional drugs with similar properties. The effect of this drug on sleep apnea is instant. Mirtazapine is an anti-depressant and it takes about two weeks to three weeks for the anti-depressant action to work. In sleep apnea patients, however, it works immediately. So it's a different mechanism.

This article was reported by Ivanhoe.com, which offers Medical Alerts by e-mail every day of the week. To subscribe, go to ivanhoe.com.

ACHOO

Pneumonia hospitalizations for people over 64 increased by 25% from 2000 to 2002, up from previous rates of hospitalization for the previous two years. Of 9 million deaths among hospitalized patients, 22% were among those with a pneumonia-related admittance. The proportion of comorbid conditions increased from 66% to 80% from 1990 to 2002.

TAKE IT BACK

Respiratory gas administration devices manufactured by Vapotherm were voluntarily recalled after the US government reported that 29 hospitals found Ralstonia organisms colonizing the devices, and cultures from about 40 pediatric patients also had the bacteria. The CDC and FDA recommended monitoring for symptoms of infection, and Vapotherm said it would recall and disinfect the devices. Contamination was first reported in 2005. The company issued new updated disinfection methods.

MUSCLING IN

Inhaled corticosteroids are more effective than leukotriene receptor antagonists for controlling asthma in children. A study by UC San Diego of 140 children revealed that Fluticasone was superior in its effects on asthma control, pulmonary function and inflammatory biomarkers. Fluticasone also led to significantly greater improvements than did montelukas. Exhaled nitric oxide was shown to be both a predictor of asthma control days and a response indicator. For more on the study see J Allerg Clin Immunol 2006;117:45-52.

DON'T TAKE IT LYING DOWN

Kids with sleep apnea showed more respiratory disturbance when they slept on their backs, according to a study at the University of Texas Health Science Center. Researchers found that the mean RDI of children who slept on their backs was much greater than the total RDI. Previous studies showed no connection between sleep position and OSAS, but the researchers said this was evidently not the case in younger children. Pediatric obstructive sleep apnea syndrome is typically caused by enlarged tonsils and adenoids. Reported in Chest Physician, Elsevier Global Medical News.

FOR THE BIRDS

Donald G. Mc Neil Jr writes in the New York Times: No one knows whether an avian flu virus that is racing around the world might mutate into a strain that could cause a human pandemic, or whether such a pandemic would cause widespread illness in the United States. But if it did, public health experts and officials agree on one thing: the nation's hospitals would not have enough ventilators, the machines that pump oxygen into sick patients' lungs. Right now, there are 105,000 ventilators, and even during a regular flu season, about 100,000 are in use. In a worst-case human pandemic, according to the national preparedness plan, the country would need as many as 742,500. To some experts, the ventilator shortage is the most glaring example of the country's lack of readiness for a pandemic. It was noted that the government put out a 400-page plan but there were no ventilators to facilitate it. A typical hospital ventilator costs $30,000, and hospitals, operating on thin profit margins, say they cannot afford to buy and store hundreds of units that may never be used. Cheaper alternatives can be deployed in a crisis, but doctors say they are grossly inadequate to deal with a flu pandemic. Congress authorized $3.8 billion for flu preparedness, and nearly 90% of it is earmarked for vaccines and Tamiflu. Buying enough ventilators for a flu outbreak like that of 1918 would cost $18 billion. The federal preparedness plan leaves preparations for medical care up to state and city health officials, but the only government agency that amasses ventilators is the Strategic National Stockpile, created in 1999 by the disease centers to store medicine and equipment for use in a terrorist attack or a disaster. But the agency has only 4,000 to 5,000 ventilators. There is also a shortage of trained personnel. In a recent emergency drill at the Mayo Medical School in Minnesota, the 27 hospitals in the area could come up with only 16 extra ventilators when faced with a hypothetical outbreak of 400 cases of pneumonic plague. A paper presented in the Journal of Academic Emergency Medicine noted that in a crisis, people who are marginal would most likely be taken off ventilators and allowed to die.

COSTLY CURE

Giving antibiotics to babies may double their chance of developing asthma. Researchers at British Columbia University reviewed the health records of more than 12,000 children and found that giving antibiotics before the age of one doubled the chance of a child developing asthma. The researchers said that although the causal nature is still unclear, results showed that treatment with at least one antibiotic as an infant appears to be associated with the development of childhood asthma, while multiple use appeared to increase further risk. It was said to be likely that the body's immune system needs to be stimulated by bacteria and viruses. Without its usual enemies to deal with, the immune system starts attacking other matter, such as pollen, dust mites or the person's own body. The researchers also noted that antibiotics are the most commonly prescribed medicines for your children and they're overused.

ASTHMA AND ATOPY

New research shows that hereditary predisposition to develop asthma (atopy) is a determining factor in new cases on adult-onset asthma and that avoiding allergens may help prevent adults from developing asthma.

The Journal of Allergy and Clinical Immunology reports on a study in the Pirkanmaa District in southern Finland with 485 cases of adult-onset asthma and 665 controls. Asthmatics ages 21 to 63 who were diagnosed six months to two years previously participated in the study. Participants answered a questionnaire asking for information such as personal characteristics and work environment to whether or not they smoked. In addition to the questionnaire, blood serum samples were analyzed for antibodies and lung function measured. Results reveal that the odds of getting adult-onset asthma can be lessened by avoiding allergens that trigger atopy. The mites and molds most likely to trigger adult-onset asthma include house dust mites, storage mites and several molds that are commonly found in the home. Reported by the American Academy of Allergy, Asthma and Immunology.

TAKE A DEEP BREATH

A recent abstract reveals research on stable COPD as a predictor of benefit from high dose inhaled corticosteroid treatment. The authors, Lee, Pizzichini, Morris, Maltais and Hargreave, are with St. Joseph's Healthcare and McMaster University, Hamilton, Ontario.

According to the abstract: the role of inhaled corticosteroids in the management of chronic obstructive pulmonary disease (COPD) remains controversial. The purpose of this study was to evaluate whether sputum eosinophilia (>/=3%) predicts clinical benefit from inhaled corticosteroid treatment in patients with stable moderate-severe COPD. Forty consecutive patients with effort dyspnea (mean age 67 years; 52 pack-year smoking history; post-bronchodilator forced expiratory volume in one second (FEV1) <60% predicted, consistent with moderate-severe smoking-related chronic airflow limitation) were enrolled. Subjects were treated with inhaled placebo followed by inhaled budesonide (Pulmicort Turbuhaler(R) 1600 microg.day(-1)), each given for 4 weeks. While the treatment was single-blind (subject level), sputum cell counts before and after treatment interventions were double-blind, thus removing bias. Outcome variables included spirometry, quality of life assessment and 6-minute walk test. Sputum eosinophilia was present in 38% of subjects. In these, budesonide treatment normalized the eosinophil counts and, in comparison to placebo treatment, resulted in clinically significant improvement in the dyspnea domain of the disease specific chronic respiratory questionnaire (0.8 vs. 0.3) and a small but statistically significant improvement in post-bronchodilator spirometry (FEV1 100 ml vs. 0 ml) ($p<0.05$).We conclude that sputum eosinophilia predicts short-term clinical benefit from high dose inhaled corticosteroid treatment in patients with stable moderate-severe COPD.

PRODUCTS, COMPANIES

All information in these sections, Blood Gas Roundtable, Executive Profiles, and Products, was provided by the companies mentioned. Information may have been edited for clarity, length and appropriateness for our readership. It is Respiratory Therapy's policy not to include trademarks (™) or registration marks (®), nor to capitalize company names unless they are acronyms (ie, IBM, Xerox). Companies are responsible for the accuracy of all information.

ACCURACY AND CONVENIENCE

Mechanical spirometers are now available from Boehringer Laboratories, Inc. These fine instruments have long been widely recognized for their accuracy and convenience. Their accuracy is so reliable that they are commonly used to verify the calibration of other equipment. Boehringer Spirometers have advantages that no other brand can offer: Guaranteed for VC Maneuvers, Turbine may be sterilized by any convenient means, Multiple turbines can be used with a single counter, effectively reducing the cost of ownership, No mercury in the construction, reducing safety concerns for patients and staff. For more information contact Boehringer Laboratories, Norristown, PA, (800) 642-4945, www.boehringerlabs.com.

MAKING AN IMPACT

The Model 73X from Impact Instrumentation is the first self-contained portable ventilator developed specifically for transport and mass casualty care. Impact's design team recognized the likelihood that limited oxygen supplies would deplete during a mass casualty incident and the need for an alternative gas source was imperative. As a result, the "X" may be used with external oxygen but more importantly it is operable via its own internal compressor. In addition, the "X" automatically switches to compressor operation should oxygen supplies become exhausted and simultaneously triggers an alarm to alert the caregiver. The "X" has a simple user interface that's easily managed by personnel with limited mechanical ventilation experience. It uses adult and pediatric disposable circuits, operates for about six hours between battery recharges, interfaces with industry-standard HEPA or chemical/biologic filters, and includes a digital airway pressure display, alarms suite, airway pressure limiting, continuous operation from external power, and more. Contact Impact Instrumentation, Inc, www.impactii.com.

GET EXERCISED

Viasys Healthcare and the American College of Sports & Medicine provided a Satellite Symposium at the 53rd ACSM Annual Meeting. Importance of Quality Control Studies Prior to Using Automated Systems for the Measurements of Oxygen Uptake in Exercise Science presented Professor Per-Olof Astrand of the Karolinska Institute, and a historic overview about the measurement techniques of oxygen uptake since the 18th century. Additional topics included validation studies for the Jaeger Oxycon Mobile portable metabolic exercise system. Viasys was honored as the platinum sponsor of the event by the American College of Sports and Medicine. For more contact viasyshealthcare.com.

SPACE LAUNCH

Spacelabs Medical announced the availability of its Ultraview line of patient monitors. The compact monitor supports the company's commitment to open standards and connectivity, including WinDNA, which brings workstation functionality for charting and other hospital applications to point of care monitoring. The monitor enables hospitals to augment their existing installation of Spacelabs monitoring. A wireless networking option supports central surveillance during patient transport, and the Clinical Event Interface connects to pagers and other handheld devices. For more contact spacelabs.com.

GETTING SOME VALIDATION

Vapotherm announced that European patent rights have been validated in six countries for its apparatus and method for respiratory tract therapy. The European Patent has now been validated in Germany, France, Spain, Portugal, Italy and Austria. An integral component of the company's HFT High Flow Therapy Humidification System, the Vapotherm Patient Delivery Tube enables maintenance of breathing gas temperature by circulating water through a triple lumen, minimizing condensation and eliminating the need for heated wire circuits. The patent validation coincides with the company's recent launches in major European markets where it is now partnered with the leading respiratory product distributors. Contact vtherm.com.

BLOOD GAS ROUNDTABLE
NOVA BIOMEDICAL

Harlan Polishook

How has technology in blood gas measurement and reporting changed over the past 10 years?

One significant change that has impacted respiratory therapy has been the expanded menu of blood gas and critical care analyzers. This provides more comprehensive diagnostic

information and faster turnaround times of test results in the OR, ICU, ED, and other critical care areas. In addition, advancements in data management and connectivity have allowed test results from multiple analyzers to be transferred instantaneously from the point of care and automatically recorded in the patient record.

How has your company pursued R&D efforts to continue improving this technology?

Nova has led R&D efforts to expand the utility of blood gas analyzers by adding new critical care tests. In fact, every new test that has been added to the blood gas analyzer menu has been introduced by Nova. Currently Nova provides up to 20 tests in a single analyzer. We are also striving to provide faster test results on a smaller sample.

How have you streamlined your preventative maintenance and troubleshooting of analyzers?

Quality control is one of the most time consuming aspects of maintaining blood gas analyzers. Nova analyzers combine on-board, liquid QC materials and specialized software to provide an automated, continuous QC system. These automated systems check the entire analyzing system, utilize independent control materials that are different from the calibrating materials, set control values at or near clinical decision levels, provide peer-group comparisons, and offer electronic self-checks of correct system performance on each sample and calibration. Further, on Nova's Stat Profile Critical Care Xpress analyzer, our SmartCheck Automated Maintenance system allows the operator to initiate a maintenance cycle and then walk away from the analyzer. Priming, calibration, and quality control are all performed automatically and correctly, and in a fraction of the time of competitive analyzers.

What efforts have you made in automation?

Automation touches virtually every step of Nova analyzer operation. Nova analyzers feature fully-automated operation with analysis of selected test menus at just a push of a button. They perform an automated two-point calibration at pre-set intervals to assure that the instrument is ready for analysis at all times. Automated, on-board quality control eliminates the steps involved in manually performing QC thereby dramatically reducing labor costs. SmartCheck Automated Maintenance allows the operator to initiate a maintenance cycle and then walk away from the analyzer. The Nova Point of Care Manager automates the test order entry, accessioning, and reporting process.

Where do you see your product used most?

Nova blood gas/critical care analyzers are used routinely in centralized testing locations and at the point of care (OR, ICU, ED).

How prevalent is point of care testing vs. a centralized lab system?

As the acuity of patients seen in the hospital increases, the demand for point of care blood gases and other critical care tests has increased. As a result, more and more blood gas/critical care analyzers are being placed at the point of care. For example, blood gas/critical care analyzers are playing a role in addressing the overcrowding crisis in the emergency department by providing improved turnaround time of urgent tests such as blood gases and Chem 7. In many institutions, RTs are playing an important role in improving patient care by providing more tests from a single sample using fewer resources and generating faster results.

What type of training and customer support programs do you have in place?

The purchase of a Nova analyzer is the beginning of a long series of commitments and responsibilities from Nova to our customers. Immediately following analyzer installation, training of operators on all shifts is provided by Nova technical support and applications staff. Correlation and transition studies are included as part of the training process. We maintain a highly skilled and experienced technical support "hotline" staff to answer calls 24/7/365, as well as one-day on-site service by a trained factory representative.

How do you view your relationship with the end user of your product?

Nova views the relationship with our customers as a partnership to provide timely, reliable blood gas/critical care testing within their hospital. Due to the urgency of blood gas/critical care testing, such a partnership requires Nova to provide dependable equipment and comprehensive, responsive support. Nova support includes immediate telephone technical assistance 24 hours per day, 365 days per year; on-site service within 8 working hours; same day shipment of supplies; flexible service agreements such as our Point of Care Transition and Vendor Transition programs; and seminars and grand rounds lectures regarding various aspects of blood gas/critical care testing. Nova administers a periodic Customer Satisfaction Survey to allow customers to grade our performance and offer suggestions thereby helping us improve the partnership in ways that are meaningful to them.

What, in terms of cost savings/benefits, does your technology bring?

Nova offers more models, test menus, and price choices than any other blood gas/critical care analyzer manufacturer. We feel that this large selection is necessary to meet the very different sizes and budgetary requirements of hospitals and departments. With 19 standard models with from 3-19 tests on board, customers can get the most for their money by purchasing only those tests they need. Nova's comprehensive test menus combine with rapid test results to provide clinicians with more information faster, allowing patients to be moved through the hospital more quickly. This can result in shorter length of stay that can lead to significant cost savings for both the hospital and the patient. Implementation of an overall point-of-service program with Nova analyzers can provide tremendous cost and labor savings compared to central laboratory testing. For example, installation of Nova analyzers in the ER, OR, and ICU at Fresno Community & Universal Medical Centers (Fresno, CA) resulted in an annual cost reduction in labor and consumables of over $170,000. A similar program at University Hospitals Health System (Cleveland, OH) reduced annual labor costs by $175,000 and annual consumables costs by $150,000.

ROCHE DIAGNOSTICS

Ken Levy, Director of Hospital Point of Care

How has technology in blood gas measurement and reporting changed over the past 10 years?

The fundamentals of measuring and reporting blood gas parameters have not changed significantly. What has changed is analyzer technology. Today's blood gas analyzers are more

reliable, smaller and easier to maintain and use. The use of state-of-the-art electronics, improved user interfaces and Information Technology has helped respiratory therapy departments and the Lab keep pace with the increasing regulatory and quality requirements. For example: In the case where the lab "owns" the CLIA license, but the respiratory department performs the blood gas analysis, the use of IT products like Roche's OMNILink software permits the lab to review the calibration and QC status remotely. OMNILink also allows the lab to remotely monitor the analyzer's reagent supply, thus helping to prevent downtime during critical periods. Remote control and monitoring of operators' eligibility and performance, plus the ability to review and print all required QC reports, helps the staff responsible for quality and regulatory oversight complete their tasks without going to each location where a blood gas analyzer is stationed. In addition to improvements in IT technology, the ability to perform blood gas analysis without the need for gas cylinders or filling and polishing electrodes and sensors has decreased maintenance time, thus permitting the staff to focus on direct patient care.

How has your company led R& D efforts to continue improving this technology?

Roche has been a technology leader and innovator in many areas. Roche offered the first non-maintenance electrodes and sensors, developed the first automated QC system, and leads the industry in blood gas analyzer remote control and quality management. In addition, Roche's OMNI S blood gas analyzers are the only system to utilize radio frequency to maintain analyzer-independent memory of reagent volume, lot number and expiration dates. This permits reagents to be moved from one analyzer to another, thus utilizing reagents more efficiently based on each analyzer's test volume.

How have you streamlined your preventative maintenance and troubleshooting of analyzers?

Roche Blood Gas analyzers only require a limited amount of routine maintenance. Regular maintenance (beyond reagent change) is scheduled in the analyzer's firmware, which notifies the operator or supervisor prior to the date that maintenance is due. Roche's maintenance-free electrodes and sensors also eliminate the work required to keep electrodes in peak performance. Not only are our electrodes maintenance-free, but the on-board life of our electrodes and sensors has set the standards in the industry. In addition, Roche Blood Gas analyzers under warranty or service agreement have scheduled preventive maintenance performed by factory trained Field Service Representatives. A new Roche offering is an online service, known as Axeda. Customers who have a Roche OMNI S system and the Roche DataCare POC and OMNILink software packages can have service techs remotely connect into the system and perform trouble-shooting 24 hours a day, 365 days a year. By offering this service, we will significantly reduce the time it takes to get trained eyes on the problem. Should a field visit be required, the technician will be prepared with the information and parts required to remedy the problem.

What efforts have you made in automation?

At Roche, we believe that there are tests where automation adds significant value and other areas where it is of minimal value. Roche is an industry leader in laboratory automation; however, based on feedback from our customers we believe that the real value in automation comes in the area of automating quality control and data management. Roche's auto QC modules and IT solutions for data management and remote control are the best in the industry. It is automation in these areas that we believe saves the most time, thus reducing the clinical staff's time away from the patient.

Where do you see your product used most?

As you know, blood gas analysis is needed in a variety of locations in the hospital. The industry average turnaround time for a blood gas analyzer is 15 minutes. This can be compared to almost 60 minutes for other laboratory tests. More than two-thirds of the blood gas tests performed today are in a location outside of the central lab. Respiratory Therapy departments, emergency departments, ORs, ICUs and NICUs are examples of locations where requests for blood gas tests originate. Often there is a trade-off between moving the blood gas analyzer next to the patient versus the central lab or a STAT lab near the patient (decentralized site) and that trade-off is cost per test. Bench-top systems, although larger, can often produce blood gas, electrolyte and metabolite results at a fraction of the cost of hand-held or portable systems. Also, the ability to perform a broad selection of analytes on a single sample of blood favors the use of bench-top systems. Again, the need for speed (vein to brain time) should be the first criterion used when determining which system is best suited.

How prevalent is point of care testing vs a centralized lab system?

As noted earlier, in the US more than two-thirds of blood gas testing is performed in a decentralized setting. This is not the case outside the US, where most blood gas is still performed by the central laboratory.

What type of training and customer support programs are in place?

Roche offers a variety of training and customer support options. First, we perform on-site training of key operators and trainers. We also have key training video sequences located on each OMNI S blood gas analyzer. An operator may run through the operation of the analyzer and see each step performed as prescribed. Roche Operator Manuals also outline, in detail, the complete operation and maintenance of each analyzer. In addition, should customers have questions, they are directed to call the Roche Customer Support "hot line" 24 hours a day, 365 days a year. Should an on-site technical call be required, a trained service technician will be dispatched to the site. Roche also offers continuing education opportunities for its customers. The most recent offerings address pH measurements on pleural fluid and quality control measurement and reporting for Blood Gas.

How do you assist customers with technical issues or compliance issues when possible?

Roche offers a variety of support mechanisms to assist our customers with technical and compliance issues. First, we offer 24-hour, 365-day technical phone support. Due to Roche's size and large customer base for chemistry and immunochemistry analyzers, we have a field service support organization that is best-in-class. Over 300 field service technicians are distributed across the country and available on-site to address technical issues that can not be addressed remotely via telephone or through Axeda, our newest on-line support tool. In addition, we also offer self-help via MyLabOnline. Customers may login to MyLabOnline and look up technical bulletins and MSDS information. We also offer customers, at no charge, "eQAP,"

which is a real-time, online quality control review service that lets customers perform peer-review analysis and print out quality control statistics and reports needed for CAP or JCAHO requirements.

How do you view your relationship with the end user of your product?

Roche views our relationship as a true partnership. We and our customers are in the business of improving healthcare and the quality of life. The Roche Point of Care Diagnostics Mission Statement says it all: *"Our passion is to shape the future of Diagnostics through leading solutions that empower immediate healthcare decisions to improve quality of life."* We look to our customers to provide us with open and honest input on how we can continue to improve our products and services. We ask and listen to our customers as they tell us their "challenges" and needs. Our customers are varied. Ranging from the patient or clinical care-giver to the purchasing agent or hospital executive. All have varying needs, yet all are important for us to understand and serve as well as we can.

What in terms of cost-savings/benefits does your technology bring?

Roche OMNI S blood gas analyzers offer many value-added services and benefits. From the maximum 42 day on-board stability of reagents to the 40 day supply of on-board quality control material and zero-maintenance electrodes, the analyzers' features reduce the time it takes to perform QC and to change reagent packs and maintain electrodes. These features also reduce the downtime required for the analyzer to calibrate and come back "online" after a reagent change. Roche offers Neonatal Bilirubin with results that are comparable to the laboratory standard. By offering this test near the NICU, you reduce the sample volume needed to obtain a result and shorten the time for reporting a result. Neonatal bilirubin results on the OMNI S blood gas analyzer, due to the sample being measured in the Co-Oximeter, can be performed without the need for additional reagents, thereby reducing the cost of reporting. Roche offers the only blood gas system with an FDA 510 (k)-cleared claim for the measurement of pH on pleural fluid. According to CAP and the American College of Chest Physicians, a blood gas analyzer is the method of choice for performing pH on pleural fluids. If a blood gas that is not FDA 510 (k)-cleared is used for measuring pH on Pleural Fluids, the test must be treated as a CLIA high complexity test. This requires much more quality and validation work and also requires that a laboratory-trained technician perform the testing. By using a Roche blood gas analyzer, the test is only a moderately complex test and may be performed by respiratory therapy and other technicians within the hospital. The costs saved by keeping tests to a moderately complex level may be significant, depending on the capability within the hospital. One of the most significant savings may be realized by performing "Glycemic Control" or acid base monitoring of patients in the ICU. Using the Roche OMNI S blood gas analyzer with Metabolite sensors, the ICU can now perform frequent blood glucose and/or lactate measurements on their patients. The Roche OMNI S analyzer onboard software provides patient trending and Acid Base Mapping. These two features help the clinical staff closely monitor the patient's acid-base balance as well as his or her glycemic control. There are many published studies that have documented significant clinical improvement as well as cost savings when a systematic process of glycemic control is practiced. By using the Roche OMNI S Blood Gas analyzer, patients connected to an arterial or venous line may have glucose and/or lactate samples taken without performing repeated finger-sticks.

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EXECUTIVE PROFILES

Maquet, Inc.

Doug Smith

Doug Smith is Vice President, Critical Care Division, Maquet, Inc.

AFTER SALES SUPPORT & SERVICE

Who is responsible within your company for training and education of your staff and of your customers?
Maquet Critical Care has always been a leader in clinical education, customer training and technical support for our large customer base. We have two full-time clinical education and technical training managers with over 20 years of technical and clinical experience in mechanical ventilation. They are responsible for determining the curriculum, types of training programs, documentation of support materials and program schedules for our customers as well as our internal personnel. We have a state-of-the-art technical training center where "hands-on" biomedical service training seminars are held routinely throughout the year. We also have professional relationships with two modern research laboratories that focus on mechanical ventilation, "work of breathing" and advanced lung protective strategies in Sweden and the USA.

What type of education do you provide?
We offer many different educational programs to our customers. Our two-day biomedical training seminar focuses on the technical operation, maintenance, and clinical operation of our critical care ventilation products. Additionally, our clinical applications staff can provide clinical education seminars pertaining to lung pathophysiology and mechanical ventilation that are all approved by the AARC. Maquet also sponsors a unique "Open Lung Tool" clinical training program in cooperation with the *Work of Breathing Lab* at Arkansas Children's Hospital.

How do you manage "off-hours" assistance for clinical questions?
We have a staff of 17 application specialists throughout the US who make contact with customers on a regular basis and whom can be contacted anytime if necessary. Additionally, our technical support center, which is located in our corporate office in Bridgewater, NJ is available 24 hours everyday to provide emergency technical help. If the technical support specialist cannot answer a particular clinical question, the on-call clinical application specialist is contacted immediately to provide additional support.

Do you provide technical service support?
Yes, through a dedicated staff in our Service Support Center. These specially-trained technicians are available to provide technical assistance for our customers' biomedical staff. Whether it is troubleshooting problems, reviewing technical issues, or addressing user questions the technical service staff is ready to assist. If additional technical or clinical support is required they can schedule an on-site visit by one of our certified field service engineers or clinical application specialists. This technical support is provided to our customers 24 hours each day.

What formal education program does your company provide for biomedical training and service?
As a leader in customer support and education, Maquet offers first class technical training by factory certified training staff. These service seminars cover in-depth operations of SERVO ventilation operating systems, as well as maintenance and repairs, calibration, functional checks and advanced troubleshooting of the ventilator platform. These two-day training seminars are held in our corporate headquarters where our modern classroom is equipped with the latest equipment and educational materials that enrich the classroom instruction and enable hands-on service training.

What do you feel is important to support the customer/end-user of your product?
We want our customers to be highly proficient and exhibit excellence in clinical performance. Through increased education, the clinician can better understand the new technology that is available in our SERVO products. Our clinical application specialists provide detailed instruction on the use, operation and advanced functionality to all the end user clinicians involved with respiratory care. We understand that our customers face the challenges of increasing patient acuity, limited financial resources, and improving patient care. Maquet believes that as a partner with each customer, together we can meet these challenges and promote improved patient outcomes though technology and education.

What activities does your company involve itself with to promote the products?
Maquet is very active in the promotion of our products with the many national publications, national healthcare trade shows, regional and local respiratory societies meetings to ensure that we reach as many of our customers and potential customers as possible. In addition we are a corporate partner of the AARC organization in support of the goals and mission of the respiratory care profession worldwide. This cooperation with the AARC provides additional opportunities for communication and education to the respiratory care community. We take great pride in our support of the local respiratory care organizations. Last year, both the New York and New Jersey State Societies for Respiratory Care awarded Maquet as its "Vendor of the Year" during their annual meetings. In addition, Maquet also sponsors nationally known speakers regarding such topics as lung recruitment, volumetric CO2, ventilator graphics, and non-invasive ventilation. This year Maquet is also sponsoring a two-day symposium in New York City, where day one will focus on lung recruitment strategies, while the second day will introduce new and emerging technologies concerning patient-ventilator interaction. This symposium will be held August 28 through 29. For additional information regarding the listing of world renowned speakers, topics and discussion groups please see the symposium website at http://programs.regweb.com/meridian/maquet2006.

How does your company reach out to its customers regarding product performance and R&D?
Every year, Maquet has worked with the AARC during the summer forum and national congress to address issues and the latest trends seen in respiratory care that affect not only our customers but all respiratory care practitioners. We also maintain various focus group sessions for the Adult, Pediatric and Neonatal clinical users. The resultant information from these sessions is provided to our factory's R&D department for

further research and possible product development. The success of these "Voice of the Customer" programs is evidenced by our continual new product releases for our SERVO product over the last 4 years. Due to this high level of customer focus and feedback mechanisms we have been able to release new features and functionality every 9 to 12 months since the launch of the Servo-i product.

What mechanisms are in place to assist hospitals in their educational requirements and ongoing education?
Maquet has always been known for introducing the latest technology in mechanical ventilation. To better appreciate the patient benefits of new technologies, Maquet believes that this appreciation must come from educational programs suited for the clinician. We have developed a clinical lecture series that can be tailored to meet the needs of each customer. These on-site courses are conducted by our clinical application specialists in conjunction with product training or with our clinical management program. We also launched "Critical Care News," a publication focused on the latest treatments, trends and clinical studies regarding the mechanically ventilated, critical care patient and their clinicians. This publication is provided at no cost to any interested clinician and can be received in hard copy or electronic format. Anyone can sign up at the Maquet website, www.maquet.com.

Where do you see the future of your product in relation to the end-user requirements?
The Servo-i ventilator platform was designed with an "open architecture system" meaning that as technology is developed, the ventilator can grow with the technology and be tailored to meet the customer need at the time. This design guarantees that purchasing Servo ventilator technology will remain a safe investment now and in the future. Our strong commitment to research and development is paramount to our customers to ensure that their investment in Maquet provides lasting and sustainable economic advantages.

Along with this major investment in research comes the obligation to help our customers implement new techniques and technologies into the standards of care for their patients' benefit. That is where the combination of our unique technology and our commitment to education and training separate Maquet from other manufacturers in the industry. Our driving goal is to live up to our corporate motto: "Maquet – The Gold Standard."

ndd Medical Technologies

Todd Austin

Todd Austin is VP Sales and Marketing, ndd Medical Technologies.

Please describe your product(s) or product line and what sets it apart from other products in the field.
ndd's core science is ultrasonic flow measurement. This technology is defining the next generation of devices used to evaluate expired flow patterns in patients with airflow obstruction.

How do your products or improvements in your products directly affect patient care?
Our products have been used in clinical and epidemiological studies establishing disease prevalence and therapeutic outcomes. The ease-of-use provides simple patient self evaluation while the robust technology assures investigators quality data.

Tell us about advances in the area your product serves or in treatment modalities.
There continue to be many advances in the care of patients with asthma and COPD. ndd is uniquely positioned to provide simple and robust devices for the diagnosis and management of lung disease.

Discuss your R&D process.
The products and innovations provided by ndd are the result of long standing relationships with opinion leaders and a clear vision of what our technology can bring to a mature market such as respiratory care.

Discuss the services you offer to educate clinicians and healthcare professionals about the uses of your product.
ndd sponsors and participates in many public health screening where our product is used by local experts to provide consultation to participants. Additionally, included with the purchase of our product is a Quick Start Training CD for clinicians.

Please discuss the role of clinicians in developing and upgrading your products.
Due to our close involvement with clinicians and opinion leaders, we continually implement the input received from our customers.

What new technology do you see as having an impact on your area of specialization?
The newest advances in communication technology and security are implemented in our clinical trial and home monitoring devices providing simple, safe and secure data transfer via internet, modem, Bluetooth and other methods.

How does the international marketplace and international clinical community impact your research, development and product placement?
ndd is a worldwide company. Our products are distributed in all major markets and we support local scientific congresses in many of these markets. Our simple, robust devices are used in many in-country research projects where access to remote areas is challenging.

What are your goals in terms of R&D for the next three years?
ndd is in the final stages of development and release of our lung function product. ndd's simple, robust product philosophy will be integral to the design which will utilize our patented ultrasound technology and state of art design, providing the market the most innovative product available. Our vision will continue to guide the development of products ideally suited to improve healthcare for patients with lung disease.

Tell us how you use conferences, forums, seminars and such to promote your product and its efficacy.
We support and attend worldwide events and advertise in many publications which serve our market.

CARDINAL HEALTH

Hendrik Struik

Hendrik Struik is Vice-President / General Manager of Cardinal Health Respiratory Care. Cardinal Health, Inc. Medical Products & Services, Respiratory Care

Headquartered in Dublin, Ohio, Cardinal Health, Inc is a global company comprised of businesses with a long history of serving the healthcare industry. The company manufactures and distributes pharmaceuticals and medical supplies, offers a range of clinical services and develops automation products that improve the management and delivery of supplies and medication for hospitals, physician offices and pharmacies. Through this diverse offering, Cardinal Health delivers integrated health-care solutions that help customers reduce their costs, improve efficiency and deliver better care to patients. Cardinal Health's Respiratory Care business is a market leader in the respiratory market focused on providing clinically advanced products for ventilation, medication delivery and oxygen therapies. Cardinal Health Respiratory Care is committed to establishing a lasting relationship with the Respiratory Community to improve patient care by integrating the best products, people, services, and partners. As a founding partner of the American Association for Respiratory Care (AARC), Cardinal Health provides the most comprehensive portfolio of high quality, market leading respiratory products. In addition, our tenured sales force and Resource Service Center (with experienced respiratory therapists on staff) offer clinical product expertise and are dedicated to understanding and delivering unique solutions that meet challenging daily needs.

Patient Needs

Treating infants in need of respiratory support is one of the most delicate therapies performed in the neonatal care environment. More than 500,000 infants are born prematurely each year. Many require some form of ventilation support and, given the complications and risks associated with intubation, clinicians are constantly searching for ways to deliver effective respiratory therapy with minimum patient risk and discomfort whenever possible.

Nasal Continuous Positive Airway Pressure Therapy (nCPAP) has been used successfully with neonates for more than 30 years, helping them establish the vital functional residual capacity (FRC) they need. This therapy can serve as an alternative to intubation and, in some cases, as a step-down therapy when intubation is no longer necessary. Even though nCPAP is a proven therapy, it does not come without its own limitations such as potential for skin necrosis and increased work of breathing (WOB), while in some cases being difficult for the clinician to manage.

Innovative Product Solution

Cardinal Health Respiratory Care developed the Air*Life* Infant nCPAP System in order to provide better patient care and to support the needs of the Respiratory Therapist in the neonatal care environment. The Air*Life* Infant nCPAP System was designed to incorporate best-in-class nCPAP technology that provides a solution that addresses the current nCPAP therapy limitations and maximizes the benefits of nCPAP therapy, like reducing the potential for skin necrosis and patient's imposed work of breathing.

The Air*Life* soft, "Comfort-Fit" prongs and masks utilize advanced features like flexible bellows and anatomically contoured shapes that help provide an effective seal, reduce skin necrosis and increase patient comfort. The Air*Life* intuitive "Comfort Wrap" fixation device has five sizes to fit all of your patient's needs. The fixation device gently wraps around the patient's head and secures with adjustable closures for a custom fit that allows for single clinician application. The custom fit helps secure the generator at the proper angle, which helps reduce pressure points and minimize air leaks that can cause nuisance alarms.

The Air*Life* generator incorporates unique, patent-pending "Vortice" technology and "Low-Momentum Impinging Jets" that effectively reduce the imposed work of breathing (WOB) during both inspiratory and expiratory efforts.

When the patient begins to exhale, the destabilized air created by the "Vortices" allows the gas flow to be quickly and smoothly redirected to the exhalation tube, reducing the patient's imposed WOB. Minimizing a patient's WOB is extremely important in promoting quick recovery and healthy development for an infant. In addition, it helps calm the patient while allowing the infant to conserve precious calories needed for growth. The "Low-Momentum Impinging Jets" can entrain flow to meet the patient's inspiratory demand and deliver the gas at a lower momentum, which helps to provide a constant level of CPAP and reduces harmful noise levels around the patient.

The Air*Life* driver features the latest advancements in respiratory technology to assist clinicians in delivering, adjusting, and monitoring nCPAP therapy for their patients. The "Comfort-Flow" feature allows the clinician to simply set the desired nCPAP pressure and the driver automatically adjusts the gas flow to achieve the desired result. This not only saves the clinician time by not having to manually adjust the flow to compensate for leaks, but it also maintains a constant level of nCPAP, providing the optimal level of therapy for the patient. The "Smart Alarm System" helps maximize patient safety and clinician efficiency by differentiating between critical and non-critical alarms while a message bar indicates which parameter is in alarm state. As the clinician sets or changes the operating parameters, the alarm values automatically adjust to the new settings, helping to reduce nuisance alarms.

Patient Care

Every component in the Air*Life* Infant nCPAP System has been engineered for maximum performance, reliability, patient comfort, and clinician ease of use. Patient comfort is an important factor in the neonatal care environment because the less discomfort a patient experiences, the greater the opportunity for healthy growth and development during this critical time in the patient's recovery. The Air*Life*™ Infant nCPAP System incorporates an innovative design and patent-pending technology to help minimize skin necrosis, reduce the patient's imposed work of breathing, and maximize patient comfort. The Air*Life* Infant nCPAP System is designed to help caregivers not only initiate this vital therapy quickly and easily; but also allow for precise adjustment and easy monitoring to help reduce nuisance alarms, allowing clinicians more time for patient care.

Clinician Involvement
Cardinal Health Respiratory Care worked together with over 250 industry-leading neonatologists, respiratory therapists, nurses, and clinical advisory boards, throughout the development of this comprehensive solution for infant nCPAP. Based on the feedback obtained, Cardinal Health Respiratory Care was able to develop an infant nCPAP system with a unique combination of advanced components and an innovative and patent-pending technology. Customer trials, initiated at six hospitals, provided further feedback prior to a full market release. This confirmed the benefits of the Air*Life*™ Infant nCPAP System including delivering effective therapy that's gentler on the patient and providing an easier nCPAP therapy for the caregiver to administer.

Goals
At Cardinal Health, we share our customers' goal of providing the best patient care possible and delivering the best patient outcomes. Our single-source solution for respiratory care contains four key elements that support our continuous efforts to drive innovation in our products and services.

Technology, Service, Support
The Air*Life* Infant nCPAP System from Cardinal Health Respiratory Care was designed to incorporate best-in-class nCPAP technology and provide a solution that delivers superior infant treatment. Our team of clinical, R&D, and product experts are ready to provide assistance with implementation, training and upgrades of the Air*Life* Infant nCPAP System. Cardinal Health Respiratory Care has also created a Respiratory Resource Center with a state-of-the-art call center to answer questions from customers about the Air*Life* Infant nCPAP System.

Cardinal Health has developed a Respiratory Care Advisory Council comprised of neonatal doctors, respiratory care directors, and respiratory therapists from multi-hospital groups, IDNs, GPOs, and specialized children's hospitals to guide in developing the Air*Life* Infant nCPAP System and other products. Cardinal Health Respiratory Care recognizes that respiratory therapists are on the front lines when it comes to providing quality infant care, and their knowledge is extremely important in advancing patient outcomes and future product innovations. Cardinal Health Respiratory Care is working with the American Association for Respiratory Care (AARC) to develop and deploy educational programs for respiratory therapists, including CEU programs for the Air*Life* Infant nCPAP System. It's all part of Cardinal Health Respiratory Care's commitment to providing innovative, integrated, and easy-to-use products and services that enable health-care professionals to deliver top-quality patient care every day.

For more information about our complete line of respiratory care products, please contact your Cardinal Health Respiratory Care representative or call our Resource Center at (800) 637-1500. Information also can be found at www.cardinal.com/respiratory.

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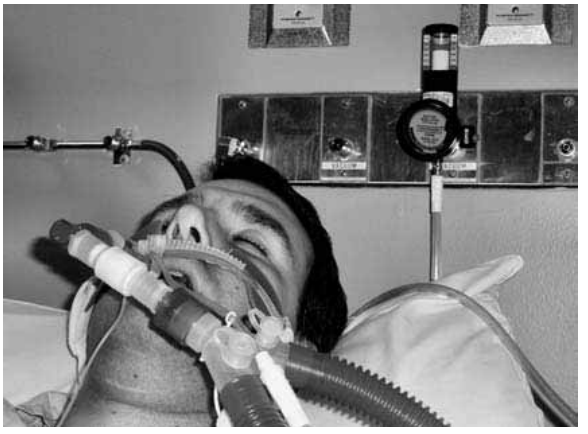

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Published by Goldstein and Associates, Inc.

Breathing Hope Into Belize

K. Sabato

The author, with Nurse Williams, who took on the role as a main resource for ventilation.

Picture a child with chest retractions, at times clear down to the bed, with nasal flaring, and a mottled appearance. One preterm, 2 kg infant is born in 1999 in Belize. A breathing tube is placed and a nurse begins hand ventilation. Blood gases are not taken because there is no blood gas machine. No surfactant is delivered because it is much too expensive, or just not available. Availability of sedatives is limited, and there is no mechanical ventilation. Dedicated special baby care nurses will tirelessly continue to hand ventilate for the next couple of days. Forty-eight hours was the target for hand ventilation. If the child could breathe without the assistance of the nurse at that point, survival might be possible. This was the practice in Karl Heusner Memorial (KH), the largest public hospital in Belize City, Belize, until we began our program. What follows, is a short story of how one developing country successfully introduced life saving technology to offer hope for its tiniest, most precious population.

In 1999 Dr Egbert Grinage (an individual I now refer to as the Dr Dolittle of Belizean children) sent the following email to pediatric care centers nationwide: *Is there a Neonatal Pediatric Respiratory Care Practitioner (RCP) interested in coming to Belize to help set up mechanical ventilation program for their sick neonates?*" Prior to 1999 Dr Grinage had completed a pediatric fellowship at Children's Hospital and Research Center Oakland (CHRCO) and had experienced first hand the impact of mechanical ventilation on survival of preterm and sick term infants. He also witnessed the important role RCPs played in assuring safe, effective set up and operation of mechanical ventilation and other life supporting therapies used to treat these young infants. Tim Yeh, MD, the Medical Director of the PICU at CHRCO, received the email. Dr. Yeh forwarded the email to me. I immediately knew that this was something I needed to respond to. I wrote to Dr Grinage and expressed my interest. Dr Grinage had remembered me (or at least my red stethoscope that I had used to impress upon him the importance of listening!) and selected me to assist him in carrying out his dream.

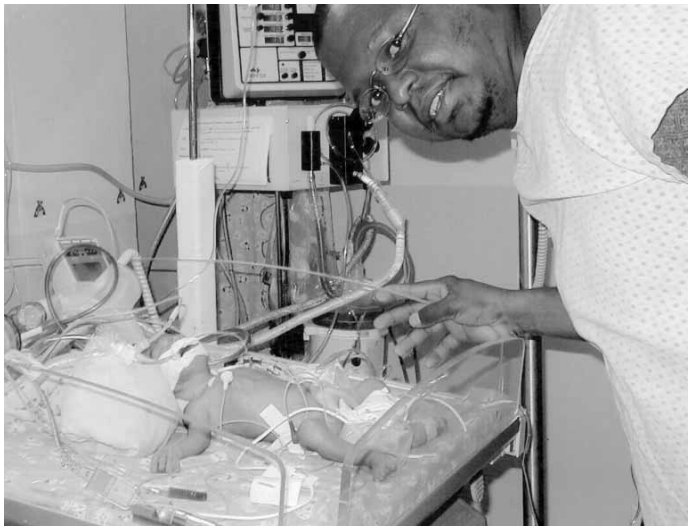
Dr Grinage spent endless hours attempting to solicit the financial assistance of various local Belizean industries and associations to help with this endeavor. His zealous enthusiasm and relentless hard work resulted in several Belizean companies providing financial support. Dr Grinage then developed a group called "Friends of Pediatrics," a private organization whose stated goal is to develop and improve access to tertiary medical care for needy Belizean children.

Friends of Pediatrics offered to provide for my transportation to Belize and several Belizean families would open their homes as accommodation. OK, I was eager to go, but not alone. Such a project could not be accomplished by just one RCP. I asked to also bring a close friend and peer, a Pediatric Respiratory Care Practitioner, Lillian Fifer. Dr Grinage agreed.

So, we planned to go to Belize to help introduce mechanical ventilation. How does one do that? Neither I, nor any of my peers or friends had attempted something like this. I had no clue. What resources did they already have? Did they have any?

I have been a clinical coordinator for respiratory care for the last 18 years at CHRCO located in Oakland, California. This means I have had the opportunity to interact with many product representatives. In the months following my accepting this project, when vendors came to visit, I simply inquired if they had any excess equipment, specifically equipment that could be utilized to provide breathing assistance to neonates and children. Thankfully, they did. In fact, some were very interested in donating surplus equipment to such a worthy cause. This proved to be an example of "just ask and you shall receive," really happening!

Within a few months, several companies and individual sales representatives stepped forward and offered precious, much needed equipment. Trianim, a large distributor of respiratory supplies happened to be closing down one of their larger warehouses located approximately 30 miles from my house. They said we could have whatever we could come pick up and take away. We spent the next weekend, tirelessly picking up and carting off many needed items. That weekend pales in



The first baby intubated in Belize, with Dr Grinage.

comparison to subsequent weekends we (myself and our now willing volunteers) spent picking up, sorting, storing, labeling, packaging, and sending donated equipment. Respironics came through with donations of BiPAP machines and accessories. Westmed donated cases of nebulizers. Monaghan Medical donated spacers and peak flow meters. Trianim supplied cases of ventilator tubing, humidifiers, breathing tubes, and oxygen delivery devices. Viasys supported the program by donating state-of-the-art ventilators and to this day, continues to provide equipment, disposables, and clinical support to Belize. Though we understood our primary goal was to introduce a mechanical ventilation program, we knew respiratory diseases including asthma and RSV had to be prevalent in Belize (such illnesses are prevalent world wide), so we wanted to make sure we were prepared to offer assistance in these areas as well.

We (Lillian and I) collected all supplies that we thought would be of value, making sure that none of the donated equipment was so outdated that it may not be serviced in the years to come. We stored it… in my garage. The donations piled up, eventually filling said two-car garage. Kudos to my husband for his tolerance! Then, one evening, one of those classic "movie screen" yellow school buses (Yes, *that* yellow school bus), arrived at my home in Danville, California. Did you know that you could travel by land from Belize to Northern California? You can! That big old yellow school bus, capable of only traveling at a maximum speed of 35 miles per hour, made the 2,500 mile trip.

They maneuvered that school bus, three dedicated, Spanish-speaking-only drivers, and arrived on Halloween Eve. The doorbell rang and my 16 year-old daughter, dressed as Britney Spears, answered the door. To this day, I have no idea what went through their minds. They then tirelessly loaded the estimated $80,000 worth of donated equipment and turned around and headed back to Belize.

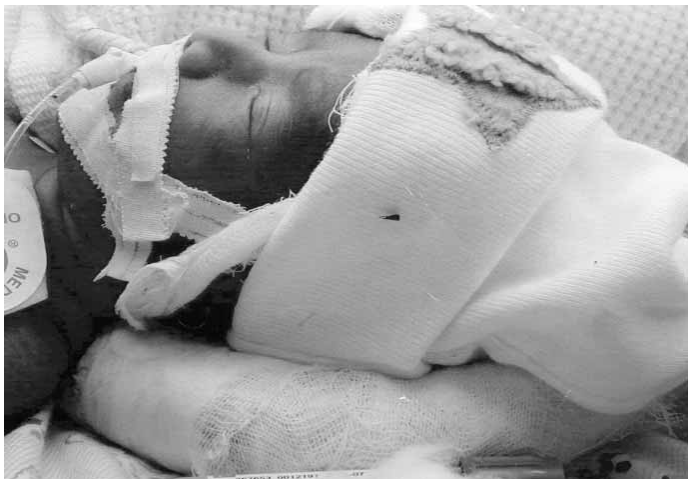
Lillian and I arrived in Belize City one day ahead of the yellow school bus. This means, it took approximately one month for the bus loaded with equipment, to make it back to Belize.

Belize is a tiny developing country in Central America and is best known for its pristine 185 mile-long barrier reef, tropical rain forest, ancient archeological sites and superb diving and snorkeling experiences. None of this did we see or experience during our two-week stay (until the last day of our visit). As soon as we arrived, our work began. Actually we never thought of it as work, but rather an opportunity to utilize our talents to help others improve survival of Belizean infants.

What was so inspiring was how easy it was to teach, especially the nurses. Their countless hours of hand ventilation had instilled in them a rich understanding of neonates' ventilatory requirements. Setting respiratory rate, inspiratory/expiratory ratio, tidal volume, peak pressure, PEEP, trigger, cycle synchrony and lung compliance were not necessarily terms they were familiar with, however, once explained, they easily understood and were able to apply them. The nurses and physicians were eager to learn and came in on their off hours, some after working 8 and 12 hour shifts, to spend countless additional hours with Lillian and me, learning how to stabilize a breathing tube, suction, and apply mechanical ventilation. We would set up a ventilator and then dismantle it and required each nurse to practice putting it back together. We ran mock deliveries, intubations and subsequent application of ventilation. We set up an equipment room complete with clearly labeled equipment and adapters.

While we were welcomed in Belize, there was an undercurrent of caution and reservation displayed by all. There had been those before us, equipment that been dropped off by others with good intentions; however, with little follow through, no clinical instruction provided and no inservicing on preventative maintenance. We discovered equipment locked in hidden rooms because no one really knew what the equipment was or how to put it all together and keep it working. Lillian and I spent many additional hours fixing equipment (such as Infant Star ventilators) that we found behind those locked doors. We were asked by many, "Will you come back?" Without hesitation, we said "yes" and we know this was a promise that could not be broken. "Follow through" would later help define the core mission of the now growing medical missionary group.

The scope of what we did while there included: crawling on the hospital's rooftops with the maintenance people fixing and assuring the old damaged oxygen lines could be fixed to support continued use of the ventilators; helping put in place a 24-hour electrical and gas maintenance program; and placing surge protectors on outlets to assure our ventilators would not be fried when the next power outage occurred (which was not infrequent). We helped clean and disinfect rooms and



Baby on a vent.

equipment. Dr Grinage attended meetings with hospital administration to try and convince the governing powers that offering advanced technology was a positive thing for their hospital and their country, and we attempted to provide estimates of the resources needed to support this new ventilation technology. We designed ventilator flow sheets that enabled staff to record ventilator parameters and the baby's response to changes. The ventilator sheets could be reviewed both to document baby's progress but also to be utilized as a learning tool. However, the majority of our time was spent providing hours of educational presentations and hands on workshops on everything from securing an artificial airway, ventilator settings, weaning, and suctioning, to extubation.

We taught, and to this day, teach only those therapies that can be carried out by staff using the resources they will have, once we are gone. Blood gases were not available, so the nurses and physicians were instructed to manage the ventilator parameters in the same manner they used when they delivered manual ventilation to the infants, by evaluating clinical status of the infant, such as observing baby's color. If infant is mottled, they may be cold. If their lips or fingernails are pale or blue, they probably need more oxygen. Sedation was limited, so we really had to concentrate on manipulating the ventilator to respond to the patient's clinical respiratory status. If the baby started breathing fast, they were instructed to decrease the inspiratory time and increase the respiratory rate to support the infant through the current instability, be it pain, fever, or stress due to a needle stick. If the baby has stopped breathing on his own, perhaps the set respiratory rate is too high. Staff was instructed to decrease the set rate until the baby initiated spontaneous breaths.

In addition to initiating a ventilation program, we also had the opportunity to work with asthmatics and babies with bronchiolitis and RSV. We introduced the concept of delivering continuous bronchodilators to asthmatics. Anti-inflammatory drugs and bronchodilators, other than albuterol, were limited. One night, an asthmatic in severe status asthmaticus presented. We stayed with the boy through the night, administering primarily, continuous albuterol. The child recovered. To this day, continuous administration of albuterol has helped many Belizean children in status asthmaticus. We placed pulmo-ades in the emergency department, which significantly decreased the wait of patients needing breathing treatments.

The first infant was ventilated during our stay. The Belizean newspaper reported it best, so I quote, "At 3:00 pm on Sunday December 3, 2000, Baby Y, an infant of 27 weeks gestation, decided to enter the world. Five hours later, Baby Y made history by becoming the first baby to be hooked up to a lung respirator at the Karl Heusner Memorial Hospital. The respirator, which is essentially an artificial lung, does the work of taking oxygen to the body and removing carbon dioxide. This cycle, which, in days gone by, was done manually with the nurse standing over the child for hours at a time, is expected to save countless numbers of premature babies in the future." The paper report was correct – the ventilation program had begun.

In November 2003, I brought another group from Oakland to Belize. This trip we returned with well over $200,000 worth of donated equipment, including 3 VIP Bird ventilators, ECG monitors, pulse oximeters, and an incubator. VIP Bird ventilators were donated to the Special Baby Care Unit (SBCU) at KH (since the old Infant Stars were now on their last legs). Again, a large supply of respiratory equipment was shipped in to Belize this time by ship. The equipment again arrived just in time. I was the only RCP on this trip. We brought a nurse, two physicians and a biomedical engineer. The biomedical engineer worked with the hospital's engineering staffs to again evaluate gas and electrical delivery systems and in the maintenance of the donated ventilators. We held classes on the "Belizean" version of Pediatric and Neonatal Advanced Life Support at Belize Institute for Management. Over 150 healthcare providers including doctors and nurses from the private and public sectors including KHMH and the district hospitals attended the course. I also visited the SBCU and Pediatric units at KHMH to again teach the nurses about ventilatory management.

In 2005, we made two visits to Belize. In the spring, I returned with another RCP, Jeanette Asselin who is the manager of the Neonatal/Pediatric Research Group at CHRCO. As before, we brought supplies and equipment. This time, equipment included large donations of catheters from Kimberly-Clark, sensors and oximeters from Nellcor, and much needed surfactant from Ross-Abbott. While I worked with equipment and did more inservicing, Jeanette reviewed logs of admissions to evaluate how the ventilation program was going. She subsequently developed a database and entered (with help) 4 years of admissions to the SBCU at KH. She returned in the fall to work on this and begin several other data projects with Dr Grinage to help them begin to evaluate and publish assessments of programs, such as ventilation, oncology and cardiology; and other things like the incidence of some congenital anomalies. At the American Association for Respiratory Care Congress in December 2005, we presented some of our preliminary data on the Belize ventilation program and incidence of the survival of ventilated term and premature infants.

As part of our commitment to this endeavor, I joined with a physician here at CHRCO, Jeri Idowi MD, who formed a medical missionary group called Medical C.A.R.E. (Care for All Races Everywhere). In addition to our trips to Belize, we have brought our educational and clinical expertise to Nigeria. This spring we will have traveled to the University College Hospital in Ibadan, Nigeria, to start a teaching program to include both mechanical ventilation of infants and repair of simple heart defects. Our hope is to continue support to both Belize and Nigeria and perhaps expand our programs to other countries as well.

I would like to acknowledge Jeanette Asselin for her contribution in the preparation of this article.

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Monitoring Hypoxia: One Step Beyond PaO_2

Bruce Toben, RRT, NPS; Marcia Zucker, PhD

INTRODUCTION

The basic objective of the heart and lungs is to provide adequate oxygen for aerobic metabolism at the cellular level. This biologic imperative is a multi-organ system function that requires continuous interaction between pulmonary, cardiovascular, hematologic and cellular physiologies. The overall process of oxygen transport from inspiring ambient gas through electron transfer in the mitochondria is efficient, performing well in steady state, exercise and conditions of reduced metabolic requirements. However, when pathophysiologic conditions alter any part of the oxygen transport system, such that oxygen supply does not meet oxygen demand, cellular function can be adversely affected.

Traditionally, the measurement of PaO_2 (partial pressure of arterial oxygen) has been used as a clinical marker of oxygen supply. From this laboratory value, determinations of oxygen need are commonly made and criteria for various interventions are set. However, assessments and therapies solely centered on this one analytical measurement may not yield the desired understanding of the cellular end-effect because PaO_2 is only one factor in determining adequate oxygen supplies available for metabolism. Instead, those charged with the responsibility of patient care must investigate all avenues of oxygen transport and monitor those criteria best aligned with the etiology(s) of the hypoxic event.

OXYGEN TRANSPORT

The partial pressure of inspired oxygen (PiO_2) is characterized by the total atmospheric pressure or barometric pressure (P_B). At sea level the PiO_2 is 159 mmHg and represents approximately 21% of the P_B. During inspiration, atmospheric gas is warmed to 37°C and mixes with water vapor and carbon dioxide. The altered gas composition is reflected in a diluted partial pressure of alveolar oxygen (PAO_2), estimated to be ~103 mmHg. Oxygen passively diffuses across the alveolar-capillary membrane, dissolving in the plasma (PaO_2) and binding to the hemoglobin molecule (Hb) within the erythrocyte. Thebesian veins carrying deoxygenated blood from the myocardium empty into the left heart and contribute to a small anatomic shunt, resulting in a PaO_2 of approximately 100 mmHg. Systemically, arteries divide, reducing their diameter as they disseminate through organs and tissues reducing to arterioles and then transitioning into capillaries with an average PO_2 of 35 mmHg. The capillary network provides blood supply to the cells. Oxygen is liberated from hemoglobin and transported through the cell membrane to the mitochondria, where cytochrome oxidase catalyzes the oxygen reduction. Throughout this process, oxygen serves as an electron acceptor, necessary in oxidative phosphorylation, the synthesis of ATP for energy production. The mitochondrial PO_2 range is between 4-20 mmHg and is conducive to aerobic metabolism.[1] Intracellular PO_2 levels below this point produce anaerobic glycolysis with the production of lactate. The oxygen cascade (Figure 1) highlights the oxygen transport sequence and common causes that lead to decreased intracellular oxygen concentrations.

HYPOXEMIA

A reduction in *arterial blood* oxygen levels is referred to as "hypoxemia." Clinically significant hypoxemia is defined by a PaO_2 of <55 mmHg, predicted by the PiO_2 and age, but often decreases due to altered physiology and disease processes. Hypoxemia can also be described as an arterial oxygen saturation (SaO_2) <88%, or an arterial oxygen content (CaO_2) <17.8 vol%. Short term physiologic responses to hypoxemia range from elevated levels of dyspnea and anxiety, to tachypnea and tachycardia, to glucose intolerance.[2] Prolonged effects of hypoxemia include pulmonary artery hypertension, polycythemia, and altered chemosensitivity of the skeletal muscles.[3] If the severity of hypoxemia is allowed to persist, pathology will develop as a consequence of reduced oxygen at the cellular level, hypoxia, as opposed to just a decrease of oxygen measured in the arterial blood (hypoxemia). As hypoxemia progresses to hypoxia, the physiologic responses become more profound (Table 1). Increases in the acuity of the patient's overt symptoms are not necessarily reflective of this

The authors are with the Clinical Affairs Division, International Technidyne Corporation. The authors wish to acknowledge Danielle DeMilia for assistance in developing the graphical illustration.

Table 1: Physiologic Responses: Hypoxemia vs. Hypoxia

Hypoxemia	Stimulates peripheral chemoreceptors (carotid and aortic bodies) Increases ventilation
	Increases pulmonary vascular resistance (PVR) Increases pulmonary vasoconstriction Increases blood viscosity through increased hematocrit
	Stimulates hematopoiesis Increases RBC production Increases 2,3 diphosphoglycerate
	Alters afferent nerve skeletal muscle activity Produces muscle fatigue
	Alters metabolism Causes glucose intolerance
Hypoxia	Disrupts normal cellular function Inhibits glucogenesis; metabolism of glucose to ATP
	Promotes anaerobic glycolysis Increases lactate production, non-volatile metabolic acidosis
	Retards CNS function Blunts cognitive behavior Impairs hand-eye coordination
	Advances tissue /organ dysfunction Promotes early cell death

important physiologic transition. Further investigation exploring the elements of hypoxemia allows the accurate diagnosis and treatment of the hypoxemic/hypoxic patient.

HYPOXIA

Hypoxia is defined as a reduction in *cellular* oxygen concentration. Traditionally, hypoxia is classified into four pathophysiological groupings: hypoxic, anemic, stagnant, and histotoxic. The commonality in all four hypoxic categories is insufficient oxygen available to the mitochondria for normal aerobic metabolism. As a consequence, hypoxic events trigger various physiologic responses which have both protective qualities and untoward reactions. The formulas found to be clinically valuable in the diagnosis and management of hypoxia are discussed in detail below and are presented in Table 2.

Hypoxic Hypoxia is a reduction in cellular oxygen due to a supply issue. This can be observed when a patient is subjected to: low P_B, sub-ambient oxygen concentrations (<21%), airway obstruction, V/Q mismatch, restrictive pulmonary disease or thickened alveolar-capillary membrane disorders. These conditions not only cause hypoxemia, but also promote hypoxia. When evaluating patients being treated for acute hypoxic hypoxia, interpretation of PaO_2 must be relative to the supplemental oxygen being used for therapeutic support. One monitoring tool used to provide insight into the degree of acuity is the alveolar-arterial oxygen gradient ($P(Aa)O_2$). This is the difference between the calculated PAO_2 and the measured PaO_2. The normal gradient varies from 50 to10 mmHg when breathing an FiO_2 (fractional concentration of inspired oxygen) between 1.0 - 0.21, proportionally. The gradient significantly widens with the severity of cardiopulmonary disease and is useful to trend when tracking the effects of ventilation and oxygenation maneuvers. Some clinicians do not find this monitoring tool effective because of variations derived with age and the full array of FiO_2's.[4] Additionally, the $P(A\text{-}a)O_2$ requires the input of the respiratory quotient which is technically difficult to measure on critically ill patients and the standard 0.8 value is often inappropriate for postoperative, septic and trauma victims.[5] Another formula commonly used to assess the degree of oxygen impairment is the P/F ratio. This calculation sets a relationship between the PaO_2 and the FiO_2. A P/F ratio <200 is used to define the oxygenation criteria for ARF (Acute Respiratory Failure).[6] Over recent years, the development of unique neonatal/pediatric therapies has led to the creation of the oxygen index (OI), an oxygenation expression to further define pulmonary dysfunction on mechanically ventilated patients. Combining both oxygen and mean airway pressure (MAP) indices, the OI has been found to be beneficial as a decision making criterion when implementing both nitric oxide[7] and ECMO[8] therapies. The value of incorporating the MAP into the OI links the contribution of ventilator induced lung injury with the diagnostic evaluation process. The OI has been used as a prognostic indicator in children with ARDS (adult respiratory distress syndrome) adding to its clinical value.[9,10]

Anemic Hypoxia is a reduction in cellular oxygen due to a loading issue. In this type of oxygen transport deficiency there is ample exchange of gas across the alveolar-capillary membrane; however, there is an insufficient concentration of functional hemoglobin to carry the oxygen to the tissues. Anemic hypoxia is a red blood cell (RBC) or Hb driven

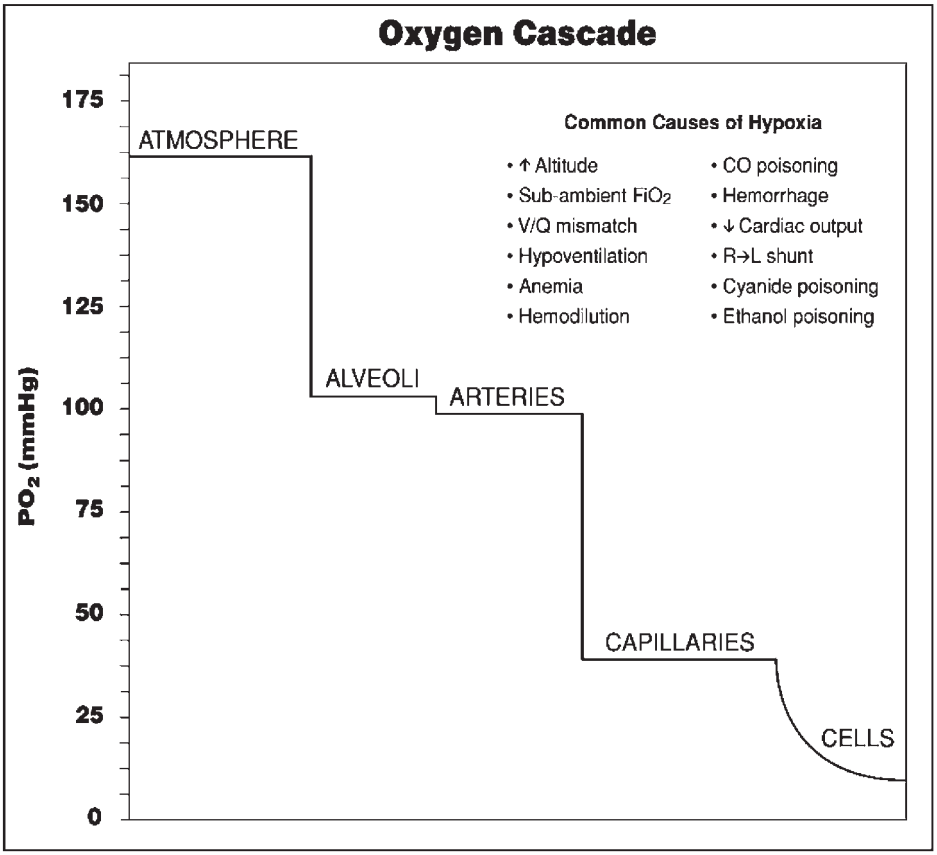

Figure 1: Oxygen Cascade

deficiency, rarely affecting the oxygen carrying contribution of the plasma. Consequently, anemic hypoxia often exists without notable reduction in PaO_2, and therefore measuring the PaO_2 alone can be misleading in estimating the degree of tissue insult due to reduced oxygen availability. Anemia, carbon monoxide poisoning and marked reduction in hematocrit from hemodilution (often seen with cardiopulmonary bypass pump priming solutions) are common causes of anemic hypoxia. The best mechanism to monitor this type of hypoxia is by assessing CaO_2 because it includes Hb as a primary variable in the equation. Through this calculation, effects of therapies, ie, blood transfusions and interventions to control homeostasis, can be easily appreciated by observing an increase in the oxygen carrying capacity of the blood.

Stagnant (hypokinetic) Hypoxia is a reduction in cellular oxygen due to a transport issue, moving the oxygen load from the pulmonary capillaries to the tissue. Once sufficient oxygen diffuses into the blood and an adequate amount of Hb is saturated with oxygen, a minimal cardiac output is required to ensure the cells receive the oxygen in a timely manner. Pathologies promoting stagnant hypoxia fail to meet these minimal circulatory requirements. Cardiogenic shock, significant polycythemia and persistent fetal circulation are examples of cardiovascular and hemodynamic conditions where oxygen supply may not meet tissue demand. The oxygen delivery (DO_2) formula integrates cardiac function and CaO_2 to measure the dynamic characteristics of the oxygen transport system. When pharmacologic interventions are applied that alter ventricular function, or ventilator setting adjustments are made that could influence right heart filling, the monitoring of DO_2 can be strategic to ensure positive outcomes. Under steady state conditions, uptake of oxygen from the arterial blood represents the oxygen consumed by cellular metabolism. The fraction of oxygen uptake (VO_2) from the oxygen delivered is the oxygen extraction ratio (OER). Oxygen extraction is never 100% in any tissue, and the extraction capability differs between tissues but averages approximately 0.28. When DO_2 decreases and oxygen extraction reaches its maximum, an oxygen debt will develop in the tissue. As a result, anaerobic metabolism with increased production of lactate will ensue. As a practical guideline in acutely ill patients, if OER exceeds 0.65-0.75 for a prolonged period of time, inadequate tissue oxygenation and consequent organ dysfunction is likely.[11] The mixed venous oxygen content ($C\bar{v}O_2$) and the arterial-mixed venous oxygen content difference ($Ca\text{-}\bar{v}O_2$) are another set of integrated calculations that increase when cardiac output is diminished resulting in hypoxia. These trends rise due to reduced capillary transit time with normal or elevated oxygen uptake. As a compromised cardiovascular system begins to return to normal, DO_2 increases and the systemic effects of hypoxia improve. Observation of the return to normal values of the $C\bar{v}O_2$ and the $Ca\bar{v}O_2$ can add supplemental confirmation to the course of corrective actions.

Histotoxic Hypoxia is a reduction in cellular oxygen due to a utilization issue. In this form of oxygen defect, normal ambient gas composition is inhaled through unobstructed airways, diffusion through the alveolar-capillary membrane is unimpeded, oxygen is properly bound to Hb, and cardiovascular physiology is normal. However, once oxygen arrives at the cell, there is either an inability to unload oxygen from Hb or a defect in the transport mechanism to move oxygen through the cell

Table 2: Formulas to Monitor Hypoxia

Monitor	Symbol	Formula	Normal Values
A - a gradient	$P(A\text{-}a)O_2$	$[(P_B - PH_2O) \times FiO_2] - (PaCO_2 \div R)$	< 50 mmHg[+]
PaO_2 / FiO_2 ratio	P/F ratio	$PaO_2 \div FiO_2$	> 400
Oxygen index	OI	$(FiO_2 \times MAP) \div PaO_2$	n/a
Arterial oxygen content	CaO_2	$(Hb \times 1.34^{++} \times SaO_2) + (PaO_2 \times 0.003)$	> 20 vol%
Mixed venous oxygen content	$C\bar{v}O_2$	$(Hb \times 1.34^{++} \times S\bar{v}O_2) + (P\bar{v}O_2 \times 0.003)$	15 vol%
Arterial - mixed venous oxygen content	$C(a\text{-}\bar{v})O_2$	$CaO_2 - C\bar{v}O_2$	5 vol%
Oxygen delivery	DO_2	$CI \times CaO_2$	520 mL O_2/min/m^2
Oxygen uptake	VO_2	$CI \times Ca - \bar{v}O_2$	131 mL O_2/min/m^2
Oxygen extraction ratio	OER	$DO_2 \div VO_2$	0.25-0.30

A = alveolar, a = arterial, C = content, CI = cardiac index (cardiac output body surface area), CO_2 = carbon dioxide,
D = delivery, F = fractional concentration, Hb = hemoglobin, i = inspired, MAP = mean airway pressure, O_2 = oxygen,
P = partial pressure, P_B = barometric pressure, PH_2O = water vapor tension (47 mmHg at 37°C),
R = respiratory quotient (CO_2 production O_2 consumption, normal = 0.8), S = hemoglobin saturation,
V = volume, $\bar{v}$ = mixed venous
[+] = Normal value when breathing an FiO_2 of 1.0. If FiO_2 is 0.21, normal value 10-15 mmHg.
[++] = Oxygen-carrying capacity of hemoglobin reported as 1.34, 1.36 and 1.39 mL O_2/g Hb.

membrane into the mitochondria. Oxygen must be continuously replenished within the mitochondria to allow electron transport for oxidative phosphorylation and the synthesis of ATP. Cyanide, hydrogen sulfide and ethanol poisoning disrupt cytochrome oxidase,[12] the enzyme responsible for cellular oxygen transport, and are therefore etiologies of histotoxic hypoxia. When cardiac reserve is good, but apparent signs of hypoxia are present, a significant narrowing of the $Ca\bar{v}O_2$ can be a valuable indicator of histotoxic hypoxia, in addition to a lower than expected OER. The extent of oxygen extraction or cellular uptake can be trended with both the OER and $Ca\bar{v}O_2$ formulas as corrective actions are applied to counter the effects of cellular toxins. If these interventions are effective, the $Ca\bar{v}O_2$ begins to return to its normal base line, approximately 5 vol% while OER elevates to normal levels.

COMBINED HYPOXIC EVENTS

Often hypoxic patients exhibit multiple sources for their oxygen deprivation. Those with COPD (chronic obstructive pulmonary disease) may show defects from V/Q mismatch (hypoxic hypoxia) and cor pulmonale (stagnant hypoxia). Victims of smoke inhalation may suffer from airway edema/obstruction (hypoxic hypoxia), carbon monoxide poisoning (anemic hypoxia) and cyanide toxicity (histotoxic hypoxia). Premature infants of very low birth weight commonly present with respiratory failure from surfactant deficiency (hypoxic hypoxia), persistent fetal circulation (stagnant hypoxia) and >95% fetal Hb (promoting reduced unloading of oxygen from Hb at the cellular level - histotoxic hypoxia). Since these mixed conditions can add to the complexity of patient management, careful interpretation of blood gases and oxygen monitoring formulas is critical in assessing acuity and governing therapeutic interventions.

EVALUATION OF PaO_2

If the effects of hypoxia go undetected and unresolved, morbidity significantly increases, eventually leading to death. Monitoring the systemic symptoms of hypoxia, regardless of cause, requires analysis of PaO_2 in conjunction with other relevant clinical markers. Traditionally, when blood gas specimens are sent to the laboratory for PaO_2 analysis, there is an inherent delay in the availability of results.[13] This leads to a postponement in critical treatment decisions due to combinations of various elements including: transportation of the sample, logging the specimen appropriately within the laboratory data management system, analysis, and results reporting. In the critical care setting, assessing the effectiveness of interventions to counter hypoxia mandates real-time knowledge of PaO_2 and such delays can hinder outcomes. Some therapies produce immediate alterations in cardiopulmonary function and precise titration of these interventions are required. Inhaled nitric oxide, heliox therapy, HFOV, APRV, PEEP and ECMO are examples of aggressive treatments that require close monitoring and supervision of PaO_2. In the surgical arena procedures that can compromise cardiopulmonary function, ie, lung volume reduction, repair of cardiovascular anomalies, coronary artery grafting and valve repair, also necessitate blood gas measurements in a timely manner. One method documented to reduce the turnaround time of results is the use of bedside point-of-care (POC) devices.[14] These instruments can accurately analyze a blood gas specimen in under 90 seconds, frequently including logging the patient/sample into a data management system and reporting both measured and calculated analytes.[15] Due to the use model in POC testing, the time and costs associated with specimen transport are removed from the sample measurement process, potentially providing clinical and financial benefits to the patient and institution.

SUMMARY

Providing oxygen to the metabolic pathway is a fundamental requirement and the primary function of the cardiovascular and

pulmonary systems. Hypoxia can have various etiologies including a decreased PAO_2, reduced gas diffusion across the alveolar-capillary membrane, decreased hemoglobin oxygen carrying capacity, diminished cardiac output and a defect in cytochrome oxidase. Each set of hypoxic events requires its own unique monitoring tools, although analysis of PaO_2 is common to all. It is essential that hypoxia, regardless of cause, be assessed and treated in a time-critical manner to avoid long term sequelae, morbidity and death. Bedside POC testing has the capability to improve outcomes through reduced turnaround times, giving the clinician accurate, timely results to incorporate with other bedside physiologic data to completely assess the hypoxic patient.

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Noninvasive Ventilation: Should Half Your Extubated Patients Receive NIV?

Paul Garbarini, MS, RRT, Clinical Applications Manager

There is sufficient evidence based literature to support the routine use or at least a trial of Noninvasive Ventilation (NIV) in patients with COPD, hypercapnic respiratory failure and immunocompromised patients. There have been numerous studies examining the efficacy of NIV in reducing re-intubation rates. Most of these studies on NIV have centered on avoidance of intubation and its associated morbidity. The January 15th issue of the Journal of Respiratory and Critical Care Medicine features a thought provoking NIV randomized controlled trial, Early Noninvasive Ventilation Averts Extubation Failure in Patients at Risk: A Randomized Trial http://ajrccm.atsjournals.org/cgi/content/abstract/173/2/164. One hundred sixty two (162) patients were enrolled. Reasons for MV included 30% chronic respiratory disorders, 22% pneumonia, 16% CHF, 11% neurologic disease, 9% sepsis, 7% post-op respiratory failure and "other." Baseline characteristics appeared equivalent between the control and NIV groups. Enrollment criteria included a minimum of 48 hours of prior MV and successful completion of a spontaneous breathing trial. Exclusion criteria were based on contraindications to NIV. The primary study end-point was the decrease in respiratory failure after extubation. This study stands out in several aspects:

- Patients were started on NIV immediately post-extubation rather than after post-extubation respiratory failure ensued. NIV was maintained for 24 hours post extubation (avg. 19 hours).
- NIV was applied continuously.
- All patients who met any of the following criteria were placed on NIV - Age greater than 65 years, cardiac failure was the cause of intubation or APACHE-II score of > 12 on day of extubation. Not surprisingly, 45% of all extubated patients met criteria for NIV post-extubation.

Some previous studies that examined the effect of NIV in avoiding post-extubation respiratory failure failed to show a benefit, but they initiated NIV after respiratory failure developed. The results were:

- Respiratory failure after extubation decreased 50% in the NIV group. (p 0.029)
- Reintubation rate decreased 50% in the NIV group (p 0.12)
- ICU mortality was 3% in NIV group vs. 14% in controls (p 0.15). There was not a significant decrease in hospital mortality overall; however, patients with hypercapnia during the SBT did demonstrate reduced reintubation rate, hospital mortality and 90 day survival.

The authors noted that this study differs from previous trials in that a higher proportion of patients had chronic respiratory disease. This further supports the use of NIV in patients with hypercapnia.

COMMENTS

As the authors note, this study does not support routine early use in all patients post extubation deemed "at risk" (per authors criteria, eg age, APACHE, etc.) without further trials, but does provide additional support for early NIV in hypercapnic patients.

During the SBT, the average f/Vt was only 75, so it appears these patients were not what I would consider "borderline." It would be interesting to stratify the patient outcomes by f/Vt and see if there was any correlation between f/Vt and hypercapnia as the reported standard deviation in f/Vt was ~36 (~50%).

PRACTICAL IMPLICATIONS

Should all at risk patients be placed on continuous NIV immediately post extubation? Based upon these study results, I would speculate that the cost-benefit ratio of such an approach in at least hypercapnic patients should be considered. The complications associated with NIV are minimal. In the current study the authors noted nasal bridge damage in 6% of patients and gastric distention in 1% of patients. Even the study group as a whole showed some benefit with early prophylactic NIV.

Resource allocation requires availability of NIV immediately post extubation. Most facilities have a limited number of dedicated NIV ventilators. (This study utilized a dedicated acute care NIV machine and the authors correctly noted that use of "table top BIPAP devices" (my paraphrase) have been shown to not perform adequately in maintaining target pressures when utilized for ventilation (as opposed to CPAP for sleep apnea applications). Yet many facilities employ such devices in the ICU and if acute care NIV machines are utilized, they are often all in use or there is a significant delay in locating an available unit. Routine use of NIV would require significant capital investment in dedicated acute care NIV ventilators which typically average $10,000. An alternative approach would be to utilize an ICU ventilator, which provides a dedicated NIV mode. These ventilators should incorporate leak compensation algorithms/adjustment capabilities. Such devices are now available and make the immediate transition to NIV much more practical in that the same ventilator and circuit are utilized. [Disclaimer: Hamilton Medical does have available several invasive ventilators with dedicated NIV modes.]

The author is with Hamilton Medical.

Still an Option for Today's Neonates - A Primer

Justin Tse, RRT-NPS

Before 1971, many premature infants died in the US due to respiratory distress syndrome (RDS). In 1971, Gregory and associates introduced CPAP to the neonatal population. Neonate's mortality decreased with the adoption of CPAP. Since then, many ways to administer NCPAP to neonates have evolved. So has our understanding of NCPAP's effects on neonatal physiology. I am going to give a brief overview of NCPAP and the physiologic effects on the premature population. First, the pathogenesis of respiratory distress in infants is complicated and requires a brief explanation. Prematurity leads to decreased surfactant synthesis and release. This in turn leads to an increase in alveolar surface tension and decrease in alveolar surface area (atelectasis). Atelectasis results in hypoxemia, hypercarbia, and acidosis (both respiratory and metabolic). Due to atelectasis, an increase in pulmonary vascular resistance and vasoconstriction occur leading to pulmonary capillary leak and to formation of hyaline membranes. Many physiologic effects occur due to NCPAP application. These include lung mechanics and volume, gas exchange, and cardiovascular function. We should also understand that inadequate or excessive levels of CPAP can worsen clinical status. Decreased lung compliance secondary to atelectasis, decreases FRC which increases work of breathing. This decrease in FRC also increases V/Q mismatching. By applying appropriate levels of CPAP, FRC is increased. This reduces work of breathing, improves ventilation and V/Q mismatch. Improving V/Q mismatch improves gas exchange. Hypoxemia and hypercarbia are corrected due to increased alveolar surface area. Appropriate levels of CPAP bring intrathoracic pressure back to normal which helps normalize vascular resistance and improve cardiac function. Inappropriate high levels of CPAP can cause overdistension of normal alveoli which increases intrapulmonary shunting as well as decrease cardiac output by decreasing venous return and leads to phyoxemia. Underdistention of alveoli can also lead to the same problems alluded to before.

The AARC Clinical Practice Guidelines list the following as indications for NCPAP.

- Abnormalities on physical examination — the presence of increased work of breathing as indicated by an increase in respiratory rate of > 30% of normal, substernal and suprasternal retractions, grunting and nasal flaring; the presence of pale or cyanotic skin color and agitation.

- Inadequate arterial blood gas values — the inability to maintain a PaO_2 greater than 50 torr with FIO_2 of $\leq$0.60 provided VE is adequate as indicated by a $PaCO_2$ of 50 torr and a pH$\geq$7.25.

- The presence of poorly expanded and/or infiltrated lung fields on chest radiograph.

- The presence of a condition thought to be responsive to CPAP and associated with one or more of the clinical presentations described above: respiratory distress syndrome, pulmonary edema, atelectasis, apnea of prematurity, recent extubation, tracheal malacia or other similar abnormality of the lower airways, and transient tachypnea of the newborn.

- Early intervention in conjunction with surfactant administration for very low birth weight infants at risk for developing respiratory distress syndrome.

- The administration of controlled concentrations of nitric oxide in spontaneously breathing infants.

The AARC guidelines also list the following contraindications:

- Although application of continuous positive airway pressure to neonates and infants by nasal prongs (NCPAP), nasopharyngeal tube (NP-CPAP), and infant nasal mask (NM-CPAP) have been used in bronchiolitis, this application may be contraindicated.

- The need for intubation and/or mechanical ventilation as evidenced by the presence of: Upper airway abnormalities that make NCPAP, NP-CPAP, or NM-CPAP ineffective or potentially dangerous (e.g., choanal atresia, cleft palate, tracheoesophageal fistula); Severe cardiovascular instability and impending arrest; Unstable respiratory drive with frequent apneic episodes resulting in desaturation and/or bradycardia; Ventilatory failure as indicated by the inability to maintain PaCO2 <60 torr and pH>7.25

- Application of NCPAP, NP-CPAP, or NM-CPAP to patients with untreated congenital diaphragmatic hernia may lead to gastric distention and further compromise of thoracic organs.

Since its inception in 1971, CPAP has been widely used for the treatment of neonates. It has had its ups and downs over the years but still remains a useful therapy for the treatment of the neonate. The usefulness of CPAP has increased over the years with technological improvements in airway monitoring and with the interface equipment (newer nasal prongs, masks, as well as better techniques in securing the equipment to the patient). As technologies improve, so should our understanding of the interaction of these technologies to neonatal physiology.

The author is Clinical Implementation Specialist, Hamilton Medical

Co-Sleeping Through the Night: SIDS and Homecare

Lauren Gabbaian

Speaking to an average American mother about the practice of regularly sleeping in the same bed as an infant might elicit a grimace and other signs of distaste. Common concerns about co-sleeping include the perceived risk of rolling over and smothering the child, intrusions on parental intimacy and the impact to the unconscious of the infant's witnessing its parents having sex, the future independence of the child, the perceived increased risk of infection for both the parents and the child, and the potential difficulty of breaking the child of the habit when the parent feels it's time. The American Academy of Pediatrics (AAP) has even increased fears of co-sleeping by publishing reports of an increased risk of Sudden Infant Death Syndrome (SIDS) in infants sleeping in adult beds.[1,6,9] Parenting folk wisdom since the early 1900s has dictated that children should sleep away from their parents as soon as possible; studies by parenting gurus from Freud to Benjamin Spock, to Richard Ferber in the mid-1980s, have only reinforced the desirability of such a practice. However, recent research and books by co-sleeping expert William Sears and others have attempted to prove that the benefits of co-sleeping should make it the preferred infant-parent sleeping arrangement in the United States. Advantages include greater ease in breast-feeding, enhanced mother-child bonding, more secure attachment style, less incidence of thumb-sucking, the need for fewer child security objects, and even, paradoxically, a decreased risk of SIDS when certain precautions are taken, as co-sleeping advocate James McKenna has pointed out.[3]

Cross-culturally, the United States is an anomaly in terms of its sleeping practices. In a study conducted by Burton & Whiting,[7] out of 100 communities sampled, the United States was the only one in which children slept in entirely separate rooms from their parents and were typically trained to do so at six months.[4,7] This can be attributed in part to the studies of Richard Ferber, whose book, Solve Your Child's Sleep Problems, has been reprinted 45 times since its initial publication in 1985.[2] Ferber's work has largely advocated the "controlled-crying method," by which parents would familiarize their children with sleeping alone and through the night by having them sleep in nearby but separate rooms and gradually reducing late night contact until the child is fully capable of self-soothing. Ferber claimed in one article that the entire process of familiarization could be "easily carried out" within a week[2] despite evidence that in many cases it took significantly longer. For example, the process was dramatized in a special, hour-long episode of the sitcom "Mad About You." For the better part of the episode only Paul (Paul Reiser) and Jamie (Helen Hunt) are visible, agonizing outside a closed door, behind which their child Mabel shrieks away; they wait each time with more anxiety for the moment they will be allowed to open the door to coo at their baby and do whatever else they can think of to alleviate her tears (without picking up or even touching) in the space of an always-too-short and regulated period of time. Until recently, many parents believed they had no other choice but to go through this heart-wrenching experience if they wanted a healthy, well-adjusted, independent child. Despite the pain involved in the process of conditioning a child, Ferber's book was seen as the be-all end-all method of sleep conditioning for the better part of two decades.

Perhaps the greatest concern parents have had with the idea of co-sleeping comes from the parental desire to maintain some level of sexual intimacy and the fear that the infant's witnessing the "primal scene" (scene of parental sexuality)[8] would negatively affect his or her little unconscious. An episode of "Sex and the City" comes to mind, where Miranda, the single mother, leaves her darling Brady in the care of her exceedingly maternal and married friend, Charlotte. In the process of having sex with her husband, Charlotte spots a wakeful baby in his crib across the room and goes crazy, thinking she's scarred the child for life. When Charlotte calls her friend to confess, Miranda replies calmly that it was very unlikely that Brady knew what he was seeing, or that he would be able to remember it in the future. Real-life pediatrician and co-sleeping advocate Rachel Kramer echoed Miranda's reassurances, adding her belief that the effect of seeing parents naked or in the act was probably no more deleterious than that of seeing a snippet of TV violence inadvertently. While this is partially true, an 18-year longitudinal study found that late-adolescent women who had witnessed a

Lauren Gabbaian is associate editor of Respiratory Therapy.

"primal scene" were more likely to have gotten an STD or to have become pregnant. Exposure to parental nudity made women slightly more likely to have used certain drugs. However, the opposite effects were seen in men (ie, men saw a reduced likelihood of sexual "problems," etc). When viewed in this light, it seems Brady is lucky to have been a boy!

DEATH-BED?

Another study, released in 1999 by the Consumer Products Safety Commission (CPSC), found that between the years 1990 and 1997, 660 children under the age of 2 years (more than 75% younger than 3 months) had died sleeping in an adult bed, and that nearly 25% of the deaths had been specifically attributed to suffocation after someone had rolled over them. The remainder of the deaths were caused by strangulation or suffocation by relatively common items in an adult bed, like pillows and headboards.[3,8] The 2005 AAP study mentioned earlier provided evidence that the risk of SIDS was increased for co-sleeping children and advised parents to have children sleep only on their backs, in a separate bed in the same room, and be put to sleep with a pacifier at between a month and a year of age—after proper breastfeeding procedures have been established and before dental problems arise.[6]

Co-sleeping advocates were quick to answer to the two studies, however, by first pointing out that the 64 deaths by SIDS in adult beds are still decidedly fewer than the approximately 2,500 lives claimed by SIDS per year in total.[3]

Second, co-sleeping advocates reinforce the fact that co-sleeping families must follow certain guidelines before letting baby sleep in the same bed. The bed must be firm (ie, no water beds), and there must not be anything fluffy lying on the bed, including pillows, stuffed animals, and big comforters, that might suffocate the baby. The bed must also fit snuggly within its frame, be positioned so that sides are not adjacent to any wall or near curtain cords, and must not have a head board, guard rails, or anything else in which the baby's head might get stuck, resulting in strangulation. To avoid some of these risks while maintaining the benefits of co-sleeping, parents often opt for a co-sleeper cot—a bed extension that looks like a crib with one side removed and which is attached to the parents' bed.[3,8,10] The AAP advocates this option over having the baby sleep in an adult bed.[10] Mothers are also strongly cautioned against smoking if she intends to co-sleep, as this is thought to be a risk factor in SIDS.

CO-SLEEP MAY PREVENT SIDS

Recent studies have revealed that co-sleeping may actually reduce the incidence of SIDS. For example, Japan is said to have some of the lowest rates of SIDS in the world,[3] and parents there often co-sleep with their children until they are *15 years old*.[7]

But why does co-sleeping have such a large effect on the prevalence of SIDS? McKenna (as cited in Greenfield & Suzuki)[4] argued that SIDS is caused by an underdeveloped breathing system, and that in sleeping next to mom, baby can better learn to regulate the system. McKenna & Mosko's more recent research shows that infants who co-sleep wake up more frequently than "near-miss" SIDS infants and SIDS victims' siblings. This data would seem to imply that a key factor in SIDS is a difficulty in switching from being asleep to being awake. The mother's being so close in the co-sleeping environment, and thus her increased responsiveness, are possible factors in preventing SIDS.

Advocates of co-sleeping also spoke out against the implications of the CPSC study (ie, that parents cannot prevent themselves from rolling over in their sleep and suffocating their baby). As Dr. Kramer asks new mothers who are hesitant about co-sleeping, "Have you ever rolled over your husband?" Kramer says that mothers who breast feed have an acute awareness of their babies when they sleep, and avoid rolling over on them. However, the risk of roll-over is greatly increased if the co-sleeping adult is under the influence of drugs, alcohol, or anything else that may decrease awareness. Young children have not yet developed as sensitive a physical awareness as adults, so parents are also cautioned against co-sleeping with more than one child at a time. This warning is understood even in Mayan cultures where parents must quickly cycle each child from bed to bed to almost constantly accommodate for new additions to the family.[7] Therefore, if parents simply follow the guidelines for safe and effective co-sleep with their baby, bed-sharing does not have to be a deadly experience.

OTHER BENEFITS

In addition to the cancellation of much of the risk involved in co-sleeping, there are also many benefits to sleeping alongside a child. Greater ease in breastfeeding is a major factor in many families' decision to co-sleep. Advantages to breastfeeding include increased protection from contagious disease, infection, and different kinds of cancer for both the mother and the child. Breastfeeding also helps reduce the risk of SIDS—it is possible, according to Kramer, that because formula is digested more slowly than breast milk, babies sleep longer and have a more difficult time waking up. Such advantages have led the AAP to recommend at least one year of breastfeeding, and the World Health Organization to recommend at least two, Kramer said. But since a baby's immune system is not fully developed until five or six years of age, according to Kramer, the mother, must serve as the child's adjunct immune system by breastfeeding, and as such should maintain the process as long as possible. Any way to increase the length of the breastfeeding period, making it easier and more accessible, Kramer noted, is a step in the right direction. Having the baby sleep in another room is bad for both baby and mom in that they both end up fully awake and unable to easily return to sleep every time the baby gets hungry. With co-sleeping, on the other hand, all mom has to do is position baby to suck, and she can even go back to sleep while baby is feeding; neither party has to reach a full state of awareness, and will wake up fully rested in the morning, according to Kramer and confirmed by Morelli.[7]

Other major benefits of breastfeeding stem from the physical aspect of togetherness. Despite protests by Ferber and his followers, working and single mothers have co-slept with their babies for years as a means of maintaining the mother-child bond that may be loosened as mom goes to work during the day and that can be strengthened during the night. This is especially important as more and more women are entering the workforce and must increasingly juggle work and family. However, a more pressing, if not more paradoxical benefit can be seen in a study performed by Anisfeld, et al (as cited in Greenfield)[4] having to do with baby carriers: experimenters compared the effect on attachment of carrying a child in a baby carrier, with which there is a high level of physical contact, to placing a child in an infant seat, with which there is no physical contact. After an

average of 8 months using either one of the randomly assigned seats, it was found that children in the baby carrier were significantly more likely to be securely attached to their primary caregiver than children in the infant seat. This would seem to imply that physical closeness, as seen in the practice of co-sleeping, can lead to more self-sufficient and well-adjusted human beings in the future. (For more information on attachment theory, see Van Ijzendoorn & Sagi.)[11]

There is also strong evidence that points to the increased incidence of habits like thumb-sucking,[4] and the retention of security objects like blankets and dolls by children who do *not* co-sleep. Some Mayan parents simply laughed after hearing that American parents often have to sing their children to sleep, and Mayan children as young as 9 years of age expressed their pity at hearing about the "poor" American girls who have to sleep in their own rooms.[7]

All such hard-to-break habits and attachments to objects seem to serve only to replace the person the children really want sleeping next to them. As mentioned earlier, evening rituals, like lullabies and storytelling, are simply nonexistent in at least the Mayan culture, since mother and child and entire family always sleep at the same time: because nothing exciting is likely to happen after their parents are asleep, Mayan children are not reluctant to go to bed at night and bedtime rituals are simply not necessary. As Morelli put it, while Americans see sleeping as a time for closeness with a partner, people of other cultures seem to see sleeping as much more of a social event involving the entire family.

It is in stark contrast with co-sleeping families, therefore, that most American parents want their children on their own at such an early age. But the final concern of many potentially co-sleeping parents is how they will remove the child from the parents' bed after the habit of co-sleeping has been established. Kramer suggests moving the child when he or she is ready (ideally between 2 and 3 years old, though it may come down simply to when the parents want the child out), onto a mattress on the floor of the parents' room, and gradually moving the mattress closer to the door to acclimate the child to the idea of being separated from his or her parents. This is very similar to the system used by the Mayans, who, in preparation for a new addition to the family, will move the current co-sleeping child to another family member's bed. Kramer also mentioned that parents will often make the room sound more desirable by calling it something like "The Big Kid's Room." As Morelli reported in the case of the Mayans, Kramer said that the transition from co-sleeping to a child's own room is generally not a difficult one, but it varies from child to child.

In light of Ferber's and Sears' having softened their militant insistence on opposing parenting styles, and Ferber's having offered his approval of the formerly-despicable co-sleeping method, and much to the glee of failed Ferberizers and closet bed-sharers,[1] it is important to note that one size cannot possibly fit all in terms of a baby's sleeping arrangements. As both Ferber and Sears will undoubtedly emphasize in the upcoming revisions to their respective books,[1] each baby is different and the methods prescribed in any book may have to be tailored to fit the circumstances. Perhaps Kramer was slightly more to the point: "There are many more ways of being, than there are books out there." The mix-and-match individual parenting style may be just the thing to resolve the debate.

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A Short History of Spirometry and Lung Function Tests

129-200 AD: Galen did do a volumetric experiment on human ventilation. He had a boy breathe in and out of a bladder and found that the volume of the gas was, after a period, unchanged. Galen did no absolute measurement of lung volumes.

1681: Borelli tried to measure the volume inspired in one breath. He did this by sucking a liquid up a cylindrical tube. He already occluded the nostrils.

1718: Jurin J. blew air into a bladder and measured the volume of air in the bladder by the principles of Archimedes. He measured 650 ml tidal volume and maximal expiration of 3610 ml.

1727: Hales St. approves the results of Jurin, 3610 ml of maximal expiration. His method of measurement is not known.

1749: Bernouilli D. describes a method of measuring an expired volume.

1788: Goodwyn E. sucked water into a pneumatic vessel which was weighted on scales. He stated that the vital capacity could reach as much as 4460 ml. He corrected for temperature, but he did not use a nose-clip.

1793: Abernethy tried to determine how far expired gases had been depleted of oxygen. He collected the expired gases over mercury. Abernethy measured a vital capacity of 3150 ml.

1796: Menzies R. plunged a man into water in a hogshead up to his chin and measured the rise and fall of the level in the cylinder round the chin. With this method of body plethysmography he determined the tidal volume.

1799: Pepys W.H., Jr found the tidal volume to be 270 ml by using two mercury gasometers and one water gasometer.

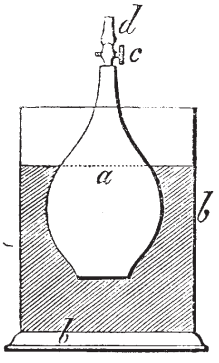
1800: Davy H. measured his own vital capacity 3110 ml, his tidal volume 210 ml with a gasometer and the residual volume 590-600 ml by a hydrogen dilution method.

1813: Kentish E. used a simple Pulmometer to study ventilatory volumes in disease. An inverted bell jar standing in water, with entry at its top controlled by a tap, and graduated in pints down the side.

1831: Thrackrah C.T. describes a Pulmometer similar to that of Kentish, but air enters the glass jar from beneath. There is still no correction for pressure, so that machine measures still not only respiratory volumes but also the power of the expiratory muscles.

1844: Maddock, A.B. publishes in the Lancet a letter to the editor about his "*Pulmometer, which I* [Maddock] *have found extremly useful for acertaining the power of the lungs under different circumstances and conditions.*" ... "*The principle of the machine was first suggested by the late Mr. Abernethy.*" Maddock did not mention Thrackrah or Kentish.

1845: Vierordt published his book "Physiologie des Athmens mit besonderer Rücksicht auf die Auscheidung der Kohlensäure." Even if Vierordt's main interest was the determination of the exhaled gases, he already did a very exact determination of the volumetric parameters. For his experiments he used an "Expirator." Vierordt already described some parameters still in use today in modern spirometry, like f.ex. residual volume ("Rückständige Luft"), vital capacity ("vitales Atmungsvermögen"), ...



1852 (1844): Hutchinson, John publishes his paper about his water spirometer which is still used today with little alterations only (major changes today are the addition of graphic and timing devices, and the reduction of the mass of the bell).

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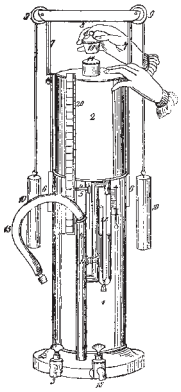
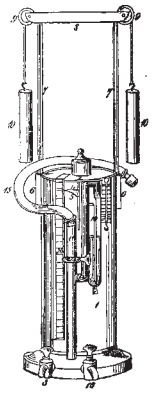
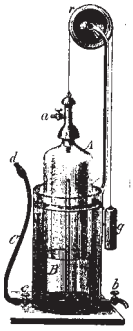




Hutchinson recorded the vital capacities of over 4000 persons with his spirometer. He classified the persons for example as *Paupers, First Battalion Grenadier Guards, Pugilists and Wrestlers, Giants and Dwarfs, Girls, Gentleman, Deseased cases.*. He showed the linear relationship of vital capacity to height and also showed that vital capacity does not relate with weight at any given height. Hutchinson had already started his work with spirometers in 1844.

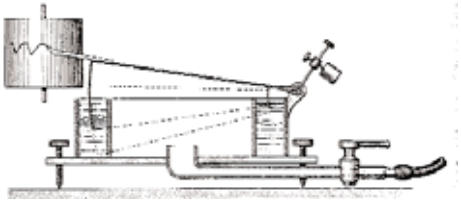


1854: Wintrich developed a modified spirometer, which was more simple to use than the spirometer of Hutchinson. Wintrich did an examination of about 4000 persons with his spirometer, thereof about 500 pathologic cases. He concluded that 3 parameters determine the vital capacity: body height, weight and age.

1859: Smith E. developed a portable spirometer and tried to measure gas metabolism.

1866: Salter added the kymograph to the spirometer to record time as well as the volume obtained.

1868: Bert P. introduces the total body plethysmography. He did intense experiments with animals in a closed plethysmographic system. He presented his studies to the Société de Biologie under the title "Changement de pression de l'air dans un poumon pendent les deux temps de l'acte respiratoire" [Alterations of the pulmonary air pressure during the two periods of respiration]. He did not do spirometric measurements together with the plethysmography, nor did he plethysmographic measurements on humans.



1879: Gad J. publishes a paper about the "Pneumatograph," which allows one to register additionally to the known parameters resulting from spirometric examination and also the volume changes of the thorax during inspiration and expiration: *Wer sich experimentell mit Fragen über die Mechanik der Athmung beschäftigt, wird bald das Bedürfniss empfinden, einen Apparat zu besitzen, welcher gestatted, die die Athmung begleitenden Volumenänderungen des Thorax aufzuschreiben*. Gad did an intense testing of his Pneumatograph with a rabbit before he did his first measurements of human respiration parameters. Additionally Gad suggested a new name for his Pneumatograph, *Aeroplethysmograph*.

1902: Brodie T.G. was the first using a dry bellow wedge spirometer, the precursor of the still today used Fleisch spirometer.

1904: Tissot introduces a closed-circuit spirometer.

1929: Knipping H.W. introduces a standardized method for spiroergometry. (Already in 1883 Speck C. had developed an ergometer called the '*ergostat*', 1896 Bouny E. had done studies using a first bicycle ergometer).

1959: Wright B.M. and McKerrow C.B. introduces the peak flow meter.

1969: DuBois A.B. and van de Woestijne K.P. present the whole body plethysmograph on humans.

1974: Campbell et al presents a cheap and light development of a peak flow meter.

SPIROMETRY AND PATIENT MANAGEMENT

In the first study of its kind, researchers found that the use of spirometry influences physician management of obstructive lung disease in a primary care practice. Researchers from Ottawa, Canada asked physicians in eight centers in Eastern Ontario, Canada, if they thought their patients (all current or former smokers) had airflow obstruction and if they planned to change the patient's management plan, before and after seeing the patients' spirometry test results. Of the 1,034 patients tested, spirometry results showed that 178 had airflow obstruction (17.4%), 93 of which had previously undiagnosed airflow obstruction (9%), and a prior diagnosis of airflow obstruction was reversed for 115 subjects (11%). In 154 of 1,030 cases (15%) physicians said they would change their management plans based on the results of the spirometry test results. The most common changes included counseling patients to stop smoking and changing medications. The study appears in the October issue of CHEST, the peer-reviewed journal of the American College of Chest Physicians (Chest 2005;128:2443-2447, © American College of Chest Physicians as "Spirometry in the Primary Care Setting – Influence on Clinical Diagnosis and Management of Airflow Obstruction," by Robert E. Dales, MD; Katherine L. Vandemheen, BSc; Jennifer Clinch, MSc and Shawn D. Aaron, MD). The study's objective was to determine if screening spirometry in the primary care setting influences the physician's diagnosis and management of obstructive lung disease. Diagnosis and management was assessed before and after the intervention of screening spirometry. Participants were a total of 1,034 patients who had ever smoked and were at least 35 years of age presenting to primary care practices for any reason. The setting was at rural primary care practices. Physicians were asked prior to and following presentation of spirometry test results if they thought airflow obstruction was present and if they planned to change management based on the results. A new diagnosis of unsuspected airflow obstruction was made by the physician in 93 patients (9%), and a prior diagnosis of airflow obstruction was removed after spirometry in 115 patients (11%). After viewing the spirometry results, physicians reported that they would change patient management in 154 patients (15%). Most planned management changes occurred when airflow obstruction was newly diagnosed (57 of 93 patients, 61%) and when the diagnosis of airflow obstruction remained unchanged (80 of 195 patients, 41%). A 6-month chart review documented the addition of respiratory medications in 8% of patients. The study concluded that screening spirometry influences physicians' diagnosis of airflow obstruction and management plans especially in patients with moderate-to-severe obstruction.

Neonatal Pneumothorax: Comparison Between Neonatal Transfers and Inborn Infants

Daniele Trevisanuto, Nicoletta Doglioni, Paola Ferrarese, Stefania Vedovato, Erich Cosmi, and Vincenzo Zanardo

ABSTRACT

Objective: To assess the differences in clinical characteristics, management, and outcome between the neonatal transfers and inborn neonates with pneumothorax.

Methods: The records of 36 neonatal transfers (Group A) and 25 inborn (Group B) neonates with symptomatic pneumothorax were retrospectively analyzed.

Results: In Group A, gestational age (36 ± 2 vs. 31 ± 4 weeks; P < 0.01), birth weight (2720 ± 537 vs. 1736 ± 1028 g; P < 0.01), exclusive oxygen-therapy before the event (47% vs. 20%; P < 0.05) were significantly higher than in Group B. The need of resuscitation at birth (19% vs. 44%; P < 0.05), conventional mechanical ventilation (20% vs. 56%; P < 0.05, presence of associated major congenital malformations (0% vs. 20%; P < 0.01), length of hospital stay (9 ± 6 vs. 32 ± 32 days; P = 0.01) and mortality (0% vs. 16%; P = 0.01) were significantly lower in Group A than in Group B.

Conclusions: Neonatal transfers and inborn neonates with pneumothorax have different clinical characteristics and outcome. This information could be useful for all persons involved in the interhospital care of perinatal patients.

INTRODUCTION

Neonatal transport teams should be prepared to intervene in a wide range of emergency situations.[1,4] Pneumothorax is a life-threatening condition requiring prompt diagnosis and treatment and is far more frequent in the neonatal period than in later life. The incidence varies widely depending on selective features such as frequency of neonatal asphyxia, techniques of resuscitation, incidence of respiratory problems, methods of administering assisted ventilation, and even the quality of X-ray examinations and experience of personnel interpreting these images.[5,6]

The authors are with the Pediatric Department, Medical School, University of Padova, Padova, Italy. Reprinted from J Perinat Med 2005;33(5):449-54. © Walter de Gruyter 2005.

The characteristics of neonates with pneumothorax born in high level care centers were previously reported.[7,8,10] However, there is a lack of information about infants with pneumothorax born in low-level care hospitals in need of transfer. We hypothesized that the clinical features, management, and outcome could be different between these two groups. This information could be useful for the neonatal transport team components and, in the context of an outreach education program, could reinforce the cooperation between all persons involved in the interhospital care of perinatal patients.[9]The aim of this study was to compare the clinical characteristics, management, and outcome between neonatal transfers and inborn neonates with symptomatic pneumothorax.

METHODS

All patients with symptomatic pneumothorax transported from August 1, 2000 through July 31, 2003 by the Pediatric Department, University of Padova Neonatal Transport Team, were eligible for inclusion in the study. The transport team, comprised of a neonatologist and a nurse, provides the neonatal critical care transport in the East Veneto Region, Italy, with a total population referral of 2.3 million in a radius of approximately 150 km. In the referral area, there are approximately 25,700 births/year in 25 delivery units. Of these units, 16 are classified as Level I (= care for normal near-term and term infants), 8 as Level II (= intermediate care), and 1 as Level III (= complete neonatal intensive care). All neonates were transferred by ground ambulance.

Data were obtained from the transport files and the records of the patients. All interventions, both procedural and pharmacological, were documented by the team members. The status of transported patients and the care they received were recorded for the pre-transport, interhospital transport, and neonatal intensive care unit (NICU) stay intervals.

Data on gestational age, birth weight, Apgar scores, need for resuscitation at birth, mode of respiratory support, postnatal stage at diagnosis, management, underlying primary lung disease, presence of major congenital malformations, length of

Table 1 Characteristics of the 2 studied groups.

	Transferred neonates (n 36)	Inborn neonates (n 25)	P value
Gestational age, weeks	36±2	31±4	<0.01
Birth weight, g	2720±573	1736±1028	<0.01
Cesarean section, n (%)	28 (78%)	19 (76%)	0.87
Tension pneumothorax, n (%)	**23 (63%)**	**19 (76%)**	**0.31**
Postnatal age At diagnosis, h	35±44	39±47	0.71
Need of resuscitation at birth, n (%)	7 (19%)	11 (44%)	0.03
Mean airway pressure>7 cm H_2O, n (%)	5 (14%)	12 (48%)	<0.01
Need for mechanical ventilation, n (%)	**21 (58%)**	**14 (56%)**	**0.85**
Surfactant treatment, n (%)	**8 (22%)**	**12 (48%)**	**0.04**
Blood gas parameters (at diagnosis)			
pH	7.23±0.13	7.23±0.11	0.95
pCO_2 (mm Hg)	50±16	53±18	0.59
pO_2 (mm Hg)	72±40	53±20	0.04
HCO_3 (mmol/L)	21±4	20±4	0.69

Table 2 Underlying primary lung disease of the patients.

	Transferred neonates (n 36)	Inborn neonates (n 25)	P value
Respiratory distress syndrome, n (%)	18 (50%)	13 (52%)	0.87
Spontaneous pneumothorax, n (%)	14 (38%)	3 (12%)	0.02
Pneumonia, sepsis, n (%)	2 (6%)	3 (12%)	0.36
Asphyxia, n (%)	2 (6%)	1 (4%)	0.78
Lung hypoplasia, n (%)	0 (0%)	5 (20%)	<0.01

hospital stay, and mortality were recorded for all patients and subsequently entered into a computerized database.

The severity of the pneumothorax was radiologically defined as mild (collection of air in the pleural space without mediastinal shift) or severe (presence of a tension pneumothorax with collection of air in the pleural space and mediastinal shift.)[10]

Primary lung disease diagnosis was given at the time of discharge from the NICU. The diagnosis of pulmonary hypoplasia was based on historical, clinical, and, for mortality cases, histological features.[5] Pneumothorax was defined as spontaneous when no iatrogenic factors were implicated, and the clinical course and the radiographs allowed to exclude a specific primary pulmonary disease (ie respiratory distress syndrome, "wet" lung, etc).[6] The notes and radiographs of all babies were reviewed to confirm the diagnoses.

As controls, we considered all inborn patients with a diagnosis of pneumothorax admitted to our NICU during the study period.

The statistical package Statistica, STAT SOFT version 6, was used for statistical calculations. Data are presented as mean ± SD or median (range), as appropriate. Parameters were compared using the Chi-square for categorical data, the *t*-test for parametrical data, and the Mann-Whitney *U* test for non-parametrical data. A P value <0.05 was considered significant. The Ethical Committee of our Institution approved the study.

RESULTS

During the study period, a total of 584 critically ill neonates (568 transports) were transferred by the Padova University Neonatal Transport Team. Among them, 36 (6.1%) had a diagnosis of symptomatic pneumothorax. They were born in 17 different centers. During the same period, 25 inborn patients with a diagnosis of pneumothroax were admitted to our NICU. The characteristics of the two groups are shown in Table 1. Gestational age and birth weight were significantly higher in the group of the transferred neonates than in the inborn infants group. There were 2 (6%) and 12 (48%) very low birth weight infants and/or neonates with gestational age ≤ 31 weeks in the transferred and inborn group, respectively (P = 0.03). Mode of delivery, severity of the pneumothorax (tension pneumothorax), need for mechanical ventilation and postnatal age at diagnosis of the pneumothorax were comparable between the two groups. Resuscitation at birth, a mean airway pressure >7 cm H_2O and surfactant therapy were required less frequently by the transferred neonates than inborn infants. With the exception of the PaO_2, blood gas parameters at the time of diagnosis of pneumothorax were comparable between the two groups (Table 1).

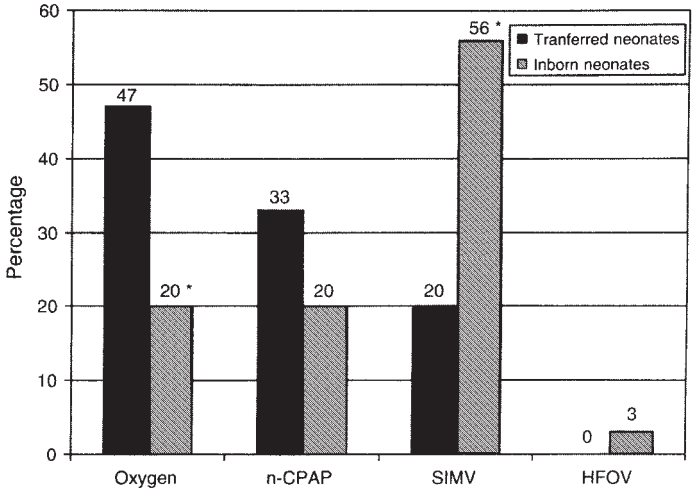


Figure 1. Respiratory treatment of the patients before the diagnosis of pneumothorax. *P < 0.05

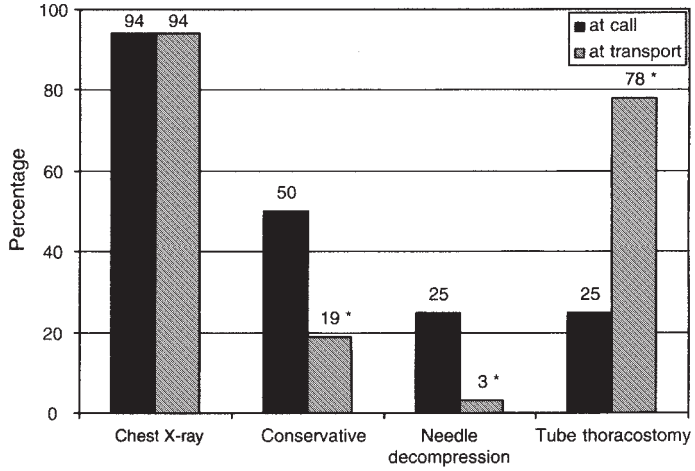


Figure 2. Pneumothorax management of the transferred neonates at call and after the transport team arrival. *P < 0.05

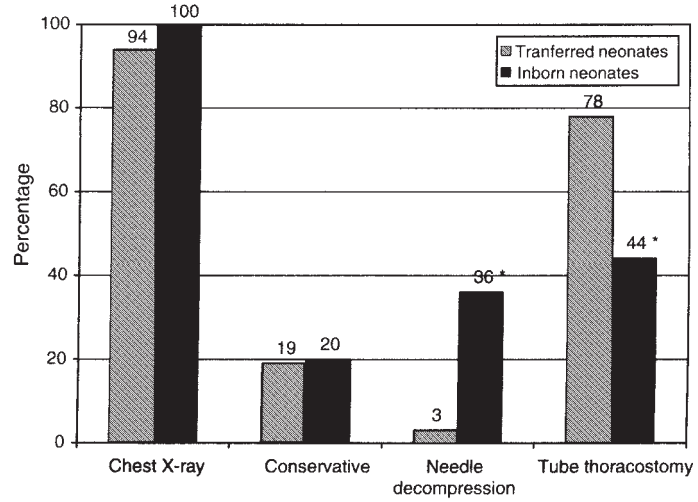


Figure 3. Definitive management of the pneumothorax. *P < 0.05

Table 2 reports the underlying primary lung diseases of the patients. The diagnosis of spontaneous pneumothorax was found more frequently in the transferred neonates group (38% vs. 12%; P = 0.02), while the diagnosis of lung hypoplasia was limited to the inborn neonates group (20%).

Before the event, respiratory treatment was limited to supplemental oxygen more frequently in the transferred group than in the inborn group (47% vs. 20%; P < 0.05). Conversely, a higher percentage of inborn neonates were mechanically ventilated before the diagnosis of pneumothorax (56% vs. 20%; P < 0.05). No differences were found between the two groups for nasal-CPAP therapy and high frequency oscillatory ventilation (HFOV). (Figure 1)

The management of the transferred neonates at call and at the time in which the transport team arrived is reported in Figure 2. Before the transport team arrived, infants were managed with conservative therapy (50%), needle decompression (25%) and tube thoracostomy (25%). After the arrival of the transport team, most of them were treated with chest drainage (78%); conservative therapy and needle decompression were reserved to 19% and 3% of the patients, respectively.

For the definitive management, a higher frequency of transferred neonates were treated with chest thoracostomy compared to the inborn infants (78% vs. 44%; P < 0.05). (Figure 3)

Systemic analgesic therapy (Fentanyl) for chest drainage insertion was performed in 11 out of 27 (41%) transferred neonates and in 10 out of 11 (91%) inborn infants (P < 0.01). Outcome was different between the two studied groups. (Table 3)

DISCUSSION

In this study, for the first time, we compared the characteristics, management, and outcome of the neonatal transfers and inborn neonates with pneumothorax. Spontaneous pneumothorax usually occurs during the first few breaths soon after birth.[6] Radiological surveys have demonstrated an incidence of 1.0-2.0% of all live births;[3] symptomatic pneumothorax, however, has been noted in only 0.05-0.07% of live births.[2,6] Similarly to these studies, in our population (61 patients with pneumothorax in 77,1000 live births in 3 years) the incidence of symptomatic pneumothorax was 0.079%. As expected, the incidence was higher in our high risk pregnancies center (0.23%) than in the other level I and II hospitals of the East Veneto Region (0.054%).

Along with the incidence, our study shows that the clinical characteristics (gestational age and birth weight) between transferred and inborn neonates with pneumothorax were also different, suggesting that the pathogenetic mechanisms of pneumothorax in these two groups of patients were different.

Pneumothorax can occur spontaneously (no iatrogenic factor implicated), or as a result of ventilatory assistance, or, rarely, as a complication following certain procedures, such as amniocentesis or perforation of segmental bronchi by suction catheters.[6] Pneumothorax is sometimes a manifestation of an underlying lung disease such as meconium aspiration, respiratory distress syndrome, transient tachypnea of the newborn, pneumonia, and, more seriously, pulmonary hypoplasia.[5] Respiratory distress syndrome (surfactant deficiency) was the underlying primary lung disease for a large part (about 50%) of our population. This information could be

Table 3 Outcome of the patients.

	Transferred neonates (n 36)	Inborn neonates (n 25)	P value
Major congenital malformations, n (%)	0 (0%)	5 (20%)*	<0.01
Length of hospital stay, (days)	9±6	32±32	0.01
Mortality, n (%)	0 (0%)	4 (16%)	0.01

* Congenital diaphragmatic hernia, polycystic kidney, sacrococcygeal teratoma, pulmonary hypoplasia secondary to chronic amniotic fluid leakage (2 patients).

important for preservation of the potentially life-threatening complication of pneumothorax, especially for infants born in low-level care hospitals needing transfer.

The reason for the high rate of cesarean section in the transferred group remains unknown. However, it is noteworthy that, among them, 16 out of 28 (57.1%) were born by elective cesarean section. This modality of birth could have influenced the respiratory morbidity in this group of patients. In fact, previous work demonstrated that infants born by elective cesarean delivery at term were at increased risk for developing respiratory disorders compared with those born by vaginal delivery.[12] Among the transferred neonates, the diagnosis of spontaneous pneumothorax was more frequent; however, pulmonary hypoplasia was found in a large part of our inborn population with pneumothorax (20%). The diagnosis of spontaneous pneumothroax among the transferred newborns, is confirmed by the fact that conventional iatrogenic factors implicated in the pathogenesis of pneumothorax, such as need of resuscitation at birth and mechanical ventilation, were found in a lower incidence. Furthermore, at the time of the diagnosis, respiratory management was limited to oxygen therapy for the most part of them (47%).

The management of these infants was another interesting point of our study. Pneumothorax is a life-threatening condition that needs prompt recognition and therapy. It is probable that the earlier a pneumothorax is drained, the less damage will occur from hypoxia, hypercarbia, and venous and arterial changes as a result of the raised mediastinal pressure. Early diagnosis and treatment, therefore, should be beneficial.[6,7,10] Previous studies showed that the diagnosis of the pneumothorax is late, occurring when infants were already decompensated.[7] Unfortunately, our data do not permit to evaluate the onset of pneumothorax in our populations with certainty, as reported in other studies.[7,10] However, at the time of diagnosis, blood gas parameters were compensated in most patients and were comparable between the two studied groups.

It is noteworthy that our transport team positioned 18 out of 27 (66%) chest tube drainages in the transferred group. The percentage of tension pneumothorax was similar between the two study groups; for this reason the different management of these neonates cannot be explained by the severity of the pneumothorax. As the thoracostomy procedure is a very rare event, the ability of the peripheral hospital's staff to perform it is low. This fact could have led the staff to opt for a less invasive procedure, such as needle decompression, while waiting for the arrival of the transport team.

In comparison with inborn infants, a significantly higher percentage of the transferred neonates were treated with a chest drainage tube. This finding could be explained by the fact that appropriate stabilization of the sick patients prior to transfer is considered essential to reduce adverse events that may otherwise occur during the transfer process.[1,4,9]

Another interesting finding of this study was that the systemic analgesic therapy (Fentanyl) for chest drainage insertion was given to only 41% of the neonates with pneumothorax born in the peripheral hospitals. In these neonates, instead, a local analgesia with Lidocaine was preferred by the local operators as well as by the transport team. This therapeutic choice is probably due to the potential side effects of the Fentanyl (ie respiratory depression, skeletal/thoracic muscle rigidity) that could precipitate the clinical status of the patient and require positive pressure ventilation and/or muscle relaxants. This risk seemed to be overestimated during the transport process. In fact, the same team, in the context of our NICU, used the analgesic therapy with Fentanyl in 91% of the treated infants with pneumothorax. These data suggest that reviewing the transport records of all transported patients and developing and implementing patient care protocols could help to improve quality of care.[1,4,9]

Finally, our results show a different outcome in terms of length of hospital stay and mortality between these two groups of patients. Probably, these findings are due to the different characteristics (gestational age, birth weight, primary lung disease, presence of major congenital malformations) of the two studied groups. It may have been of interest to evaluate whether the transported infants experienced excess morbidity from pneumothorax as compared to inborn controls of the same gestational age. Unfortunately, this comparison is impossible because the demographic characteristics of these two groups of patients were significantly different. Nowadays, an adequate prenatal diagnosis permits to hospitalize these high-risk pregnancies in high-level care centers, thereby reducing the need for a postnatal transport of critically ill neonates.[1,4] On the one hand, these considerations do not allow the comparison of our two groups for prognosis and outcome; on the other hand, they show that the outcome was favorable for most of our transferred neonates with pneumothorax.

In conclusion, our study shows that transferred neonates and inborn infants with pneumothorax are different for clinical characteristics, management, and prognosis. This information could be useful for all those involved in the care of neonates in need of transfer.

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Respiratory Rehabilitation After Acute Exacerbation of COPD May Reduce Risk for Readmission and Mortality – A Systematic Review

Milo Puhan, Madlaina Scharplatz, Thierry Troosters, Johann Steurer

ABSTRACT

Background

Acute exacerbations of chronic obstructive pulmonary disease (COPD) represent a major burden for patients and health care systems. Respiratory rehabilitation may improve prognosis in these patients by addressing relevant risk factors for exacerbations such as low exercise capacity. To study whether respiratory rehabilitation after acute exacerbation improves prognosis and health status compared to usual care, we quantified its effects using meta-analyses.

Methods

Systematic review of randomized controlled trials identified by searches in six electronic databases, contacts with experts, hand-searches of bibliographies of included studies and conference proceedings. We included randomized trials comparing the effect of respiratory rehabilitation and usual care on hospital admissions, health-related quality of life (HRQL), exercise capacity and mortality in COPD patients after acute exacerbation. Two reviewers independently selected relevant studies, extracted the data and evaluated the study quality. We pooled the results using fixed effects models where statistically significant heterogeneity ($p \leq 0.1$) was absent.

Results

We identified six trials including 230 patients. Respiratory rehabilitation reduced the risk for hospital admissions (pooled relative risk 0.26 [0.12–0.54]) and mortality (0.45 [0.22–0.91]). Weighted mean differences on the Chronic Respiratory Questionnaire were 1.37 (95% CI 1.13–1.61) for the fatigue domain, 1.36 (0.94–1.77) for emotional function and 1.88 (1.67–2.09) for mastery. Weighted mean differences for the St. Georges Respiratory Questionnaire total score, impacts and activities domains were -11.1 (95% CI -17.1 to -5.2), -17.1 (95% CI -23.6 to -10.7) and -9.9 (95% CI -18.0 to -1.7). In all trials, rehabilitation improved exercise capacity (64–215 meters in six-minute walk tests and weighted mean difference for shuttle walk test 81 meter, 95% CI 48–115).

Conclusion

Evidence from six trials suggests that respiratory rehabilitation is effective in COPD patients after acute exacerbation. Larger trials, however, are needed to further investigate the role of respiratory rehabilitation after acute exacerbation and its potential to reduce costs caused by COPD.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) represent a major burden for patients and health care systems. For patients, acute exacerbations are a common reason for hospital admissions and severely affect health-related quality of life (HRQL)[1] and prognosis.[2] Mortality rates during hospitalizations are around 10%[3,4] and during the year following a hospitalization may be as high as 40%.[3,5]

From the health care provider's perspective, COPD is resource consuming.[6] A small proportion of COPD patients of around 10% suffering from acute exacerbations accounts for over 70 percent of costs caused by COPD because of emergency visits and hospitalizations.[6-8] The readmission rate is typically high in these high-risk patients. A recent large study found a readmission rate of 63% during a mean follow-up of 1.1 year with physical inactivity amongst the significant predictors for readmissions.[9]

Recent position papers of the American College of Physicians and American College of Chest Physicians provided recommendations on the management of acute exacerbations.[10,11] However, a weakness of these papers was that they did not provide recommendations how future exacerbations and hospitalizations could be prevented despite being one of the main goals of COPD management.[11,12] One solution that has been adopted in clinical practice is to provide

Authors Puhan, Scharplatz and Steurer are with the Horten Centre, University of Zurich, Switzerland. Troosters is with the Respiratory Division, Respiratory Rehabilition, and Faculty of Kinesiology and Movement Science, Kotholieke Universiteit Leuven, Belgium. Respiratory Research 2005, 6:54. This is an Open Access article distributed under the terms of the Creative Commons Attribution License. Originally published 08 June 2005, © 2005 Puhan et al; licensee BioMed Central Ltd.

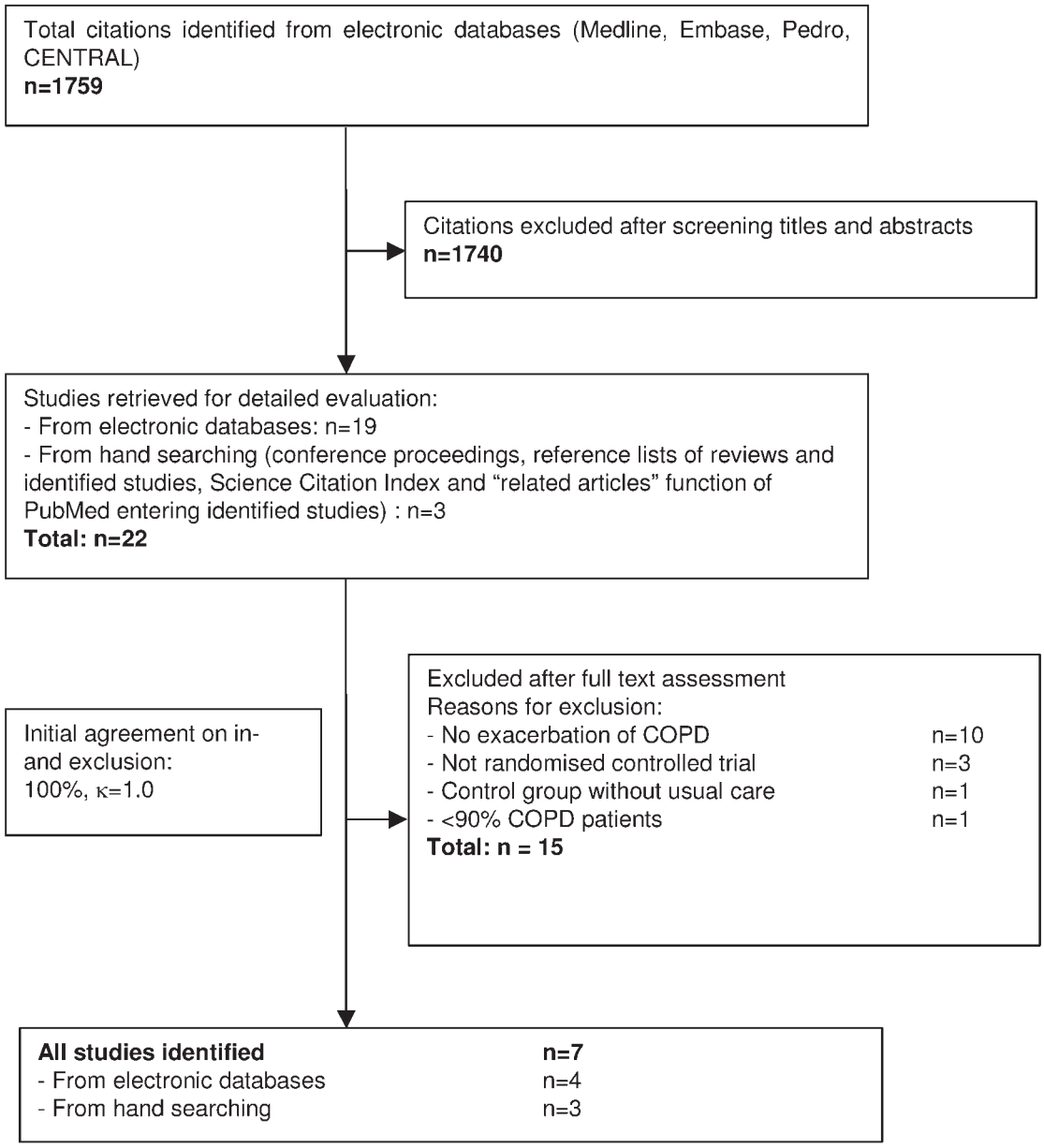

Figure 1
Study flow from identification to final inclusion of studies.

rehabilitative care after treatment of acute exacerbation including physical exercise, patient education focusing on self-management strategies and psychosocial support. The rationale to offer rehabilitation in patients recently treated for acute exacerbation is to enhance HRQL as in stable COPD patients,[13] but also to modify factors associated with increased risk for post-exacerbation morbidity and mortality. A recent study showed that exacerbations results in acute muscle deconditioning and weakness.[14] Hence patients with frequent exacerbations have more pronounced skeletal muscle weakness and a more limited six minute walking distance,[15] which is in turn a risk factor for exacerbations and mortality.[3,16]

Thus respiratory rehabilitation may have the potential to reduce hospital admissions by improving exercise capacity. It is hence surprising, and in contrast to the large body of evidence supporting respiratory rehabilitation in stable patients,[13,17] that the effects of respiratory rehabilitation in patients after acute exacerbation has never been studied systematically. Therefore, our aim was to conduct a systematic review of all randomized controlled trials that compared respiratory rehabilitation after acute exacerbation and usual care.

METHODS

Identification of studies

We used five strategies to identify studies including electronic databases, consultations with experts from North America and Europe, our own files, bibliographies of articles that met the inclusion criteria and conference proceedings of the International Conference of the American Thoracic Society and the Congress of the European Respiratory Society.

An information specialist conducted electronic database searches in MEDLINE (Ovid version, New York, New York, from

Table 2: Quality assessment

Study	Prognostically homogenous study population	Concealment of random allocation	Prestratification on prognostically relevant variables	Description of randomisation procedure	Registration of loss to follow-up	Registration of co-interventions for each group	Blinding of outcome assessors	Check success of blinding
Behnke [19, 20]	+/-	-	-	-	+	+/-	-	-
Kirsten 1998 [22]	+/-	-	-	-	+	+/-	-	-
Man 2004 [24]	+/-	+	+	+/-	+	-	-	-
Murphy 2005 [21]	+/-	+	-	-	+	-	-	-
Nava 1998 [23]	+/-	-	-	+/-	+	-	-	-
Troosters [25, 26]	+/-	+	-	-	+	-	-	-

+: Fulfilled; +/-: Partially fulfilled; -: Not fulfilled or no information provided

inception to April 2005), EMBASE (DataStar version, Cary, North Carolina from inception to April 2005), PEDRO (online version, University of Sydney, Australia, April 2005) and the Cochrane Central Register of Controlled Trials (Oxford, United Kingdom, 2005, Issue 1). We did not restrict the search to COPD patients with exacerbation only because exacerbation is not indexed as a Medical subject heading term and we feared to miss relevant studies with a narrow search. We used a broad search strategy using the terms "lung diseases obstructive," "chronic obstructive lung disease," "chronic obstructive pulmonary disease," "rehabilitation," "exercise," "exercise movement techniques," "physical endurance," "muscle training," "kinesiotherapy," "clinical trial," "controlled study," and "epidemiologic methods." We also searched the Science Citation Index database (Web of Science, Thomson ISI, Philadelphia, Pennsylvania) and the "related articles" function of PubMed (National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894) by entering all included studies.

Inclusion criteria

We included randomized controlled trials comparing respiratory rehabilitation of any duration after acute exacerbation of COPD with conventional care. Respiratory rehabilitation programs needed to include at least physical exercise. We included studies if more than 90% of study participants had COPD. Main outcome measure was unplanned hospital admissions and secondary outcomes included exacerbations, outpatient visits, dyspnea, HRQL as measured by disease-specific or generic questionnaires, functional and maximum exercise capacity, mortality and adverse events during rehabilitation. We did not apply any language restrictions.

Study selection

The bibliographic details of all retrieved articles were stored in a Reference Manager file (Professional Edition Version 10, ISI ResearchSoft, Berkeley, California). We removed duplicate records resulting from the various database searches. Two members of the review team (MAP, MS) independently scrutinized the titles and abstracts of all identified citations and ordered the full text of any article that was deemed potentially eligible by one of the reviewers. The two reviewers evaluated the full text of all retrieved papers, made a decision on in- or exclusion and discussed the decisions. Any disagreement was resolved by consensus with close attention to the inclusion/exclusion criteria. We recorded the initial degree of discordance between the reviewers and corrected discordant scores based on obvious errors. We resolved discordant scores based on real differences in interpretation through consensus or third party arbitration.

Data extraction and quality assessment

We performed the data extraction using pilot-tested data forms. One reviewer extracted details about study patients, interventions and outcome measures as well as the results in a predefined data form and the second reviewer checked the data extraction for accuracy. We contacted all authors of the primary studies to obtain missing information. Two reviewers independently evaluated the quality of included trials using a detailed list of quality items assessing components of internal validity.[18] We did not rate the two items "blinding of patients" and "blinding of persons who implements intervention" because patients and treatment providers cannot be blinded in studies comparing respiratory rehabilitation and usual care.

Methods of analysis and synthesis

We summarized the results of the data extraction and assessment of study validity in structured tables. We pooled trial results using fixed effects models if there was no significant heterogeneity ($p \leq 0.1$ with Q statistic for continuous and Cochran chi-squared test for binary outcomes). In anticipation of significant heterogeneity we established a priori hypotheses to explain differences in outcomes across studies. First, heterogeneity may arise from the setting patients were recruited (in or outpatient treatment of exacerbation), second from different lengths of follow-up, third from different length of the intervention and finally from differences in the methodology of the intervention. Pooled risk ratios and 95% confidence intervals (CIs) were computed by calculating weighted mean differences and pooled risk ratios using STATA (version 8.2, Stata Corp., College Station, Texas).

RESULTS

We show the study selection process and agreement on study inclusion in Figure1. Out of the 22 potentially relevant articles, we included seven reports (Table 1). Two articles were based on the same trial. One reported the results after six[19] and the other one after 18 months.[20] In five trials, patients were recruited after inpatient care and in one trial[21] after hospital at home treatment for acute exacerbation. Two trials reported on the short-term benefit of inpatient rehabilitation programs[22,23] and four trials had rehabilitation programs of six weeks to six months duration.[20,21,24,25] One trial was published as an abstract only,[25] but additional information was available from an earlier publication [26] and from the author. Altogether 140 patients were randomized to the rehabilitation intervention, and 90 were randomized into respective control groups.

Initial agreement of reviewers on quality assessment was 85% for all items (chance corrected kappa = 0.70). All disagreement

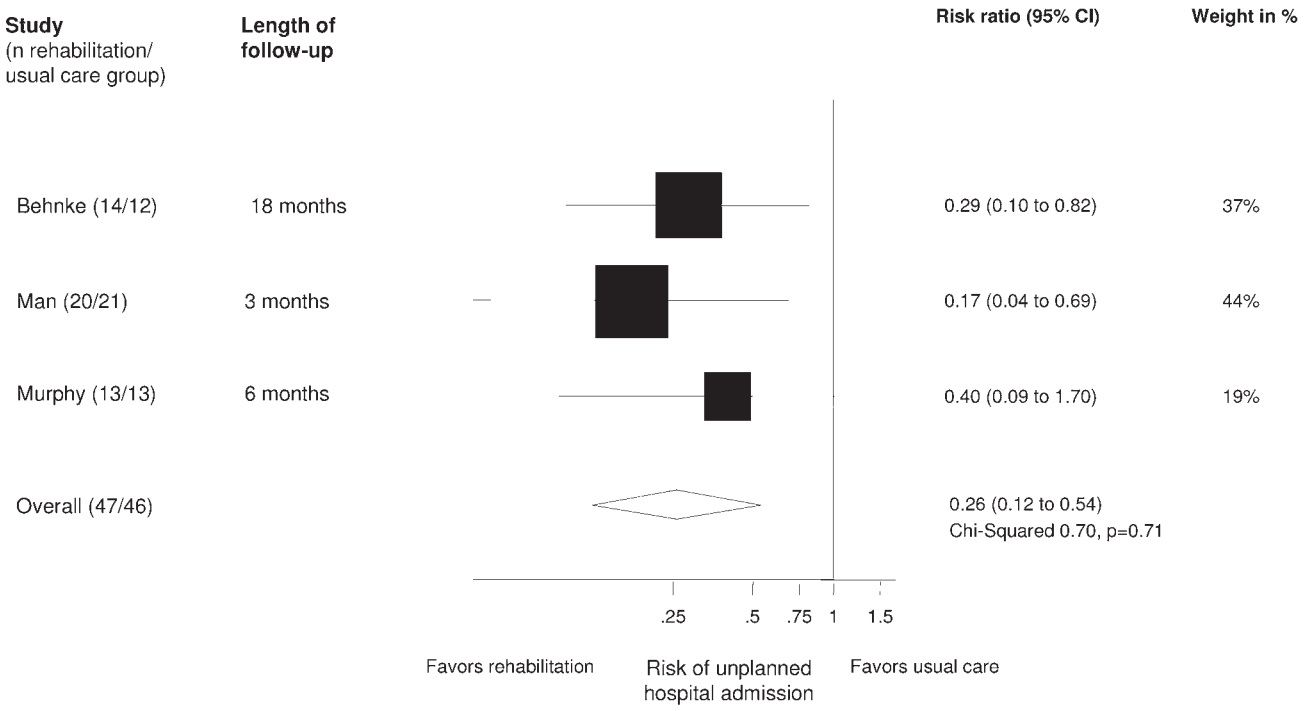

Figure 2
Effect of respiratory rehabilitation on unplanned hospital admissions. Boxes with 95% confidence intervals represent point estimates for the risk ratio.

could be resolved by consensus. The quality of trials was moderate (Table 2). Three trials provided details about the randomization procedures and three trials about concealment of random allocation, while in none of the trials the outcome assessors were blinded.

Effect on hospital admissions

Figure 2 shows the effect of respiratory rehabilitation on unplanned hospital admissions for each study [20,21,24] and the pooled relative risk ratio of 0.26 (0.12–0.54). The other trials included either only inpatients [22,23] or did not record hospital admissions during the follow-up.[25]

Effect on HRQL

Three trials assessed HRQL using the Chronic Respiratory Questionnaire (CRQ)[20,24] and the St Georges Respiratory Questionnaire (SGRQ)[21,24] (Figure 3). With both instruments, the trials found large effects exceeding the minimal important difference of 0.5 on the CRQ and of 4 on the SGRQ. Weighted mean differences (expressed as points change on a scale from 1 to 7) on the CRQ were 1.37 (95% CI 1.13–1.61) for the fatigue domain, 1.36 (0.94–1.77) for emotional function and 1.88 (1.67–2.09) for mastery. Weighted mean differences for the SGRQ total score, impacts and activities domains were -11.1 (95% CI -17.1 to -5.2), -17.1 (95% CI -23.6 to -10.7) and -9.9 (95% CI -18.0 to -1.7). For the CRQ dyspnea and SGRQ symptoms domain, results were too heterogeneous to be pooled ($Q = 6.44$, $p = 0.01$ for CRQ dyspnea domain and $Q = 3.50$, $p = 0.06$ for SGRQ symptoms domain), but all studies showed a consistent effect in favor of the rehabilitation intervention.

Man and Murphy also used generic HRQL instruments and found improvements by respiratory rehabilitation of 10.6 (-0.3 to 21.6) and 20.1 (3.3 to 36.8) on the physical composite and mental composite score of the Short-Form Survey 36[24] and of 0.18 (95% CI 0.04 to 0.32) with the EuroQol score.[21]

Effect on dyspnea

In the trial by Behnke,[20] the mean difference between groups on the transition dyspnea index was 6.9 (3.9 to 9.9) at the end of the treatment period and 8.6 (6.3–10.9) after 18 months. Kirsten[22] found significant differences in Transition dyspnea index scores after a short inpatient rehabilitation ($p < 0.05$, no additional data available) and Nava[23] also observed a significant effect of rehabilitation on dyspnoea (difference between groups 17 mm on visual analogue scale after a 50 meter walk, $p < 0.01$). Murphy[21] used the Medical Research Council dyspnea scale and also found that respiratory rehabilitation decreased dyspnea by 0.3 although this did not reach statistical significance (95% CI -0.92 to 0.32).

Effect on exercise capacity

All trials showed a significant benefit of respiratory rehabilitation on the six-minute walking distance (Figure 4). We did not pool the results of the six-minute walking tests because of statistically significant heterogeneity ($Q = 28.33$, $p < 0.001$), which could not be explained by our a priori defined sources for heterogeneity. The trials reported by Behnke[19] and Kirsten[22] were conducted in the same institution and showed much larger effects (mean effects of 215 and 158 meters on the six minute walking test) compared to the trials of Nava[23] (68 meters) and Troosters[25] (64 meters). All studies showed a consistent benefit in favor of the rehabilitation group, which exceeded the minimal clinically important difference of 53 meters. The meta-analysis of the shuttle walk tests results showed a weighted mean difference of 81 meters (95% CI 48 to 115) between the rehabilitation and usual care groups.

Table 1: Characteristics of included studies

Study	Population	Intervention	Follow up	Outcomes
Behnke 2000 [19] and 2003 [20]	26 COPD patients (mean age 67 years, 77% males, mean FEV_1 = 36% predicted) after inpatient treatment for acute exacerbation.	**Rehabilitation:** Within 4–7 days after admission, inpatient respiratory rehabilitation with endurance exercise (5 walking sessions/day for 10 days), followed by six months of supervised home-based endurance exercise (3 walking sessions/day for 6 months) **Usual care:** Standard inpatient care without exercise and standard community care with respirologist.	18 months	CRQ, Transition dyspnea index, 6 MWT, hospital readmission, mortality
Kirsten 1998 [22]	29 COPD patients (mean age 64 years, 90% males, mean FEV_1 = 36% predicted) after inpatient treatment for acute exacerbation.	**Rehabilitation:** Within 6–8 days after admission, inpatient respiratory rehabilitation with endurance exercise (5 walking sessions/day for 10 days). **Usual care:** Standard inpatient care without exercise.	11 days	Transition dyspnea index, 6 MWT
Man 2003 [24]	42 COPD patients (mean age 70 years, 41% males, FEV_1 = 39% predicted) after inpatient treatment for acute exacerbation.	**Rehabilitation:** Multidisciplinary outpatient respiratory rehabilitation (within 10 days of discharge) with endurance and strength exercise and patient education for 12 weeks (2 sessions/week). **Usual care:** Standard community care with respirologist	12 weeks	CRQ, SGRQ, Short form survey 36, shuttle walk test, hospital readmission, hospital days, emergency admissions, mortality
Murphy 2005 [21]	26 COPD patients (mean age 66 years, 65% males, mean FEV_1 = 40% predicted) after home for hospital treatment for acute exacerbation.	**Rehabilitation:** Supervised home-based respiratory rehabilitation with endurance and strength exercise for 6 weeks (2 supervised sessions/week and daily unsupervised sessions). **Usual care:** Standard community care with respirologist	6 months	SGRQ, EuroQol, MRC dyspnea scale, shuttle walk test, 3-minute step test, hospital readmission
Nava 1997 [23]	70 COPD patients (mean age 66 years, 73% males, mean FEV_1 = 32% predicted, 76% needed mechanical ventilation) admitted to inpatient care for treatment of acute exacerbation.	**Rehabilitation**: Within 3–5 days after admission, inpatient respiratory rehabilitation with four steps of increasing intensity. Step I, if unable to walk: Mobilisation and strength training for lower extremities. Step II, if able to walk: Endurance exercise (walking) Step III, if possible: Endurance exercise (cycling and stair climbing) and respiratory muscle training IV, if possible: Endurance exercise (cycling at highest tolerated intensity, 2 sessions/day for 3 weeks) **Usual care:** Only steps I and II.	6 weeks	Dyspnea on exertion, 6 MWT, mortality
Troosters 2002 [25, 26]	48 COPD patients (mean age 62 years, 85% males, FEV_1 = 39% predicted) after inpatient treatment for acute exacerbation.	**Rehabilitation:** Outpatient respiratory rehabilitation with endurance and strength exercise for 6 months (3 sessions/week in first 3 months, then 2/ week). **Usual care:** Standard community care with respirologist.	6 months (6 MWT) and 4 years (survival)	6 MWT, mortality

6-MWT: 6-minute walk test; CRQ: Chronic Respiratory Questionnaire; SGRQ: St. Georges Respiratory questionnaire; MRC: Medical Research Council

Effect on mortality

The individual study relative risks for mortality ranged from 0.40 (0.18–0.86) to 1.00 (0.07–15.04, Figure 5). The pooled risk ratio was 0.45 (0.22–0.91). Although no significant heterogeneity was present, it should be noted that the length of follow-up differed substantially between these studies. We did not include one trial[23] in the primary meta-analysis because severity of disease of included patients differed considerably from those of the other studies. For this trial a mortality of 20% for patients of either group (12/60 in rehabilitation group and 4/20 in control group) was observed while staying in the respiratory intensive care unit with a mean survival of 18.1 days (SD 7.2) for patients with and 12.4 days (SD 11.1) for patients without rehabilitation ($p > 0.05$). Of the 12 patients of the rehabilitation group who died, only five started a walking training (stage 2, Table 1). If this trial is included in the meta-analysis the pooled risk ratio is 0.59 (0.34–1.05) favoring the rehabilitation group.

Adverse events

Two trials explicitly recorded adverse events. Neither Man nor Behnke observed adverse events during the rehabilitation.

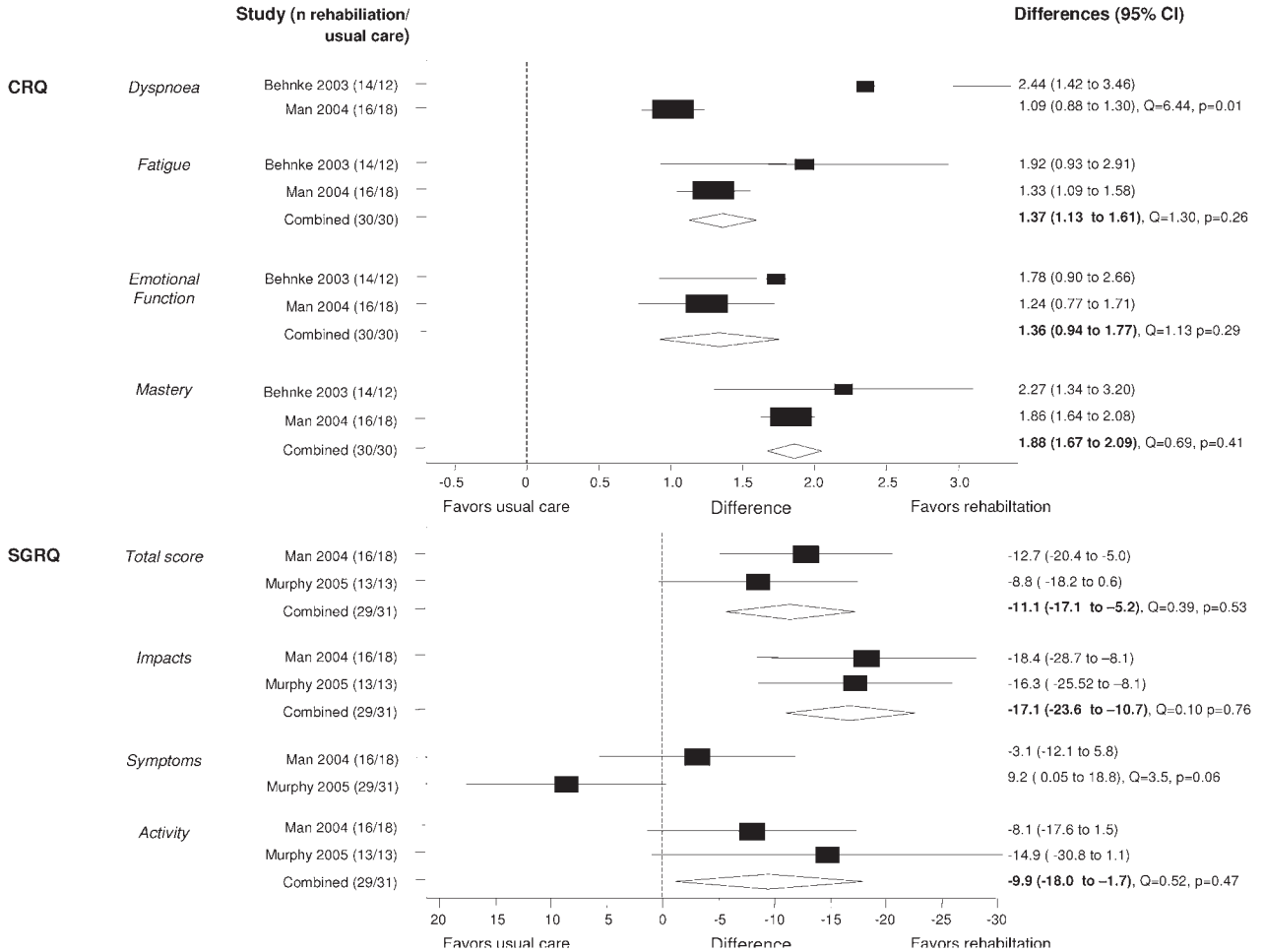

Figure 3
Effect of respiratory rehabilitation on Health-related quality of life as assessed by the Chronic Respiratory Questionnaire (CRQ) and St. Georges Respiratory Questionnaire (SGRQ). Boxes with 95% confidence intervals represent point estimates for the difference between respiratory rehabilitation and usual care.

DISCUSSION

The meta-analyses showed that respiratory rehabilitation after acute exacerbation of COPD reduced the risk for hospital admissions and mortality and led to large improvements of HRQL and exercise capacity.

Strengths of this systematic review include the extensive literature search, rigorous adherence to a predefined protocol and contacts to authors of the included trials who all provided additional information about their data. A limitation is the small number of patients included in the trials and methodological shortcomings that limit conclusions.

The effect of respiratory rehabilitation after acute exacerbation appears to be large. For HRQL and exercise capacity, the effects were well above the threshold for the minimal important difference for the CRQ (0.5 point difference [27]), St. Georges Respiratory Questionnaire (4 points[28]), SF-36 (5 points[29]) and Six-minute walking distance (around 53 meters[30]). In addition, the number of unplanned hospital admissions and mortality was reduced substantially. When one assumes that respiratory rehabilitation improves activity level in patients with COPD, it seems plausible that rehabilitation reduces readmission rate as inactivity has been shown to be a predictor of readmissions.[9]

Compared to respiratory rehabilitation in stable COPD patients,[13] its effects tend to be even larger after acute exacerbation. Several factors may contribute to this. First, as mentioned above, exacerbations lead to significant reductions in muscle function[14] and quality of life.[1] This initial deterioration may render patients more likely to improve from respiratory rehabilitation. Second, since patients were hospitalized, there may be a deficiency in self-management, or education. This may be partially targeted with the rehabilitation intervention, and patient education, as an additional part of multidisciplinary rehabilitation programs, may be of particular benefit to modify behavior. Indeed, a recent study showed impressive results of a patient management program including home exercises for COPD patients after acute exacerbation.[31] The mean number of hospital admissions per patient was reduced from 1.6 to 0.9 in the year following a hospital admission due to acute exacerbation. It is well known from earlier studies that the recovery period is long even in patients who have no further exacerbations and that another exacerbation within 6 months limits recovery markedly.[32] Our meta-analyses showed that respiratory rehabilitation during the recovery period is superior compared with usual care to improve prognosis and HRQL.

A word of caution is needed when interpreting the current

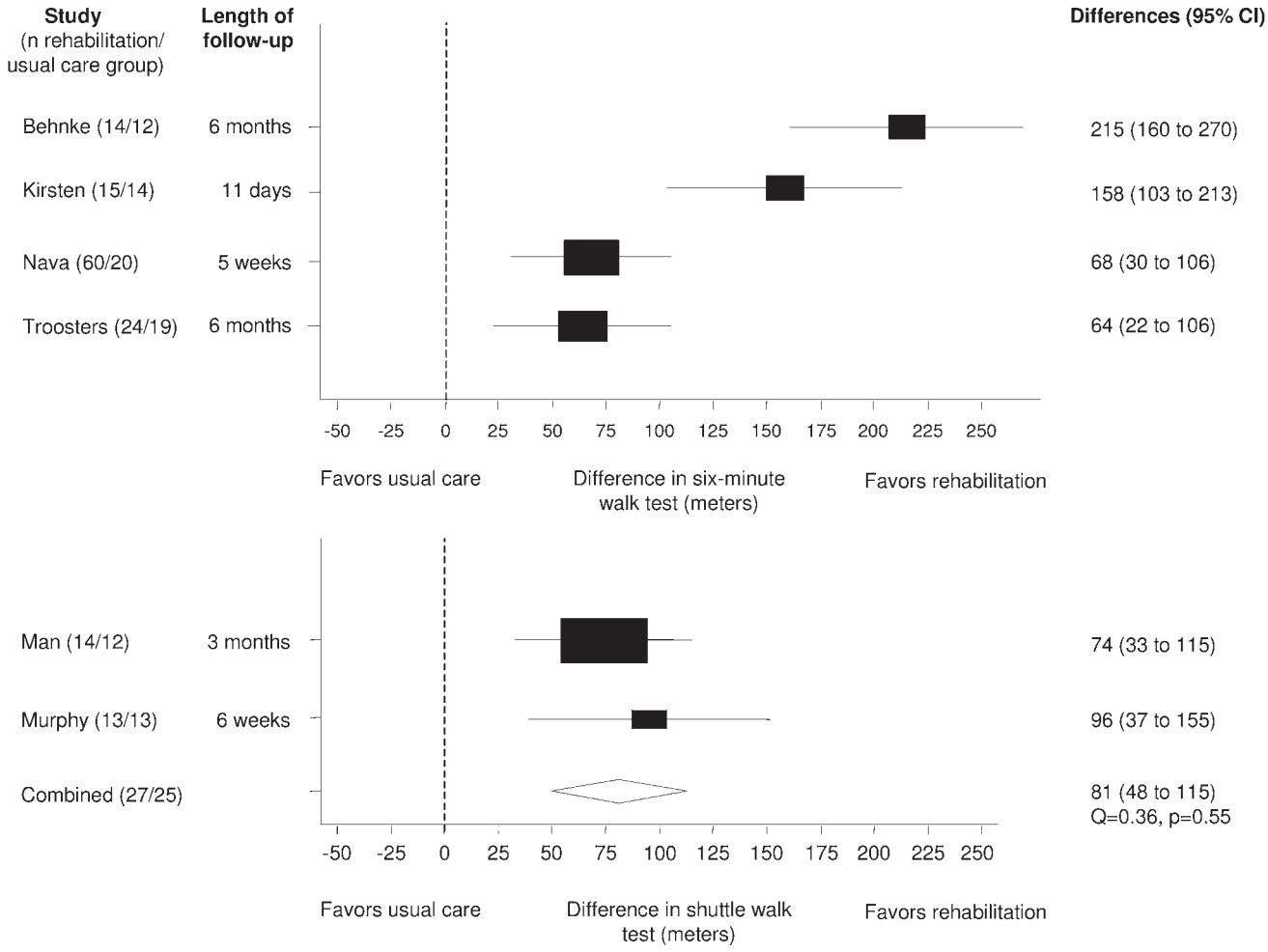

Figure 4
Effect of respiratory rehabilitation on six-minute walking and shuttle walk distance. Boxes with 95% confidence intervals represent point estimates for the difference between respiratory rehabilitation and usual care.

analysis. A clear limitation of the trials is their relatively small sample size. All trials, in particular the trials reported by Behnke [20] and Kirsten[22] showed large effects of respiratory rehabilitation on HRQL and exercise capacity. Small trials tend to overestimate the effect of an intervention compared to large trials.[33-36] This phenomenon can partly be attributed to a publication bias, that is, the fact that small trials are more likely to be published if they show statistically significant treatment effects.[37] On the other hand, methodological shortcomings of small trials such as inadequate generation of the randomization code, insufficient concealment of random allocation and lack of blinding contribute to discrepancies between the results of single large trials and pooled estimates based on small trials.[35] In our systematic review, the trials had methodological limitations and it cannot be excluded that the estimates provided by the meta-analyses represent overestimations of the effect of respiratory rehabilitation after acute exacerbation.

Larger trials seem justified to challenge the data presented in this article. Such trials should assess the effect of respiratory rehabilitation on unplanned out- and inpatient care but also include data on patient-important outcomes such as HRQL. Conducting trials on respiratory rehabilitation after acute exacerbation is, however, challenging. First, recruitment of patients is difficult because not all of them may want to be randomly allocated to respiratory rehabilitation or usual care in a situation of poor health status. Second, one needs to take into consideration that exercise capacity is particularly low after acute exacerbations so that the exercise program should be designed carefully. Strength exercise and tolerable whole body exercise modalities such as interval exercise may be particularly suitable for these patients.[38,39] Third, the definition of usual care raises a number of difficulties. Patients willing to participate in the trial are likely to have a preference for respiratory rehabilitation. If they are randomized to the control group, they might ask for respiratory rehabilitation at any time during the follow-up. Given the clear benefits of this intervention in stable patients, confirmed in meta-analyses,[13] patients should not be refrained from rehabilitative strategies. It would perhaps be ethically justifiable to conduct a large rehabilitation trial in places where respiratory rehabilitation is currently not readily available to the general patient. This appears to be the case in many countries including Switzerland,[40] the UK[41] and Canada.[42] These countries are just few examples of countries where the lack of access to rehabilitation has been pointed out as an important caveat in health care. In these places patients could be randomized to additional respiratory rehabilitation or standard treatment by general practitioners and respirologists because respiratory rehabilitation can be offered to a small proportion of COPD patients only. Alternatively relatively short

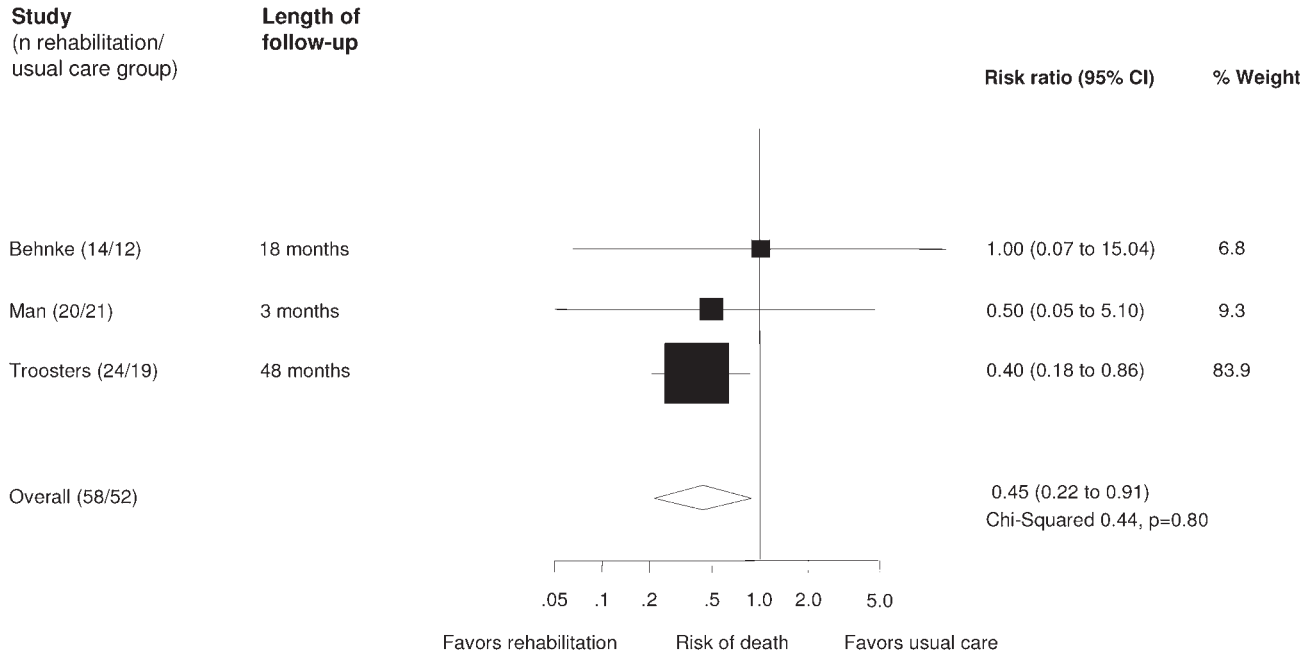

Figure 5
Effect of respiratory rehabilitation on mortality. Boxes with 95% confidence intervals represent point estimates for the risk ratio.

term studies (3–6 months follow-up) could be conducted with re-admission as a primary end point. It has been shown that re-admission occurs often soon after discharge.[43,44] Obviously, such studies could never address mortality as a primary end point, due to a lack of events. Whatever design investigators choose, a careful discussion of ethical and methodological issues is necessary before conducting large trials.

The present data show that respiratory rehabilitation has the potential to reduce the large COPD-related costs due to hospital admissions. It may not only reduce the number of acute exacerbations but also their severity. Patients may learn to notice imminent exacerbations and seek medical attention earlier leading to a shift from inpatient to the less costly outpatient treatment of acute exacerbations. The significant reduction in hospital readmissions is suggestive of a beneficial cost-benefit balance. However, larger trials should provide the final evidence base for formal cost analyses to test the hypothesis that respiratory rehabilitation after acute exacerbation is cost effective.

The data presented in this review are the first to show a survival benefit of respiratory rehabilitation in patients at risk. Although the results should be interpreted with caution, as mentioned above, this study provides the most solid evidence currently available that mortality is reduced. In summary, current evidence suggests that respiratory rehabilitation reduces unplanned hospital admissions and mortality and improves HRQL and exercise capacity when initiated immediately after acute exacerbations.

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Knowledge Based Weaning: Knowledge-Based Systems for Automatic Ventilatory Management

Michel Dojat, Eng, PhD; Laurent Brochard, MD

INTRODUCTION

Despite their enormous potential to facilitate bedside management, the practical role of computers in critical care environments is generally restricted to the storage and the retrieval of data coming from electronic medical devices and hospital information networks.

Benefits of the use of computers in health care may be extended by the design of computerized medical assistants that can efficiently discharge the clinical staff of repetitive tasks (which, in practice, often are not performed) and, importantly, help practitioners to make efficient decisions in time. In intensive care and anesthesia, the demand for computerized medical assistants is potentially considerable, in order to filter and synthesize the growing mass of clinical parameters and information available. The progressive introduction of computerized protocols has been proposed to standardize the bedside decision making process for mechanical ventilation and to reduce unnecessary variation among practitioners,[32] reinforcing the potential impact of computerized medical assistants.

VENTILATION MANAGEMENT TODAY

Modern methods of mechanical ventilation partially assist the patient's ventilation by adding a variable amount of mechanical support to his/her spontaneous activity. In this context, since the needs of the patient are evolutive, it is essential to continuously control the ventilatory support, in order to avoid excessive work of breathing and effort, discomfort and dyspnea on the one hand, or excessive support, hyperinflation and dyssynchrony on the other hand.

In parallel to this ideal automatic adaptation, it may be necessary to plan the long term adaptation of the therapy according to specific medical goals. For instance, it may be indicated to gradually decrease the level of assistance in order to facilitate the weaning from the ventilator or to take into account large variations of physiological needs during the patient wake-up from anesthesia or drug intoxication.

Planning and control are two different tasks that have a common goal: choosing actions over time to influence a process, based on some model of that process.[9] Control is a local task to determine what to do the next instant.

AUTOMATED VENTILATION MANAGEMENT: A PRACTICAL AND SUCCESSFUL EXPERIENCE USING THE NÉOGANESH SYSTEM–HÔPITAL HENRI MONDOR, CRÉTEIL, FRANCE

The initial objective of the design of the knowledge-based system called NéoGanesh, was to build a closed-loop system 1) efficient for the automatic control of mechanical support, 2)

Michel Dojat is Research Engineer, Institut National de la Santé et de la Recherche Médicale, INSERM – UJF U594, Créteil, France. Laurent Brochard is Professor of Intensive Care Medicine, Service de Réanimation Médicale, Hôpital Henri Mondor, AP-HP, Créteil, France. This is the synopsis of an article that appeared in: G. Iotti, eds., Respiratory Care Clinics. Special Issue on Closed-Loop Control Mechanical Ventilation. WB Saunders Co., Philadelphia, Vol.7, Issue 3, Sept. 2001. Note: This synopsis differs in details from the published versions. This article expresses the author's opinion. This article was provided by Draeger Medical AG & Co. KgaA, Lubeck, Germany, draeger-medical.com.

which could be extended to gradually improve its reasoning and planning capabilities and 3) which could be tested at the patient's bedside to measure its performance at each step.

A KNOWLEDGE-BASED SYSTEM WORKING IN CLOSED-LOOP

Instead of computerizing a specific recipe for ventilation management,[37,47] the design of NéoGanesh tried to respect the golden rules of knowledge engineering: make an explicit model of medical tasks and reasoning involved, and distinguish between the conceptual model and the representation paradigms (symbolic level) used to implement it.[13] NéoGanesh is based on current Artificial Intelligence techniques: a knowledge representation that mixes objects, rules and temporal abstractions[16] in a distributed architecture.[14]

It combines a "tactical" component and a "strategic" component. The "strategic" component relies on the model and representation of the intensivist's decision-making process. The "tactical" component uses three physiological parameters to modify the level of assistance during pressure support mode ventilation, and to maintain the patient within a zone of acceptable ventilation defined as Zone of Respiratory Comfort: $12 < RR < 28$ cycles/min, $Vt > 300$ ml or 250 if weight < 55 Kg, $PetCO_2 < 55$ mmHg or 65 mmHg if COPD.

The system is based on the modeling of the medical expertise required to mechanically ventilate patients with the pressure support ventilation mode. It does not include mathematical equations of a physiological model. There are three reasons for that: i) in pathological situations, physiological models are uncertain and can require data that are not available in real-time, or data where the estimation is difficult or imprecise.

Data validation is still an open problem; ii) physiological models do not always represent useful information to the clinician in decision making. For instance, to follow up the recovery of patient after anaesthesia, pharmacological equations are imprecise and not used in practice; iii) the decision making process of clinicians may be less variable than the complex physiology of patients.

This is reinforced by the introduction of protocols or guidelines for mechanical ventilation based on objective measurements like respiratory frequency or the rapid shallow breathing index. In conclusion, it seems simpler to model decision-making based on objective measurements, rather than based on physiology and multiple assumptions of the patient's behavior.

Therefore the NéoGanesh system is more a "decision-driven" system than a "patient-driven" system, although it indeed uses data coming from the patient.

The introduction of a new mode of ventilation such as PAV,[50] ALV[28] or ARIS[5] is a long and difficult process. Therefore, the choice is to i) to ventilate patients with a standard ventilation mode, pressure support ventilation, largely used for weaning, and ii) to add heuristic knowledge to improve its use and to facilitate the weaning process.

SOME CLINICAL RESULTS

NéoGanesh has been used in closed-loop and tested in more than sixty ventilated patients at Henri Mondor hospital (Créteil, France). Two types of evaluation were performed i) one set of tests to assess the capacity of the system to control the level of assistance in accordance to the patient's needs (evaluation of the tactical level) and ii) a second set of tests to assess the decision of extubation provided by the system (evaluation of the strategic level).

EVALUATION OF THE MANAGEMENT OF MECHANICAL VENTILATION

In a preliminary study, two different groups of patients were ventilated, both with NéoGanesh.

The two groups represented two different steps in the course of mechanical ventilation. The first group (n=9) was composed of patients considered as candidates for weaning, and the second one (n=10) of severe patients needing to be maintained under mechanical ventilation.

The mean time spent within the Zone of Respiratory Comfort expressed as the percentage of the total ventilation duration was 99% for the first group and 90% for the second group.

In a more recent study, 10 patients 24±4 hours were randomly ventilated on Pressure Support Ventilation (PSV) with NéoGanesh and 23±3 hours without standard pressure support ventilation (PSV) without NéoGanesh. In standard PSV, the clinician in charge could modify the pressure support level at his/her discretion. The mean pressure support level was similar with the two modes (17±4cmH_2O and 19±6 cmH_2O without and with NéoGanesh, respectively). The mean time spent in the Zone of Respiratory Comfort was 66±24% and 93±8% without and with NéoGanesh, respectively.

The number of changes in PSV setting was considerably higher

with NéoGanesh (56±40) than with standard PSV (1±2). The mean time spent in a condition of critical ventilation (RR> 35 cycles/min, Vt < 300 ml or $PetCO_2$ ↑↑ 55 mmHg) was 3% with NéoGanesh compared to 23% with standard standard PSV.

Lastly, the time spent with a high level of occlusion pressure (P0.1), suggesting a high work of breathing, was significantly reduced with the knowledge-based system. NéoGanesh tries to automatically decrease the level of pressure support.

For some patients weaning can be a long and difficult process. Continuous adjustment of mechanical assistance as performed by NéoGanesh may positively influence the weaning outcome. The level of pressure support may be a useful guide for determining the optimal time for performing tracheal extubation.

This strategy was implemented in NéoGanesh: when the patient is ventilated with a low level of assistance (9 cmH_2O for patients with an endotracheal tube or 5 cmH_2O for patients with a tracheotomy cannula), an observation period is triggered (1 or 2 hours depending whether the level of pressure support after one hour of ventilation is 15 < or ↑↑ 15 cmH_2O respectively) and a decision about extubation is displayed on the computer screen. For 38 patients, the decisions between what was given by NéoGanesh to the standard set of weaning tests (pre-weaning tests + 2 hours on T-piece + 48 hours of follow-up) were compared. The negative predictive value was equal in the two cases. However, the positive predictive value was of 89% for NéoGanesh and 77% for standard PSV, and 81% for the rapid shallow breathing index alone[11]. NéoGanesh predicted failure of weaning for 5 patients who tolerated the 2-hour T-piece trial but eventually failed weaning.

TOWARDS SMART VENTILATORS

It has been proposed to integrate medical knowledge into closed-loop controllers. Clinical results indicate the potential interests of such an approach: adaptation of assistance to the needs of the patient, reduced need for monitoring and better weaning outcomes. Further studies should now be launched to demonstrate that this new technology improves patient care or that it maintains patient care while decreasing cost. Up to now, none of the sophisticated closed-loop controllers proposed in the literature have had a major impact on clinical care. One reason suggested[18] is that these systems are pure engineer-oriented products not related to common clinical practice. Clearly, in designing knowledge-based closed-loop controllers, we changed this view in adopting a clinician-oriented approach. Based on objective criteria, weaning protocols have been proposed by medical experts.[2,19] Results from a prospective multicenter randomized clinical trial indicate that a computerized system for directing ventilator therapy can significantly improve morbidity.[17]

It is considered that, for ventilation management, medical knowledge is mature enough to be incorporated into smart ventilators that can really assist clinicians in bedside care. The work with the NéoGanesh system constitutes a first step towards the construction of such machines. Specific lung function testing maneuvers could be automatically performed by the smart ventilator in order to refine the evaluation of the patient's state, and then the therapy. This information could be used to manage several ventilatory modes. Improvement of planning capacities, via the automatic recognition of high level clinical scenarios as they are developing, is a prerequisite to improve the predictions and the dynamic adaptation of the strategy.

Interaction with the clinician could contribute to a dynamic adaptation of the strategy depending on information that cannot be directly accessible for the machine. Ventilatory care should be adapted to the patient's needs. Information provided directly by the patient about the quality of the assistance received could be incorporated into our future smart ventilators.

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Heart Rate Variability in Non-Apneic Snorers and Controls Before and After Continuous Positive Airway Pressure

Gregory J. Gates, Susan E. Mateika and Jason H. Mateika

ABSTRACT

Background: We hypothesized that sympathetic nervous system activity (SNSA) is increased and parasympathetic nervous system activity (PNSA) is decreased during non-rapid eye movement (NREM) sleep in non-apneic, otherwise healthy, snoring individuals compared to control. Moreover, we hypothesized that these alterations in snoring individuals would be more evident during non-snoring than snoring when compared to control.

Methods: To test these hypotheses, heart rate variability was used to measure PNSA and SNSA in 11 normotensive non-apneic snorers and 12 control subjects before and 7-days after adapting to nasal continuous positive airway pressure (nCPAP).

Results: Our results showed that SNSA was increased and PNSA was decreased in non-apneic snorers during NREM compared to control. However, these changes were only evident during the study in which snoring was eliminated with nCPAP. Conversely, during periods of snoring SNSA and PNSA were similar to measures obtained from the control group. Additionally, within the control group, SNSA and PNSA did not vary before and after nCPAP application.

Conclusion: Our findings suggest that long-lasting alterations in autonomic function may exist in snoring subjects that are otherwise healthy. Moreover, we speculate that because of competing inputs (ie inhibitory versus excitatory inputs) to the autonomic nervous system during snoring, the full impact of snoring on autonomic function is most evident during non-snoring periods.

Gates and Susan Mateika are with the Department of Biobehavioral Sciences, Teachers College, Columbia University, New York; Jason Mateika is with the Departments of Internal Medicine and Physiology, Wayne State University School of Medicine, and Research and Development, John D. Dingell Veterans Administration Medical Center, Detroit, MI. This work was supported by the American Heart Association. ResMed supplied the continuous positive pressure airway machines used in this study. Reprinted from BMC Pulmonary Medicine 2005, 5:9 doi 10.1186/1471-2466-5-9. This article is also available in a different format from http://www.biomedcentral.com/1471-2466/5/9, © 2005 Gates et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0).

BACKGROUND

Epidemiological findings have suggested that snoring is an independent risk factor for the development of daytime hypertension.[1-3] Moreover, studies completed in normotensive individuals suffering from obstructive sleep apnea have shown that increases in sympathetic nervous system activity (SNSA) precede the development of hypertension.[4] Given these findings, we hypothesized that nocturnal increases in SNSA and decreases in parasympathetic nervous system activity (PNSA) may exist in non-apneic normotensive snoring individuals. Additionally, we postulated that the impact of snoring on autonomic nervous system activity might be most evident during periods of non-snoring (ie either during wakefulness or during periods of non-snoring during sleep). This latter postulation was based on findings from humans during wakefulness[5-7] or sleep,[8,9] which showed that breathing frequency,[5-7,9] pattern (ie inspiratory and expiratory time)[5-7,9] and tidal volume[5,7,8] are altered in response to either snoring,[9] the application of high frequency oscillations (ie simulated snoring)[7,8] or breathing against an increased airway resistance.[5,6] Moreover, these alterations in breathing are accompanied by enhanced PNSA[6] or decreased SNSA.[10] Thus, we postulated that snoring elicits a two-fold response from the autonomic nervous system. An acute response occurs concomitantly with snoring, in which increases in SNSA and decreases in PNSA may not be clearly evident, and a longer lasting potentially permanent response in which increases in SNSA and decreases in PNSA are unmasked in the absence of snoring. To test these hypotheses, we used the technique of heart rate variability to measure PNSA and SNSA in non-apneic snorers and controls during non-rapid eye movement (NREM) sleep before and after the application of nasal continuous positive airway pressure (nCPAP).

Table 1: Anthropometric and blood pressure measures

Control						Snorer					
Subject	Sex	Age	BMI	MAP Awake	MAP NREM	Subject	Sex	Age	BMI	MAP Awake	MAP NREM
1	M	28	26.9	95	77	1	M	25	28.1	84	84
2	M	31	26.7	89	88	2	M	35	23	88	88
3	M	25	27.3	83	81	3	M	27	28	70	65
4	F	43	22.5	75	69	4	F	43	25.6	72	62
5	M	33	28	87	83	5	M	36	30	85	82
6	M	27	31	75	74	6	M	34	30	78	75
7	M	27	28.4	85	74	7	M	36	28	88	80
8	M	29	24.5	89	86	8	M	26	23	95	75
9	F	25	20	85	71	9	F	27	24	79	71
10	M	32	27	80	83	10	M	38	26	91	89
11	M	28	23.2	87	80	11	M	28	24.1	88	82
12	M	26	22.9	81	72						
Mean		**29.5**	**25.7**	**84.3**	**78.2**	**Mean**		**32.3**	**26.3**	**83.5**	**77.5**
S.E.		**1.4**	**0.9**	**1.7**	**6.2**	**S.E.**		**1.8**	**0.8**	**2.4**	**2.7**

METHODS

Eleven self-reported snoring subjects with no known medical conditions and 12 non-snoring control subjects were recruited from the community. The snoring group was comprised of 9 males (1 Asian, 1 African-American, 2 Hispanic and 5 Caucasian) and 2 Caucasian females (Table 1). The control group was comprised of 10 males (1 Asian, 1 African-American, 2 Hispanic and 6 Caucasian) and 2 Caucasian females (Table 1). All subjects gave their informed consent to participate in the study, which was approved by the Institutional Review Boards of Teachers College, Columbia University, Wayne State University and John D. Dingell VA Medical Center.

The snoring and control subjects visited the sleep laboratory on three occasions. Twenty-four hours prior to each occasion the subjects were advised to avoid alcohol and caffeine. During the first visit to the laboratory, which is referred to from hereon as the preliminary study, subjects received a physical examination, which included three separate measures of blood pressure using a standard mercury sphygmomanometer that were separated by 15 minutes. Additionally, subjects completed a general health questionnaire to confirm the absence of preexisting medical conditions. Subsequently, subjects completed a sleep study in order to familiarize themselves with the laboratory environment and to confirm that the subjects were non-apneic snoring or non-snoring individuals. Moreover, to confirm that subjects were normotensive, beat-to-beat measures of blood pressure were obtained for 1 hour during wakefulness and throughout NREM sleep (see Nocturnal polysomnography for further details). The blood pressure measures were in addition to the values obtained during wakefulness using the sphygmomanometer. If subjects suffered from another sleep disorder (i.e. obstructive sleep apnea, insomnia or upper airway resistance syndrome) they were excluded from the study. Individuals with upper airway resistance syndrome were excluded because we were interested in investigating the impact of snoring on heart rate variability independent of excessive cortical arousal from sleep.

The second study was completed in order to measure the autonomic variables outlined below during NREM sleep. This second study will be referred to as Trial 1 from hereon. Subsequent to the completion of Trial 1, the snoring and control subjects adapted to 5 cmH_2O of nasal continuous positive airway pressure (nCPAP) for 7 days at home. The selection of the nCPAP pressure was based on results from our pilot data, which showed that this level of pressure effectively eliminated snoring in non-apneic individuals. The purpose of the adaptation period was to ensure that the subjects were able to tolerate nCPAP for a minimum of 4 hours during completion of a third sleep study (Trial 2). Nasal continuous positive airway pressure was employed initially for 1 hour during the first night at home. Thereafter, the duration of treatment was increased by an additional hour each night until 4 hours of nCPAP was tolerated. During the adaptation period subjects received a phone call on days 3 and 6 to ensure that the protocol was being followed. During all sleep studies subjects were required to sleep in the supine position. The subjects were monitored via an infrared camera to ensure that this position was maintained throughout the sleep period.

Nocturnal polysomnography

The sleep monitoring montage included an electroencephalogram (C3/A2, C4/A1, O1/A2, O2/A1), electrooculogram, submental and tibialis anterior electromyogram and an electrocardiogram. Abdominal movements were monitored using a piezoelectric band (Pro-tech, Woodinville, WA) and nasal pressure was measured using a pressure transducer/airflow sensor (Pro-tech, Woodinville, WA). Thus, breathing frequency was monitored breath-by-breath. Oxygen saturation was measured using a pulse oximeter (Biox 3700, Ohmeda Corp, Boulder, CO). Snoring was measured using a microphone that was mounted on the wall located adjacent to the subjects head. During the preliminary study, blood pressure was monitored continuously and non-invasively from the third finger of the left hand using a digital infrared photoplethysmograph (Finapres 2300, Ohmeda Corp, Madison, WI). The accuracy of the blood pressure monitor was verified during pre-sleep wakefulness and nocturnal awakenings by comparing its values to measurements made with a standard mercury sphygmomanometer. To ensure that the monitoring site of the Finapres was adequately perfused with blood through the evening, the operation of the Finapres was discontinued consistently during rapid eye movement sleep (REM) and at times during NREM sleep if necessary. The total number of segments analyzed for each subject represented on average 2.2

Table 2: Sleep Measures

	Control(n = 12)		Snorer (n = 11)	
	NREM sleep (without CPAP) (Trial 1)	NREM sleep (with CPAP) (Trial 2)	NREM sleep (without CPAP) (Trial 1)	NREM sleep (with CPAP) (Trial 2)
Apnea index (apnea/hr)	0.38 ± 0.15	0.67 ± 0.34	1.19 ± 0.56	0.16 ± 0.07
Hypopnea index (hypopnea/hr)	1.80 ± 0.71	0.89 ± 0.29	2.14 ± 0.62	0.34 ± 0.19
Arousal index (arousals/hr)	12.87 ± 1.39	12.87 ± 1.02	14.11 ± 2.20	10.74 ± 1.83
Nocturnal Oxygen Saturation (%)	96.58 ± 0.23	96.7 ± 0.30	96.10 ± 0.39	96.40 ± 0.42
Sleep efficiency (%)	88.76 ± 3.62	88.09 ± 2.02	86.32 ± 2.18	83.73 ± 1.99
% of time in Stage I	11.29 ± 1.83	7.83 ± 0.90	7.22 ± 1.04	8.88 ± 1.57
% of time in Stage II	46.04 ± 1.42	45.53 ± 1.91	48.07 ± 2.58	48.48 ± 2.57
% of time in Slow Wave Sleep	22.45 ± 3.10	20.65 ± 1.42	21.95 ± 1.41	21.27 ± 2.36

Table 3: Autonomic measures obtained from controls and non-apneic snorers during wakefulness and non-rapid eye movement sleep

	Control (n = 12)		Snorer (n = 11)		
	NREM sleep (without CPAP) (Trial 1)	NREM sleep (with CPAP) (Trial 2)	NREM sleep (without CPAP) (snoring) (Trial 1)	NREM sleep (without CPAP) (non-snoring) (Trial 1)	NREM sleep (with CPAP) (Trial 2)
Heart rate (beats/min)	55.25 ± 1.53	54.58 ± 1.90	57.27 ± 1.45	55.18 ± 1.77	56.27 ± 1.74
Breathing Frequency (breaths/min)	14.89 ± 0.53	14.35 ± 0.46	13.85 ± 0.69	13.91 ± 0.53	14.23 ± 0.62
ln LF	7.24 ± 0.16	7.11 ± 0.13	7.68 ± 0.16	7.99 ± 0.27	7.41 ± 0.19
ln HF	7.99 ± 0.21	7.72 ± 0.19	8.19 ± 0.13	7.83 ± 0.18§	7.40 ± 0.21§
LF/HF	0.57 ± 0.12	0.70 ± 0.14	0.69 ± 0.08	1.43 ± 0.29§	1.20 ± 0.18*
HF (nu)	67.51 ± 3.60	64.44 ± 3.95	62.46 ± 2.60	46.71 ± 5.38§	50.32 ± 4.18*
LF (nu)	34.27 ± 4.37	39.24 ± 5.01	36.61 ± 2.58	52.0 ± 5.26§	48.79 ± 4.09*

* – significantly different from snorer – without CPAP – snoring; control – with CPAP
§ – significantly different from snorer – without CPAP – snoring

hours of data obtained from stage II and SWS recorded over the entire sleep period.

During sleep all physiological variables were analogue to digitally converted at a sampling frequency of 200 Hz/channel and input into a microcomputer using commercially available software package (Gamma, Version 4.0, Astro-Med Inc, West Warwick, RI).

Data analysis (sleep variables)

Sleep was staged in 30-s epochs according to standard criteria.[11,12] For each subject the total sleep period time as well as the percent of total sleep time spent in a given sleep stage was calculated. The total number of arousals, apneas, hypopneas, snores, and the mean, minimal and maximal oxygen saturation measured was calculated for the total sleep time. An apnea was defined as the absence of inspiratory airflow for a minimum of 10 s. The apnea index was defined as the total number of apneas per hour of sleep. A hypopnea was defined as greater than a 50% reduction in the flow signal lasting more than 10 s, accompanied by a 2% decrease in oxygen saturation. We chose to employ a 2% oxygen desaturation criteria (rather than 3 or 4%) in order to ensure that snoring associated with small changes in oxygen saturation were identified. Based on the use of this criterion we reasoned that if the number of breathing events was similar between snoring and control subjects and less than 5, we could be reasonably confident that the subjects recruited for this study were non-apneic. The hypopnea index was defined as the total number of hypopneas per hour of sleep time. A breath characterized by respiratory noises that registered as an obvious deflection from the baseline of the snoring channel was counted as a snore. In addition, the respiratory noises were subjectively determined to be snores by a polysomnographic technologist monitoring an audio-visual system. We are confident that the sounds recorded were associated with snoring since normal and heavy breathing during wakefulness did not register on the sound system while simulated snoring during wakefulness was detected.

After staging the sleep studies completed during trial 1 and 2, we randomly selected a 15-minute snoring segment from NREM sleep (stage 2 or SWS) recorded between midnight-2 am, 2-4 am and 4-6 am. Thus, 3-15 segments were selected from sleep studies completed during Trials 1 and 2. The segments selected were devoid of apneas, hypopneas and arousals. The snoring segments (Trial 1) were identified as such if 67-100% of the breaths in a given segment were associated with snoring. Three segments were selected from each study to ensure that our findings reflected the impact of snoring on heart rate variability throughout the night. However, we did not report the results obtained from the snoring segments selected from the beginning, middle and end of the night separately. Although the

data was analyzed originally in this fashion, we found that our findings were not time dependent, and thus the data from the three snoring segments were combined.
In addition to the snoring segments, we also analyzed one 15-minute non-snoring segment recorded during Trial 1. In most subjects, only one 15-minute non-snoring segment in deep stage II or SWS was available for analysis. We chose to analyze a non-snoring segment to compare heart rate variability measures in snoring subjects during non-snoring, which was independent of nCPAP application, and snoring.

Data analysis (respiratory, cardiovascular and autonomic variables)

The number of snores and breaths was calculated for each segment. Subsequently, the values calculated were divided by the total segment time and reported as snoring frequency (S_f) and breathing frequency (B_f) (snores/min and breaths/min, respectively). To obtain a measure of SNSA and PNSA the R waves of the electrocardiogram were identified using a threshold detection program. The time intervals between the detected R waves (interbeat interval - IBI) were plotted and the mean IBI was calculated for each segment. Prior to frequency analysis, each 15-minute segment was divided into three 5-minute segments and the interbeat intervals were re-sampled at 20 Hz, which provided 6000 equidistant data points per 5 minute segment.[13] For each 5-min segment, an auto power spectrum was created via a Fast Fourier transform of the interpolated IBI data. The resulting spectrum was integrated and areas associated with discrete frequency bands were determined. Power spectra within the 0.04-0.15 Hz range are considered low frequency components (LF), whereas frequencies of 0.15-0.4 Hz are defined as high frequency components (HF). It is assumed that the power content of the HF component represents PNSA whereas the power content in the LF domain (0.04-0.15 Hz) represents SNSA and PNSA at the sinus node.[13,14] The ratio of LF/HF is assumed to be a measure of SNSA.

The absolute values of LF and HF were ln transformed so that the data was normally distributed. Additionally, to minimize the effect that changes in total power have on the absolute values of the low and high frequency power, the LF and HF values were normalized.[13] The presentation of LF and HF values in normalized units represents the relative value of each power component in proportion to the total power minus the very low frequency component. Once the very low frequency component is subtracted, the remaining power equals LF+HF. Thus: Normalized LF = LF/(LF+HF); Normalized HF = HF/(LF+HF).

The normalized units assume a balanced behavior of the sympathetic (normalized LF) and parasympathetic nervous system (normalized HF values). Statistical analysis was completed on both the ln transformed and normalized values (see Statistical analysis below). However, for the sake of clarity and based on the guidelines that LF and HF values should be corrected for total power, the normalized data was used as our point of reference in the discussion (see critique of the methods for further discussion of this point).

STATISTICAL ANALYSIS

Unpaired t-tests were used to compare the anthropometric data between groups. A two-way analysis of variance in conjunction with Student-Newman-Keuls post hoc test was used to determine if differences in mean arterial blood pressure existed between groups during wakefulness and NREM sleep during completion of the preliminary study. The two factors in the design were "subject population" (i.e. snorers versus controls) and "arousal level" (ie wakefulness vs. sleep). A similar analysis was employed to determine if differences in ln LF, ln HF, LF/HF, normalized LF and normalized HF existed between groups. The two factors in the design were *subject population* (i.e. snorers versus controls) and *treatment* (ie before versus after nCPAP treatment). This analysis was also used to determine if differences in sleep architecture existed between and within groups before and after nCPAP treatment. A paired t-test was used to determine whether ln LF, ln HF, LF/HF, normalized LF and normalized HF during non-snoring in trial 1 was different from measures obtained during snoring in Trial 1. All values in the tables are presented as means ± SE and the level of significance chosen was $p \leq 0.05$.

RESULTS

Age, body mass index and blood pressure measured during wakefulness and sleep throughout the preliminary sleep study, were not significantly different between the snoring and control groups (Table 1). Additionally, apnea index, hypopnea index, arousal index and mean nocturnal oxygen saturation were not different between the snoring and control groups during Trial 1 (Table 2). Similarly, sleep efficiency and the percentage of time spent in a given stage of NREM sleep did not vary significantly between groups during completion of Trial 1 or Trial 2 (Table 2). Moreover, the sleep architecture during Trial 2 did not differ significantly from that reported during Trial 1 within both groups (Table 2).

Snoring episodes measured from the non-apneic snorers were characterized by an average snoring frequency of 11.60 ± 0.43 snores per minute. In contrast, no snoring was detected from the control group. The application of nCPAP effectively eliminated snoring in all subjects.

Breathing frequency and heart rate were not significantly different between or within groups for all conditions during Trial 1 and 2 (Table 3). The two-way analysis of variance revealed that a significant subject population (ie snorers versus controls) x treatment (ie before versus after nCPAP treatment) interaction existed for both ln HF and normalized HF. Post-hoc analysis revealed that ln HF and normalized HF recorded during snoring periods were not significantly different from control during trial 1 (ie before nCPAP treatment) (ln HF - $p = 0.47$; normalized HF - $p = 0.34$, respectively) (Table 3). In contrast, normalized HF recorded during nCPAP treatment (i.e. trial 2) in the snoring population was lower than normalized HF recorded from the control population during nCPAP treatment ($p = 0.01$) (Table 3). Moreover, 1n HF and normalized HF recorded during nCPAP treatment (ie Trial 2) in the snoring population was significantly less compared to similar measures obtained from snoring periods during Trial 1 (ln HF - $p < 0.0001$; normalized HF - $p = 0.001$) (Table 3).

A significant subject population (ie snorers versus controls) x treatment (ie before versus after nCPAP treatment) interaction also existed for normalized LF and LF/HF. Post-hoc analysis showed that normalized LF and LF/HF recorded during snoring was not significantly different from control during Trial 1 (normalized LF - $p = 0.36$; LF/HF - $p = 0.54$, respectively) (Table 3). In contrast, normalized LF and LF/HF recorded during nCPAP treatment (ie Trial 2) in the snoring population was greater than measures recorded from the control population

during treatment (normalized LF - p = 0.01; LF/HF - p = 0.01), and from similar measures recorded from snoring periods during trial 1 (normalized LF - p <0.001; LF/HF - p <0.001) (Table 3).

Within the snoring group during trial 1, ln HF (p = 0.03) and normalized HF (p = 0.01) were less and LF/HF (p = 0.02) and normalized LF (p = 0.01) were greater during non-snoring as compared to snoring (Table 3).

DISCUSSION

Summary of findings

Based on the normalized HF and LF values our major findings are that PNSA and SNSA during snoring (i.e. Trial 1) was not significantly different from measures acquired from non-snoring control subjects. However, PNSA was decreased and SNSA was increased in the snoring population compared to control when snoring was abolished with nCPAP (ie Trial 2). Similarly, PNSA was less and SNSA was greater when snoring was abolished (ie non-snoring periods during trial 1 or during nCPAP application in Trial 2) compared to when it was present (trial 1) within the snoring population. Finally, within the control group PNSA and SNSA did not vary before and after treatment with nCPAP.

Critique of the methods

Our subjects were exposed to nCPAP for a 7-day adaptation period prior to completing Trial 2. This adaptation period occurred after a baseline study was completed. Consequently, the baseline and treatment study were not randomized. Nevertheless, if the order of the trials impacted on our measures we would expect that the response to nCPAP application would have been similar between groups since both groups were comparable (eg healthy, no complaint of daytime sleepiness) in all aspects with the exception of snoring. This was not the case.

It is also unlikely that any differences between groups during Trial 2 were a consequence of discomfort associated with being unfamiliar with nCPAP treatment. Both the snoring and control subjects adapted to the treatment for a similar duration of time prior to participating in Trial 2, and no significant differences in heart rate variability occurred within the control group when comparing measures from Trial 1 and 2. Moreover, it is also improbable that the differences observed were a consequence of discrepancies in nCPAP compliance because, based on subject self-report, this measure was similar between groups. Although it is possible that some subjects did not truthfully report their compliance, we believe it is unlikely that healthy non-snorers and non-apneic snorers would have tolerated nCPAP for at least 4 hours during Trial 2 if they did not adhere to the protocol during the adaptation period. The ability of the subject's to tolerate nCPAP is supported by the measures of sleep architecture, which were similar between trials 1 and 2. Lastly, it is doubtful that the impact of nCPAP on cardiovascular function,[15] and consequently autonomic function, was different between groups since the applied pressure was identical (5 cmH_2O in all cases) for both groups.

Heart rate variability has been used in numerous studies to obtain non-invasive measures of SNSA (LF/HF and normalized LF) and PNSA (HF and normalized HF). The changes in the HF domain that we observed in our snoring subjects were likely indicative of changes in PNSA since this assumption has been well established by a number of physiological investigations.[13] In contrast, questions remain regarding the validity of LF/HF and normalized LF as a non-invasive indicator of SNSA.[14] One issue is that the LF/HF ratio assumes that HF in the denominator (ie PNSA) cancels out the influence of PNSA in the low frequency domain of the power spectrum, leaving the LF/HF ratio as a measure of SNSA. Although we assume that LF/HF and normalized LF are indicative of changes in SNSA we acknowledge that the support for this assumption is equivocal. Nonetheless, we have included this analysis along with the HF measures for those who accept that LF/HF or normalized LF reflects SNSA.

Investigators have shown that absolute values of LF and HF are impacted by changes in total power.[13] Consequently, it has been suggested that absolute LF and HF values should be normalized based on changes in total power.[13] Based on this guideline, and for the sake of clarity, we have used normalized LF and HF as our reference point in the subsequent discussion of the results. Nevertheless, independent of whether one accepts that normalization of our data is necessary, results obtained from the normalized LF (i.e. SNSA) and HF (i.e. PNSA) data are similar to the ratio of absolute LF/HF (ie SNSA) and ln HF (ie PNSA).

Parasympathetic nervous system activity and SNSA during snoring (ie Trial 1) were not significantly different from measures obtained from control subjects. This finding on its own implies that snoring does not influence autonomic function. However, our results showed that PNSA was less and SNSA was greater in the snoring group compared to control when snoring was abolished during Trial 2. Similarly, PNSA was less and SNSA was greater in the snoring group when snoring was abolished compared to when snoring was present.

These latter two findings have three primary implications. The first implication is that snoring may induce an acute increase in PNSA and a decrease in SNSA, which may mask the more deleterious effect that snoring has on autonomic function. This would account for the similarities in autonomic function observed between groups during Trial 1 despite the differences that were present during Trial 2. The second implication is that the deleterious long-lasting impact that snoring may have on autonomic function (see Physiological Mechanisms for additional discussion on this issue) is more evident during periods of non-snoring as indicated by the differences observed between the groups during Trial 2. The third implication is that short-term nCPAP treatment did not eliminate this long-lasting impact. Arguably, SNSA might have decreased and PNSA increased because of nCPAP treatment. However, the lack of response to treatment is not surprising since the subjects did not receive treatment for a prolonged period with respect to number of days and nighttime hours of exposure.

Physiological mechanisms

We can only speculate on the mechanism responsible for the potential decrease in SNSA and increase in PNSA that occurs during snoring. Snoring is often associated with increased airway resistance and the development of more negative intrathoracic pressures.[9] Additionally, snoring, or the application of high frequency, low amplitude pressure oscillations (which simulates snoring), has been associated with i) decreases in breathing frequency[5,6,9] ii) increases in inspiratory time or inspiratory time/total time ratio[5,6,9] and iii) increases in tidal volume.[5,7,8,16] Moreover, breathing frequency, breathing pattern or tidal volume are known to impact on measures of heart rate variability.[13,14] Thus, it is possible that the increase in HF that we

observed during snoring, which mirrors the amplitude of respiratory sinus arrhythmia, was caused by changes in one or more of these variables. Since snoring did not alter breathing frequency in our study, we speculate that alterations in pattern and/or tidal volume may have contributed to the increase in measures of HF. More specifically, prolongation of inspiratory time coupled with an increase in tidal volume may have led to increased activation of pulmonary vagal afferents, which have a profound influence on respiratory sinus arrhythmia, and hence measures of HF. Additionally, activation of pulmonary vagal afferents are known to inhibit SNSA,[17] thus the decrease in SNSA during snoring may have been a consequence of this activation.

Since snoring itself was not accompanied by an increase in SNSA or decrease in PNSA compared to control, the question remains as to how snoring may ultimately result in long-lasting increases in SNSA and/or decreases in PNSA during non-snoring periods. There are at least three possibilities. First, it is possible that snoring subjects participating in our study were genetically predisposed to a reduction in PNSA and an increase in SNSA. Given our experimental design, we cannot eliminate this possibility. Future studies designed to examine autonomic nervous system activity in non-apneic snorers, before and after prolonged nCPAP treatment, may resolve whether the changes in PNSA and SNSA we observed are an inheritable trait.

Second, the impact of exposure to nCPAP treatment on the non-apneic snorers compared to controls may have been different (see Critique of methods for detailed discussion on this issue). We consider this possibility highly unlikely since the nCPAP pressure used and the duration of application was similar for both populations. More importantly, even in the absence of nCPAP treatment, PNSA decreased and SNSA increased during non-snoring compared to snoring (ie non-snoring vs snoring in Trial 1).

Third, we postulate that inputs activated during snoring concurrently with vagal afferents may ultimately be responsible for the long-lasting changes in PNSA and SNSA activity that we observed. Thus, the influence of pulmonary vagal afferents may predominate during snoring, leading to a reduction in SNSA and an increase in PNSA. However, we speculate that resistive loading and snoring may concurrently enhance brainstem activity (i.e. the reticular activating system), possibly via inputs from mechanoreceptors,[18] metabolic receptors,[10,19] and upper airway receptors,[20,21] that eventually leads to increases in SNSA and decreases in PNSA once snoring is terminated. The possibility that snoring may influence brainstem activation and ultimately autonomic nervous system activity is supported by the findings of Lofaso and colleagues.[22] These investigators showed in non-apneic snorers that graded levels of arousal (based on various changes in EEG characteristics) subsequent to termination of snoring were associated with increases in heart rate and blood pressure. More importantly for our findings, Lofaso and colleagues[22] showed that even in the absence of cortical arousal (no evidence of EEG changes) blood pressure and heart rate were greater immediately after termination of snoring compared to measures obtained during snoring.[22] The possibility that both the acute and long-lasting impact of brainstem activation is masked during snoring, when pulmonary vagal afferents are most influential, is supported by studies which have shown that muscle sympathetic nervous system activity is profoundly inhibited by the activation of pulmonary vagal afferents in the presence of stimuli known to enhance SNSA.[23]

Clinical implications

The upper airway resistance syndrome has been described as a form of sleep disordered breathing that is characterized by repetitive increases in resistance in airflow within the upper airway leading to brief cortical arousals and daytime somnolence.[24] In contrast to this clinical description, our subjects did not display excessive numbers of cortical arousal compared to control and did not suffer from daytime somnolence. Nevertheless, despite the absence of cortical arousal we showed that PNSA was decreased and SNSA activity was increased during non-snoring periods in non-apneic snorers compared to control and during non-snoring periods compared to snoring periods with the non-apneic population. The latter finding is similar to results which showed that blood pressure and heart rate increased at the termination of snoring independent of cortical arousal.[22,25] Thus, alterations in autonomic nervous system activity may lead to autonomic and cardiovascular alterations in individuals with increased airflow resistance independent of evidence of cortical arousal. Moreover, our results suggest that alterations in heart rate variability may precede changes in traditional markers of cardiovascular function (i.e. blood pressure) in non-apneic snoring individuals. Given that measures of heart rate variability have been shown to be useful as a prognostic indicator of future cardiovascular events[13,14,26-30] these measures may be useful in determining whether normotensive individuals that snore (or for that matter suffer from obstructive sleep apnea) are at increased risk for the development of hypertension or cardiovascular disease. Whether the alterations that we observed in our relatively young, healthy and predominantly male snoring population would benefit from long-term treatment with nCPAP, or become more severe with age and/or the presence of other co-morbid conditions remains to be determined.

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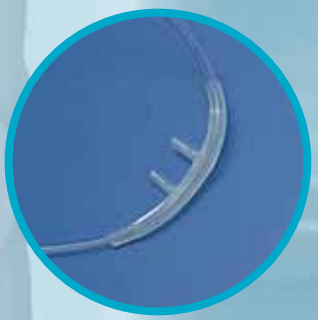

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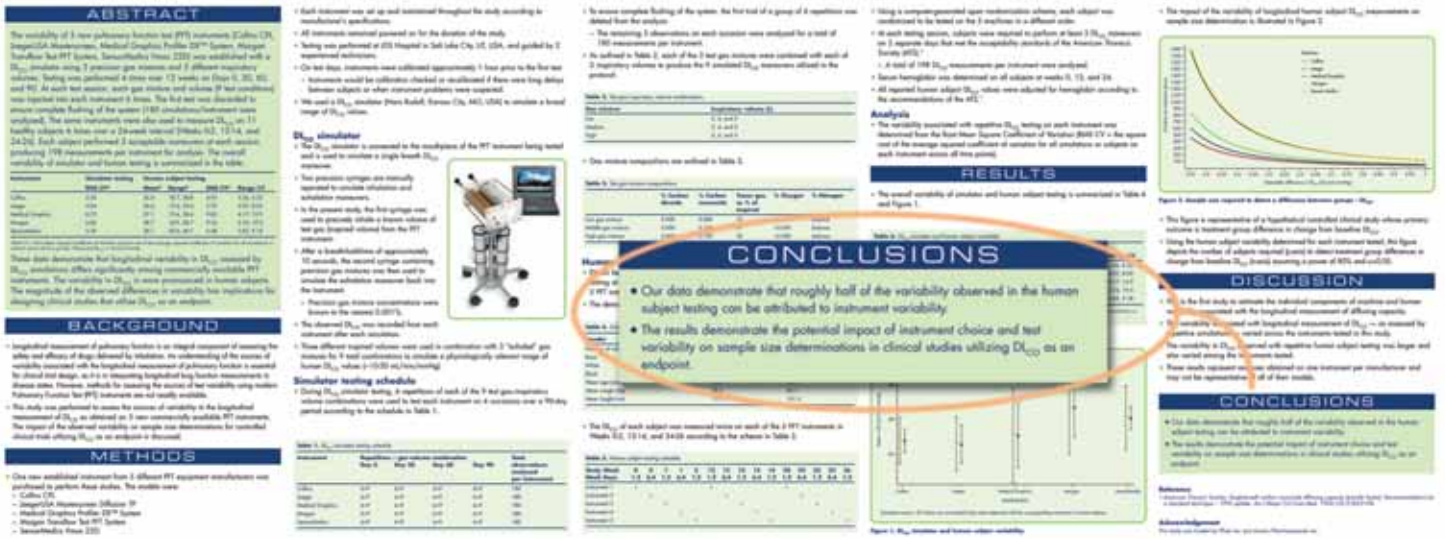
Instrument performance in the longitudinal measurement of diffusing capacity (DL_{CO})

R. Jensen,[1] J.G. Teeter,[2] R.D. England,[2] H.J. White,[2] D.H. Pickering,[2] H.M. Howell,[1] R.O. Crapo[1]
[1]LDS Hospital and University of Utah, Salt Lake City, UT, USA; [2]Pfizer Global Research and Development, Groton, CT, USA



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Instrument Performance in the Longitudinal Measurement of Diffusing Capacity (DI_{co})

R.L. Jensen, J.G. Teeter, R.D. England, H.J. White, E.H. Pickering, H.M. Howell, R.O. Crapo

ABSTRACT

The variability of 5 new pulmonary function test (PFT) instruments (Collins CPL, JaegerUSA Masterscreen, Medical Graphics Profiler DX™ System, Morgan Transflow Test PFT System, SensorMedics Vmax 22D) was established with a DL_{CO} simulator using 3 precision gas mixtures and 3 different inspiratory volumes. Testing was performed 4 times over 12 weeks on Days 0, 30, 60, and 90. At each test session, each gas mixture and volume (9 test conditions) was injected into each instrument 6 times. The first test was discarded to ensure complete flushing of the system (180 simulations/instrument were analyzed). The same instruments were also used to measure DL_{CO} on 11 healthy subjects 6 times over a 24-week interval (Weeks 0-2, 12-14, and 24-26). Each subject performed 3 acceptable maneuvers at each session, producing 198 measurements per instrument for analysis. The overall variability of simulator and human testing is summarized in the table, "Instruments," below.

These data demonstrate that longitudinal variability in DL_{CO} assessed by DL_{CO} simulations differs significantly among commercially available PFT instruments. The variability in DL_{CO} is more pronounced in human subjects. The magnitude of the observed differences in variability has implications for designing clinical studies that utilize DL_{CO} as an endpoint.

Instrument	Simulator testing	Human subject testing			
	RMS CV[a]	Mean[b]	Range[b]	RMS CV[a]	Range CV
Collins	2.52	26.8	18.7, 38.8	4.93	3.26, 6.52
Jaeger	4.04	26.6	19.4, 35.6	5.79	3.92, 8.05
Medical Graphics	6.73	27.1	19.4, 38.4	9.83	4.17, 15.9
Morgan	6.06	28.7	18.9, 38.7	9.36	2.74, 19.5
SensorMedics	2.30	28.1	20.0, 40.7	6.48	3.82, 9.18

[a]RMS CV = Root Mean Square Coefficient of Variation (square root of the average squared coefficient of variation for all simulations or subjects across all time points); [b]Measured DL_{CO} in mL/min/mmHg.

BACKGROUND

Longitudinal measurement of pulmonary function is an integral component of assessing the safety and efficacy of drugs delivered by inhalation. An understanding of the sources of variability associated with the longitudinal measurement of pulmonary function is essential for clinical trial design, as it is in interpreting longitudinal lung function measurements in disease states. However, methods for assessing the sources of test variability using modern Pulmonary Function Test (PFT) instruments are not readily available.

This study was performed to assess the sources of variability in the longitudinal measurement of DL_{CO} as obtained on 5 new commercially available PFT instruments. The impact of the observed variability on sample size determinations for controlled clinical trials utilizing DL_{CO} as an endpoint is discussed.

METHODS

One new established instrument from 5 different PFT equipment manufacturers was purchased to perform these studies. The models were:

- Collins CPL
- JaegerUSA Masterscreen Diffusion TP
- Medical Graphics Profiler DX System
- Morgan Transflow Test PFT System
- SensorMedics Vmax 22D

Each instrument was set up and maintained throughout the study according to manufacturer's specifications.

All instruments remained powered on for the duration of the study.

Testing was performed at LDS Hospital in Salt Lake City, UT, USA, and guided by 2 experienced technicians.

Jensen, Howell and Crapo are with LDS Hospital and University of Utah, Salt Lake City, UT; Teeter, England, White and Pickering are with Pfizer Global Research and Development, Groton, CT. The study was funded by Pfizer Inc and Aventis Pharmaceuticals, Inc.

Table 1. *DL_{CO} simulator testing schedule.*

Instrument	Repetitions × gas-volume combination Day 0	Day 30	Day 60	Day 90	Total observations analyzed per instrument
Collins	6×9	6×9	6×9	6×9	180
Jaeger	6×9	6×9	6×9	6×9	180
Medical Graphics	6×9	6×9	6×9	6×9	180
Morgan	6×9	6×9	6×9	6×9	180
SensorMedics	6×9	6×9	6×9	6×9	180

Table 2. *Test gas–inspiratory volume combinations.*

Gas mixture	Inspiratory volume (L)
Low	3, 4, and 5
Medium	3, 4, and 5
High	3, 4, and 5

Table 3. *Test gas mixture compositions.*

	% Carbon dioxide	% Carbon monoxide	Tracer gas, as % of inspired	% Oxygen	% Nitrogen
Low gas mixture	5.000	0.080	75	16.000	balance
Middle gas mixture	5.000	0.100	67	16.000	balance
High gas mixture	5.000	0.130	55	16.000	balance

Table 4. *Subject demographic characteristics.*

Gender	Male	Female
Number of subjects	4	7
Race:		
White	4	6
Black	0	1
Mean age (years)	45.5	35.7
Mean weight (kg)	78.3	60.1
Mean height (cm)	177.0	161.4

Table 5. *Human subject testing schedule.*

Study Week Week Days	0 1,2	0 3,4	1 1,2	1 3,4	2 1,2	12 1,2	12 3,4	13 1,2	13 3,4	14 1,2	24 1,2	24 3,4	25 1,2	25 3,4	26 1,2
Instrument 1	×					×					×				
Instrument 2		×					×					×			
Instrument 3			×					×					×		
Instrument 4				×					×					×	
Instrument 5					×					×					×

Table 6. *DL_{CO} simulator and human subject variability.*

Instrument	Simulator testing RMS CV[a]	Human subject testing Mean[b]	Range[b]	RMS CV[a]	Range CV
Collins	2.52	26.8	18.7, 38.8	4.93	3.26, 6.52
Jaeger	4.04	26.6	19.4, 35.6	5.79	3.92, 8.05
Medical Graphics	6.73	27.1	19.4, 38.4	9.83	4.17, 15.9
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SensorMedics	2.30	28.1	20.0, 40.7	6.48	3.82, 9.18

On test days, instruments were calibrated approximately 1 hour prior to the first test. Instruments would be calibration checked or recalibrated if there were long delays between subjects or when instrument problems were suspected.

We used a DL_{CO} simulator (Hans Rudolph, Kansas City, MO, USA) to simulate a broad range of DL_{CO} values.

DLCO simulator

The DL_{CO} simulator is connected to the mouthpiece of the PFT instrument being tested and is used to simulate a single breath DL_{CO} maneuver.

Two precision syringes are manually operated to simulate inhalation and exhalation maneuvers.

In the present study, the first syringe was used to precisely inhale a known volume of test gas (inspired volume) from the PFT instrument.

After a breath-hold-time of approximately 10 seconds, the second syringe containing precision gas mixtures was then used to simulate the exhalation maneuver back into the instrument. Precision gas mixture concentrations were known to the nearest 0.001%.

The observed DL_{CO} was recorded from each instrument after each simulation.

Three different inspired volumes were used in combination with 3 "exhaled" gas mixtures for 9 total combinations to simulate a physiologically relevant range of human DL_{CO} values (~10-50 mL/min/mmHg).

Simulator testing schedule

During DL_{CO} simulator testing, 6 repetitions of each of the 9 test gas–inspiratory volume combinations were used to test each instrument on 4 occasions over a 90-day period according to the schedule in Table 1.

To ensure complete flushing of the system, the first trial of a group of 6 repetitions was deleted from the analysis. The remaining 5 observations on each occasion were analyzed for a total of 180 measurements per instrument.

As outlined in Table 2, each of the 3 test gas mixtures were combined with each of 3 inspiratory volumes to produce the 9 simulated DL_{CO} maneuvers utilized in the protocol.

Gas mixture compositions are outlined in Table 3.

HUMAN SUBJECT TESTING

Eleven healthy, nonsmoking adult subjects underwent repetitive single-breath DL_{CO} testing at the LDS Hospital PFT laboratory over a 26-week

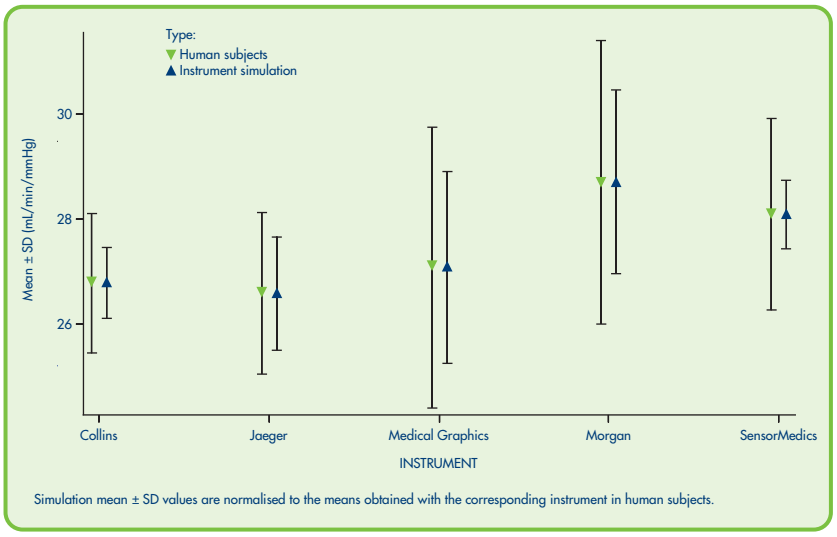

Figure 1. DL_{CO} simulator and human subject variability.

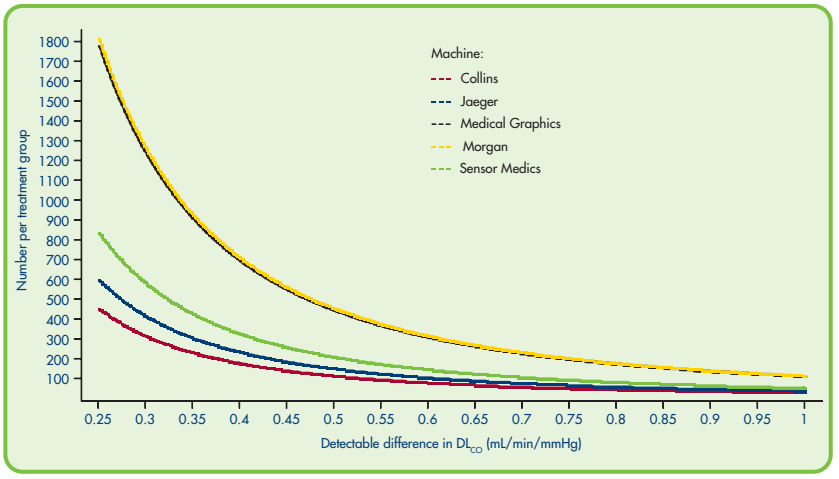

Figure 2. Sample size required to detect a difference between groups – DL_{CO}.

period on each of the same 5 PFT instruments used in the simulation tests.

The demographic characteristics of these subjects are summarized in Table 4.

The DL_{CO} of each subject was measured twice on each of the 5 PFT instruments in Weeks 0-2, 12-14, and 24-26 according to the scheme in Table 5.

Using a computer-generated open randomization scheme, each subject was randomized to be tested on the 5 machines in a different order.

At each testing session, subjects were required to perform at least 3 DL_{CO} maneuvers on 2 separate days that met the acceptability standards of the American Thoracic Society (ATS).[1] A total of 198 DL_{CO} measurements per instrument were analyzed.

Serum hemoglobin was determined on all subjects at weeks 0, 12, and 24.

All reported human subject DL_{CO} values were adjusted for hemoglobin according to the recommendations of the ATS.[1]

ANALYSIS

The variability associated with repetitive DL_{CO} testing on each instrument was determined from the Root Mean Square Coefficient of Variation (RMS CV = the square root of the average squared coefficient of variation for all simulations or subjects on each instrument across all time points).

RESULTS

The overall variability of simulator and human subject testing is summarized in Table 6 and Figure 1.

The impact of the variability of longitudinal human subject DL_{CO} measurements on sample size determination is illustrated in Figure 2.

This figure is representative of a hypothetical controlled clinical study whose primary outcome is treatment group difference in change from baseline DL_{CO}.

Using the human subject variability determined for each instrument tested, this figure depicts the number of subjects required (y-axis) to detect treatment group differences in change from baseline DL_{CO} (x-axis) assuming a power of 80% and a=0.05.

DISCUSSION

This is the first study to estimate the individual components of machine and human variability associated with the longitudinal measurement of diffusing capacity.

The variability associated with longitudinal measurement of DL_{CO} — as assessed by repetitive simulations — varied across the instruments tested in this study.

The variability in DL_{CO} observed with repetitive human subject testing was larger and also varied among the instruments tested.

These results represent analyses obtained on one instrument per manufacturer and may not be representative of all of their models.

CONCLUSIONS

Our data demonstrate that roughly half of the variability observed in the human subject testing can be attributed to instrument variability.

The results demonstrate the potential impact of instrument choice and test variability on sample size determinations in clinical studies utilizing DL_{CO} as an endpoint.

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ACKNOWLEDGEMENT

This study was funded by Pfizer Inc and Aventis Pharmaceuticals Inc.

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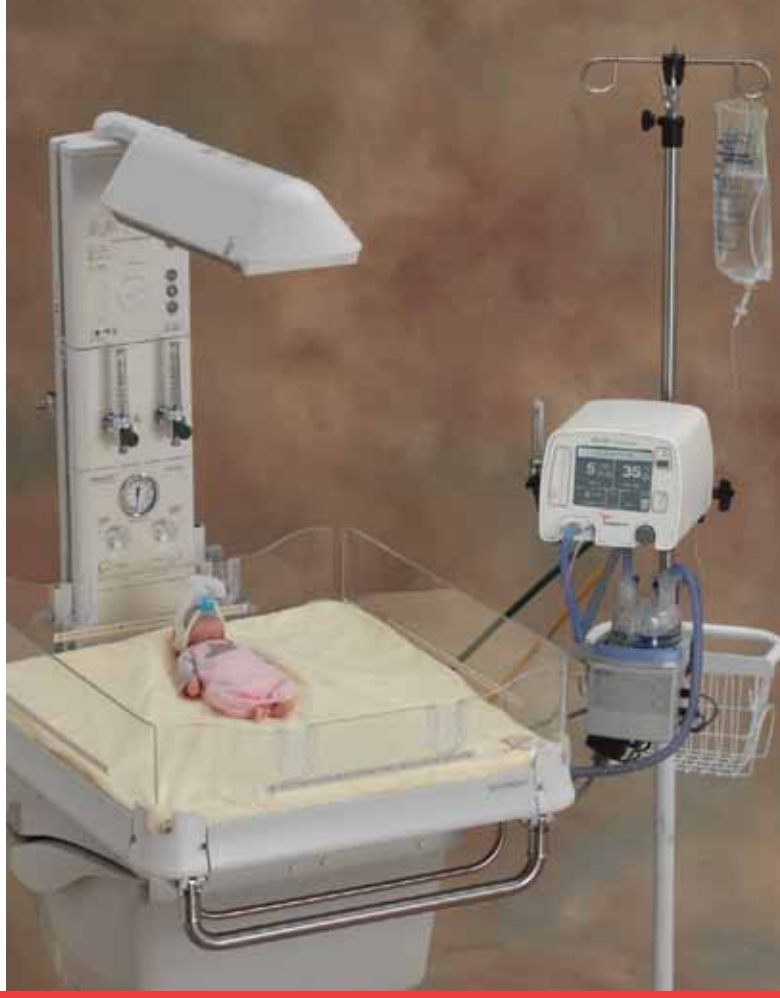

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