Research Review 2009

This jointly published Research Review highlights some of the many research accomplishments of the Ontario Respiratory Care Society (ORCS) and the Ontario Thoracic Society (OTS). The Ontario Lung Association (OLA) supports both research programs. Recipients of these research awards consistently demonstrate the value of research in the development of knowledge to improve lung health, prevent lung disease and optimize patient care. The research conducted in Ontario by the individuals profiled here and the many others supported by The Lung Association helps advance respiratory medicine and care within Canada and around the world.

The ORCS researchers featured in this edition of Research Review are drawn from the three professions that make up the majority of the membership of the ORCS: Respiratory Therapy, Physiotherapy and Nursing. They work and conduct research in diverse settings, including academic institutions, acute care hospitals and rehabilitation facilities. This is also representative of the ORCS membership.

In the first highlighted study, Dr. Mika Nonoyama, a Respiratory Therapist, describes her thesis research from her PhD in Rehabilitation Science at the University of Toronto, for which she received an ORCS Fellowship. She examined the value of home oxygen for individuals with COPD who did not meet the Ministry of Health and Long-Term Care's criteria for ambulatory oxygen. She found that only a minority of subjects benefitted from oxygen while walking and concluded that the general application of home oxygen for those with transient exertional hypoxemia is not appropriate.

With support from an ORCS Research Grant, Dr. Tom Overend, Director of the School of Physical Therapy at The University of Western Ontario, worked with Cathy Anderson, a Clinical Specialist in Physiotherapy at London Health Sciences Centre and an interprofessional team from other centres to search and analyze the literature on suctioning techniques with the goal of developing a new evidence-based clinical practice guideline (CPG) for suctioning the adult patient.

Dr. Mary Ann Murray, a nurse with extensive experience in oncology, gerontology and palliative care, recently received her PhD in Nursing from the University of Ottawa, supported by an ORCS Fellowship. Her thesis addressed the difficult choices that patients are often required to make about where they will live while they receive end-of-life care and the skills of health care professionals to assist them to make an informed choice. The development of tools and processes to support decision-making may improve patient quality of life and resource utilization.

Three OTS researchers are featured in this issue of Research Review.

Dr. Jim Lewis from The University of Western Ontario is an innovative researcher and he is conducting pioneering work on the use of surfactants for treatment of lung disease. His research profiled in this edition focuses on lung-liver interactions in ARDS and multi-organ failure. Understanding and preventing multi-organ failure associated with sepsis and SIRS is extremely important if we want to continue to improve mortality and morbidity in Ontario’s ICUs.

Dr. Steve Iscoe from Queen’s University, has provided a sophisticated study exploring hyperinflation-induced cardio-respiratory failure in rats. These studies help us to explore the pathogenesis of cardiac and respiratory decompensation that can occur in patients with severe COPD and/or asthma.

Dr. Parameswaran Nair’s research is focused on the regulation of human airway smooth muscle cytokine synthesis by cysteinyl leukotrienes. Results of Dr. Nair’s research have recently been highlighted in top medical journals such as the New England Journal of Medicine (NEJM). Continued on page 11

In This Issue

OTS Researchers
James F. Lewis .................. 2
Steve Iscoe ....................... 5
Parameswaran Nair .............. 8

ORCS Researchers
Mika Nonoyama .................. 4
Tom Overend and Cathy Anderson ...... 6
Mary Ann Murray ................. 10
Dr. James F. Lewis completed his medical degree at The University of Western Ontario in 1982 with subsequent specialty training in Internal Medicine and Respiratory Medicine both at Queen’s University and Western until 1988. He then conducted a three-year basic science research fellowship at Harbor UCLA in California under the supervision of Dr. Alan Jobe, funded by the Medical Research Council. During this fellowship, he investigated the role of pulmonary surfactant in acute lung injury using animal models of ARDS (Acute Respiratory Distress Syndrome). He then returned to a faculty position at The University of Western Ontario in 1991 as an Assistant Professor and principal investigator at the Lawson Health Research Institute. Dr. Lewis is currently a Professor in the Department of Medicine, Physiology and Pharmacology at the Schulich School of Medicine, University of Western Ontario. He is a Clinician Scientist and principal investigator at the Lawson Health Research Institute with funding from CIHR, OTS, NSERC and local institute resources. He is also the Assistant Dean-Clinical Research for Schulich School of Medicine and Dentistry, where his key areas of responsibility include conducting basic science research in the area of Acute Lung Injury (ALI), focusing on the role of the surfactant system in this setting.

Dr. Lewis supervises and trains graduate students both at the Masters and PhD level and also supervises internal medicine and respirology residents and fellows during their research rotations. He has clinical responsibilities involving various general respiratory clinical problems including asthma, lung cancer and chronic obstructive pulmonary disease. Specific administrative responsibilities include chairing the MD/PhD Committee at the Schulich School of Medicine and Dentistry. He has initiated various research training programs for senior residents and fellows including the Resident Research Career Development (RRCD) Program at the University of Western Ontario.

His interest in respirology was motivated by his experience in critical care. During his internal medical rotation, he was fascinated with the physiology and pharmacology of critically ill patients in the Intensive Care Unit and was specifically interested in patients with acute lung injury and ARDS. The frustration of treating these complex patients and the pulmonary complications associated with them motivated him to pursue further training in respirology, with a desire to conduct research in this area. Very little is known of the role of pulmonary surfactant in adult, mature lungs particularly in the setting of acute lung injury. As a result, Dr. Lewis’ research training was conducted under the supervision of a neonatologist much more versed in the area of pulmonary surfactant. This training formed the basis of his future research career at a basic science level, but with the capability of translating this knowledge to the bedside by designing and participating in clinical trials evaluating exogenous surfactant administration in patients with ALI and ARDS. Indeed, he feels fortunate to experience the “bench to bedside” approach in this area of research.

His specific area of research interests has focused on evaluating changes in the pulmonary surfactant system over the course of lung injury using animal models to reflect patients with ALI and ARDS. With a greater understanding of the pathophysiology of this disorder, Dr. Lewis and his collaborators have determined that exogenous surfactant administration is effective, but dependent on the type of surfactant used, the route of administration and the type of injury involved. Various discoveries in the basic research laboratory have formed the rationale and basis of clinical trials evaluating this therapeutic approach in patients with lung injury. These latter clinical trials are currently underway and will hopefully lead to improved outcomes of patients with this disorder.

Recently, Dr. Lewis has gone back to the laboratory and focused on determining how the pulmonary inflammatory response induced by mechanical ventilation in patients with underlying lung injury leads to systemic inflammation and subsequent multi-organ failure (MOF). The consistent clinical observation that patients with ALI/ARDS ultimately die of non-pulmonary organ failure generated their hypothesis that the lung not only contributes to peripheral organ dysfunction via hypoxemia, but also through the release of inflammatory mediators into the circulation. Dr. Lewis and his colleagues are specifically looking at the role of pulmonary surfactant in the transition of pulmonary inflammation to systemic inflammation and MOF. With optimal timing of surfactant administration and use of an appropriate surfactant preparation, they are hopeful that this therapy will ultimately mitigate systemic organ involvement and prevent the significant mortality associated with this disorder.

Continued on page 3
The various animal studies conducted by Dr. Lewis at the basic science level have been published in several peer-reviewed journals and presented at both national and international meetings. The initial, large, multi-centered clinical trial that was designed based on findings discovered in part from his laboratory was published in the New England Journal of Medicine in 1996 and a subsequent larger, more focused clinical trial is currently underway. With knowledge obtained from the laboratory and translated to the bedside, Dr. Lewis and his colleagues have gained tremendous insight not only into the potential of surfactant therapy for patients with acute lung injury but also the pathophysiology of ALI/ARDS in general.

Dr. Lewis has been involved with The Lung Association at various levels for the last 20 years. This includes chairing public forums focused on the area of asthma and COPD, conducting continuing medical education events with physicians and health care practitioners, (including respiratory therapists) and being involved administratively with the OTS Research Advisory Committee and Grants Review Committee. He has also served as a reviewer, scientific officer and chair of the Respiration Committee of the CIHR (formerly the Medical Research Council) at the national level. Dr. Lewis has received significant funding from the OTS over the last 20 years to support his basic science research endeavors. Financial aid from the Block Term Grant program as well as the Grants-in-Aid program have resulted in new data which has led to larger research projects that have significantly contributed to understanding the pathophysiology of acute lung injury.

Dr. Lewis’ interests outside of work include various sports including hockey, golf and running and of course spending time with his two teenage sons, Jack and Jesse who are awesome boys, becoming men.

**LUNG-LIVER INTERACTIONS IN ARDS AND MULTIORGAN FAILURE (2005-2006)**

**Introduction**

Our research over the last 20 years has focused on evaluating the role of the surfactant system in acute lung injury (ALI). We utilize both in vitro and in vivo approaches, including various animal models of ALI. Clinically, we have also evaluated the role of exogenous surfactant administration in patients with ALI and the Acute Respiratory Distress Syndrome (ARDS). Although our initial rationale for surfactant treatment was based on its biophysical function with the aim of improving oxygenation, the clinical observation is that patients ultimately die of multiorgan failure (MOF) rather than respiratory failure. This has led us to investigate the host defense role of exogenous surfactant, specifically in downregulating the host's inflammatory response syndrome, thereby preventing the development of MOF and death.

**Purpose of the Study**

The purpose of our recent studies funded by the Ontario Thoracic Society (OTS) is to evaluate the specific contribution of pulmonary inflammatory mediators to the systemic inflammatory response syndrome (SIRS) and then to determine the biological relevance of these lung-derived mediators on peripheral, non pulmonary organ function. We also determined the efficacy of exogenous surfactant administration in preventing peripheral organ dysfunction when given relatively early in the course of the injury.

**Methods**

To collect lung derived mediators, we initially induced lung inflammation in adult mice via internasal lipopolysacaride (LPS) administration and four hours later mechanically ventilated (MV) the lungs in situ using the isolated perfused mouse lung (IPML) model. Aliquots of the collected perfusate (lung-derived mediators) were then injected intravenously into a second cohort of normal animals with subsequent evaluation of the liver of these animals in vivo while spontaneously breathing using intravital video microscopy (IVVM). A second experiment was performed in a similar fashion but with the administration of exogenous surfactant to the first cohort of animals at the onset of mechanical ventilation and perfusion. The effects of this perfusate on the liver of normal animals were compared to those demonstrated in animals given aliquots of perfusate but not treated with surfactant.

**Results**

We found that inflammatory mediators were significantly increased in the perfusate collected from animals given LPS compared to those given saline. Subsequent injection of aliquots of this perfusate into the second cohort of animals showed significantly decreased sinusoidal hepatic blood flow, increased hepatic leukocyte recruitment and increased cell death compared to animals injected with perfusate from non-LPS inflamed lungs. These findings provide evidence for a direct link between lung-derived mediators and non-pulmonary organ dysfunction. Of most interest however, was the observation that administration of exogenous surfactant four hours after LPS and at the onset of mechanical ventilation in the first cohort of animals completely mitigated the changes observed in the livers of the second cohort of animals.

**Clinical Relevance and Conclusions**

We conclude from these studies that inflammatory mediators released from an injured lung due to mechanical ventilation significantly affect peripheral organs within a relatively short period of time after the onset of ventilation. These changes can be mitigated with exogenous surfactant administration. This is the first study to provide a direct link between lung derived mediators and peripheral organ dysfunction and also suggests that exogenous surfactant may ultimately improve the mortality of patients with ALI by preventing MOF.
The study consisted of multiple N-of-1 RCTs. Patients undertook three pairs of 2-week treatment periods, inhaling 2 lpm of oxygen for one period of each pair and a placebo mixture very close to room air, for the other. Allocation was concealed and the order of pairs was randomly determined. Participants were requested to use the gas during activities that made them short of breath. Both the patients and the outcome assessors were blind to the gas mixture provided.

3. Outcomes: Outcomes were assessed at the end of each period. Patients completed the Chronic Respiratory Questionnaire (CRQ), St George’s Respiratory Questionnaire (SGRQ), a 5 minute self-paced home walk test (breathing the gas mixture used during the previous 2-weeks; dyspnea and number of steps were counted). The amount of treatment gas used was monitored.

4. Data Analysis: An N-of-1 RCT was considered positive if the CRQ dyspnea score was higher, i.e., less dyspnea during the oxygen treatment period in all three pairs and if the difference between oxygen and placebo periods was ≥ 0.5 during at least two of the three pairs. Analysis of each N-of-1 RCT included a paired t-test; for the entire group, repeated measures ANOVA. An alpha of 0.05 was considered significant.

Results

1. Group Results: Twenty-seven patients completed the study. During the 5 minute home walk tests, patients walked 412 ± 79 steps while breathing placebo and 427 ± 79 steps while breathing oxygen (p=0.04). During this test, dyspnea was also improved, with a mean dyspnea change score of 3.2 ± 1.8 while breathing placebo and 2.8 ± 1.6 while breathing oxygen (p=0.04). There were no significant or clinical differences between oxygen and placebo in any domain of the CRQ or the SGRQ.

2. Individual Results: Two of these patients met the criteria for a responder. One of these patients was a clear responder: he walked further in the 5 minute walk test and had less dyspnea at the end of the walk while using oxygen. This patient used oxygen for an average of 17.5, 18.0, and 21.0 hours/day and placebo for 2.2, 3.6 and 6.6 hours/day. This patient requested early termination of all placebo periods at 3 days, whereas oxygen periods averaged 13 days.

Continued on page 11
Steve Iscoe, PhD

After undergraduate and graduate studies in physiology at McGill in the 70s, which then had one of the best groups of respiratory researchers in the world, and post-doctoral research with Mort Cohen at the Albert Einstein College of Medicine, Dr. Steven Iscoe joined the Department of Physiology at Queen’s in 1977 where he is now an Associate Professor. His primary responsibilities are research and teaching with some administrative service, including Associate Editor of the Canadian Journal of Physiology and Pharmacology.

Dr. Iscoe is a respiratory neurophysiologist but has always been interested in the outcome of respiratory neuronal discharges. The rationale became apparent when, trying to justify the study of respiratory control mechanisms for his thesis, he read in a pocketbook about emergency medicine the ten steps for treating respiratory failure. First, clear the airway; last, find and treat the cause of respiratory failure. As important as number 10 was, it was disconcerting to see one’s research relegated to the last position.

Over the years, Dr. Iscoe studied discharges of various nerves associated with breathing. But the arrivals of a colleague, Jenny Van Eyk and a new graduate student, Jeremy Simpson, just over 10 years ago shifted his research to something practical – the development of a simple blood test for respiratory muscle injury. They wanted to replicate for respiratory failure what was available for heart attacks – a blood diagnostic. They eventually succeeded and this marker, skeletal troponin I, can now be detected with a simple (but still unavailable) blood test.

Dr. Simpson’s curiosity led to Dr. Iscoe’s current area of interest. They induce respiratory failure in rats subjected to various types of respiratory loads. This is not new; the effects of loads have been studied for at least 100 years. But Dr. Simpson decided to test the blood of the rats for the presence of cardiac troponin, the clinical marker of a heart attack. It was present. Thus, respiratory loads cause not respiratory but cardiorespiratory failure (Simpson and Iscoe, Journal of Applied Physiology 2007) and the heart appears to be the weak link. This is also true for repeated inspiratory occlusions, a type of load that simulates obstructive sleep apnea (Simpson et al., Journal of Physiology, 2008) and for loads that force rats to breathe at an increased end-expiratory lung volume, simulating an acute exacerbation of asthma or COPD (Simpson et al., Journal of Applied Physiology, 2009). Moreover, they can protect the rats from the effects of these loads by prior activation of the muscles of an ischemic hindlimb, results that have implications for weaning patients from ventilators. Also, they are studying the effects of prior administration of a statin (because of its anti-inflammatory properties) or of supplementary oxygen on the animal’s ability to tolerate loads.

The OTS through its grants, both direct and to the Ontario medical schools (Block Term Grants), have been critical in maintaining Dr. Iscoe’s research and is a prime reason why he has enthusiastically contributed to the Top-It-Up Campaign.

Dr. Iscoe’s non-academic activities centre around renovations to his house, visiting parents, amusing the dog, cooking, and reading mystery novels or history.

HYPERINFLATION-INDUCED CARDIORESPIRATORY FAILURE IN RATS

Introduction
To respiratory investigators, respiratory loads cause respiratory dysfunction, and the effects on the heart and cardiovascular system have been ignored. However, we recently demonstrated that severe inspiratory resistive loads cause acute (< 1 h) cardiorespiratory failure characterized by low blood pressure (hypotension), multiple myocardial infarcts, and diaphragmatic fatigue. The mechanisms responsible for cardiovascular failure are unknown but one factor may be the increased load on the heart caused by the large negative intrathoracic pressures generated when breathing against an inspiratory load.

Purpose
Unlike inspiratory resistive loads, expiratory threshold loads increase intrathoracic pressure and decrease the load on the heart. Consequently, we hypothesized that anesthetized rats forced to breathe against such a load would experience diaphragmatic, not cardiac, failure.

Methods
We measured blood pressure, heart rate, pressure generation by the diaphragm in anesthetized, spontaneously breathing rats breathing against an expiratory threshold load (that is, into a column of water) that approximately doubled their end-expiratory lung volume. We also measured blood chemistry, including cardiac troponin T, a protein that is released from damaged cardiac muscle, and examined the hearts for cell death.

Results
Loading halved respiratory frequency, lowered arterial oxygen levels, increased arterial carbon dioxide levels, and increased inspiratory drive. Although breathing at an increased lung volume impairs diaphragmatic contractile function, the diaphragm did not fatigue until near load termination. Mean arterial pressure progressively fell, becoming significant (cardiovascular failure) midway through loading despite increased heart rate. Loading was terminated after an average 2 hours when mean arterial pressure dropped below 50 mmHg. Blood samples taken immediately after load termination revealed hypoglycemia, hyperkalemia and cardiac troponin T, the last indicating myocardial injury that was, according to histology, mainly in the right ventricle. This damage probably reflects a combination of decreased oxygen delivery (decreased venous return and arterial hypoxemia) and greater afterload due to hyperinflation-induced increase in pulmonary vascular resistance.

Clinical Relevance and Conclusions
In rats breathing at an increased end-expiratory lung volume, cardiorespiratory, not just respiratory, failure still occurred even though this type of load does not mechanically stress the left heart. Instead, preferential injury to the right heart occurred because of decreased oxygen delivery to it at a time when it is working harder to push blood through blood vessels that are constricted by the higher lung volume and the prevailing hypoxia. Right heart injury and dysfunction may contribute to the increased morbidity and mortality associated with acute exacerbations of obstructive airway disease.
SUCTIONING THE ADULT PATIENT: PUTTING THE EVIDENCE TOGETHER

Introduction
Several years ago, our inter-disciplinary research team embarked on a research program with the ultimate goal of producing a new clinical practice guideline (CPG) for suctioning the adult patient. Suctioning is a controlled act that our three professions (nursing, physiotherapy and respiratory therapy) are approved to perform. Phase I of our program consisted of a systematic review of the literature published since the most recent review of the suctioning technique. In this report for the Research Review, we will report on Phase I with the literature used in the previous systematic review by Brooks and colleagues. Phase III will consist of the development of a new CPG for suctioning.

Purpose of the Study
The purpose of our study was to:
1. Extract data from, and assess study quality (internal validity) of papers in the previous systematic review of the literature on suctioning in adult patients;
2. Combine these results with our systematic review of the literature published since the Brooks et al review;
3. Develop evidence-based statements for health care professionals who perform suctioning in their clinical practice.

Methods
We searched Medline, CINAHL, Embase, and the Cochrane Library from inception until September 2008, using keywords such as suction, airway, trachea, pharynx, subglottic, and oxygenation. Studies in English on adults were included. We focused on the strongest sources of evidence: systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs) and randomized cross-over designs.

Continued on page 7
(RCOs). However, to obtain information on all aspects of suctioning (e.g., harms, infection control), we also reviewed a variety of lower-level experimental designs (e.g., non-randomized trials, case reports) to provide evidence in areas where there were no higher-level studies. We followed standard procedures for a systematic review and pooled study results for meta-analysis whenever possible. Two investigators independently critically appraised and extracted data on each paper before meeting to reach consensus. The quality and internal validity of each study was rated using the Jadad4 and PEDro 5 scales for RCTs and RCOs, and the Overview Quality Assessment Questionnaire6 for SR and MA.

Results
Seven SR [open vs. closed suctioning (4), subglottic suctioning (1), prevention of suction-induced hypoxemia (1), and comprehensive review (1)], 17 RCTs, 34 RCOs, and 16 lower-level studies were included in the review. The major findings include:

1) There is no difference between open and closed suction systems with respect to incidence of ventilator-associated pneumonia (VAP), oxygenation, mortality, and length of stay (LOS) in the ICU.

2) Subglottic suctioning is effective in preventing early onset VAP, and decreasing the duration of mechanical ventilation (MV) and LOS in ICU in patients expected to require > 72 hours of MV.

3) Hyperoxygenation prevents the drop in oxygenation following suctioning, and delivery of hyperoxygenation by MV is more effective than using the manual resuscitation bag.

4) The evidence does not support the use of hyperinflation for reducing suction-induced hypoxia.

5) Hyperinflation with hyperoxygenation results in an increase in pressures such as mean arterial pressure, intracranial pressure, and airway pressure following suctioning.

Results supported by lower levels of evidence: 1) The use of saline during suctioning may cause either no change or a minimal decrease in saturation, which is not likely clinically significant. There is some suggestion that one may be able to manipulate the distribution of saline in the lung by the mode of delivery.

2) Storage of oral suctioning devices in a clean holder or other set-up should be considered.

3) Personal protective equipment should be worn when suctioning.

Clinical Relevance
Suctioning is a technique used by physiotherapists, nurses and respiratory therapists to improve lung health in patients along the continuum of care from critical care to the community. The act of suctioning is not without its risks to patients. It is thus important for clinicians to be aware of the best available evidence supporting this secretion clearance technique in order to provide optimal care with the least possible risk to the patient.

Conclusion
Our systematic review has provided a careful analysis of the best available evidence related to suctioning the adult patient. While there remain important gaps in the evidence base for this technique, the information we have provided in our review is essential to guide the health care team in the provision of best practice for our patients.

Other members of the Research Team include Dina Brooks, BSc(PT), PhD; Lisa Cicotto, RN, BScN, PhD; Michael Keim, RRT; Debra McAuslan, BScN, MScN; Mika Nonoyama, RRT, PhD.

References

We gratefully acknowledge funding support from the Ontario Respiratory Care Society and the Canadian Respiratory Health Professionals.
Parameswaran Nair, MD, PhD, FRCP, FRCPC

Currently, Dr. Param Nair is an Associate Professor of Medicine in the division of Respirology at McMaster University and a staff Respirologist at the Firestone Institute for Respiratory Health at St. Joseph’s Healthcare in Hamilton. Dr. Nair splits his professional life between clinical medicine and translational research in obstructive airway diseases. At the Firestone Institute, he sees patients with severe asthma and directs a research program that develops and evaluates non-invasive measurements of airway inflammation to help manage patients with severe asthma and COPD.

Dr. Nair graduated in 1988 with honours from the University of Kerala Medical School in Trivandrum in India. After completing a 12 month rotating internship, Dr. Nair continued his training in general and respiratory medicine at the same institution. During this period, he also obtained his initial training in respiratory research and obtained an MD for a thesis on the prevalence of exercise-induced bronchoconstriction in adolescent asthmatics. In 1992, Dr. Nair obtained his specialist certification in Respiratory Medicine from the National Board of Examinations in India. Subsequently, he went on to re-train in General and Respiratory Medicine in Brighton and in Sunderland in England and obtained his MRCP certification in General Medicine in 1996. A significant influence during this period was the mentorship for research provided by Dr. Daniel Veale who encouraged him to move to Hamilton for further training in asthma research. Dr. Nair felt very fortunate to be accepted into Dr. Fredrick Hargreave’s laboratory and subsequently in Dr. Paul O’Byrne’s laboratory where he completed his training in clinical inflammetry and in leukotriene biology. This resulted in a PhD in 2004.

Dr. Nair’s entry into the respiratory medicine program was purely by chance. Tuberculosis was and continues to be a major public health problem in India. However, very few new medical graduates were willing to choose to train in respiratory diseases as this was considered not a ‘glamorous’ specialty. However, Dr. Nair was encouraged by a professor of dermatology whom he respected very much, to make service to humanity a priority. It was a difficult decision at the time and still is occasionally. Dr. Nair has always had a desire to do original research, and with time, asthma proved to be the best opportunity for this accomplishment.

Dr. Nair’s specific research interests are to develop methods to characterize bronchitis by cell counts in sputum, understand the mechanisms for particular types of bronchitis, and to develop therapies against specific bronchitis. In addition, his laboratory examines the mechanism of accumulation of excessive smooth muscle in the submucosa of patients with long-standing asthma.

There are a number of clinical trials and basic science projects currently undertaken in his laboratory. Specifically, he and his colleagues are investigating mechanisms of eosinophil, neutrophil and smooth muscle recruitment into the airway and the effect of monoclonal antibodies directed against specific chemokines and cytokines in reversing airway eosinophilia and neutrophilia. This year, his program enjoyed some success when their demonstration of the prednisone-sparing effect of an anti-IL5 monoclonal antibody in asthmatic patients with sputum eosinophilia was published in the New England Journal of Medicine. The OTS has also funded a majority of data in the 2007 manuscript, *The effects of cysteinyl leukotrienes in modulating human airway smooth muscle function*. The data was also published in four other manuscripts: *Am J Respir Crit Care Med* 2002; 166: 738-42; *Eur Respir J* 2004; 24: 545-51; *Am J Respir Cell Mol Biol* 2007; 37: 240-7; *Am J Respir Cell Mol Biol* 2008; 39: 475-81.

Dr. Nair has been on the planning committee of the Better Breathing Conference for the past three years and chaired the annual conference in 2007. For the past three years, he has actively participated as faculty in the annual ORCS scientific conference. Dr. Nair would say when asked about himself, “I think I lead a rather mundane life of academic austerity interspersed with periods of unrestrained absolute indulgence in the company of my wife and three delightful daughters. I like to read history and philosophy and watch movies with historic themes. I spend a fair bit of my spare time debating and discussing with friends about social issues particularly related to social injustices and inequalities.”

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REGULATION OF HUMAN AIRWAY SMOOTH MUSCLE CYTOKINE SYNTHESIS BY CYSTEINYL LEUKOTRIENES (2004-2005)

**Introduction**

The smooth muscle cell produces a number of cytokines and chemokines. Interleukin-13, in particular, can rapidly induce airway hyperresponsiveness that is a characteristic feature of asthma. Cysteinyl leukotrienes, acting through G-protein coupled Cys-LT1 receptors on airway smooth muscle, promote airway smooth muscle contraction, proliferation and migration. The expression of cys-LT1 receptors on airway smooth muscle cells are increased by cytokines such as IL-13. There is no information on whether leukotrienes or their antagonist can modulate the synthetic functions of airway smooth muscle cells.

**Purpose of the Study**

To observe the effect of leukotriene alone, and with interleukin-13 on human airway smooth muscle migration and cytokine synthesis and to understand the signalling mechanism by which leukotrienes interact with interleukin-13 in modulating migration and chemokine synthesis.

**Methods**

Airway smooth muscle cells were obtained from patients undergoing lung surgery, cultured and used between the 2nd and 5th passages. Migration towards chemoattractants was assessed using Transwell culture plates. Cytokine in supernatant was measured by ELISA. Signalling mechanisms were assessed using specific antagonists and by assessing phosphorylation of kinases by Western blotting.

**Results**

IL-13 can promote airway smooth muscle migration through Src-kinase and leukotriene dependent pathways. IL-13 and cysteinyl leukotrienes synergistically increase eotaxin synthesis from human airway smooth muscle cells. This appears to be partly by increasing CysLT receptor expression on human airway smooth muscle.
cells and partly by a process of inverse agonist signaling through the CysLT1 receptor.

**Clinical Relevance**

We demonstrate novel biological effects of IL-13 on human airway smooth muscle cells. Both cysteinyl leukotrienes and IL-13 can promote human airway smooth muscle migration, and this may contribute to the accumulation of smooth muscle cells in remodeled airway submucosa. Also, IL-13 may contribute to increased eosinophil accumulation in the airway mucosa by mechanisms involving cysteinyl leukotrienes. This has relevance in drug development and targeting.

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**INTRODUCING THE ONTARIO THORACIC SOCIETY’S JOB CENTRE**

The Ontario Thoracic Society is delighted to introduce a new career resource available to the Respirology community. The Job Centre is an electronic on-line posting set up to advertise jobs wanted and jobs available for Respirology physicians in Ontario. Positions of interest may be hospital or ambulatory based, in either the community or academic center.

This new Job Centre is a resource provided by the OTS and contains a **JOBS WANTED** and **JOBS OFFERED** section.

Don’t miss this opportunity to either seek a position or to advertise an available job in the field of Respirology.

For more details please visit the Website for details:

www.on.lung.ca under Health Care Professionals tab at the top, select the Ontario Thoracic Society. Then select Job Centre at the left. or

www.on.lung.ca/Health-Care-Professionals/Ontario-Thoracic-Society/job_centre.php or contact by email: ots@on.lung.ca
Mary Ann Murray, RN, MScN, PhD

Dr. Mary Ann Murray is an Associate member of the Nursing Best Practice Research Unit, a joint initiative between the Registered Nurses Association of Ontario and the University of Ottawa School of Nursing and a part-time professor at Algonquin College in the University of Ottawa and Algonquin Collaborative BScN program. She is currently exploring other opportunities in the health care field.

Dr. Murray recently completed her PhD in Nursing at the University of Ottawa with the support of an ORCS Fellowship. She also holds three nursing specialty certifications (oncology, gerontology and hospice palliative care). Her interest in these areas developed from clinical and research experience acquired during her nursing career. She was struck by the multitude of tough, difficult decisions that patients face over the course of an illness and felt that health care professionals could do better in helping to support patients in making decisions that were informed and consistent with their values. For this reason, her doctoral research focused on designing, implementing and evaluating a needs-based intervention aimed at narrowing the evidence to practice gap in supporting patients facing these difficult decisions at the end of life. Her research interests include knowledge transfer, chronic condition management, acute care, implementation science, and patient decision support in the context of complex multi-option decisions. She is very interested in looking at ways to better support patients living with end-stage respiratory diseases such as COPD and lung cancer.

Some of the studies in which Mary Ann Murray is currently working with colleagues are a systematic review on needs of patients and families in last days and hours of life, a project looking at facilitating interprofessional communication in difficult situations with a view to developing a suite of multi-faceted education tools and approaches and a third project looking at building capacity and improving feedback mechanisms in long-term care.

Dr. Murray has published three papers from her thesis work (systematic review, research proposal and needs assessment) and another is under review. She has also presented her research several times to students and colleagues and at the International Shared Decision Making Conference in Boston in June of 2009. She has been actively involved in nursing organizations. She is Past President of the College of Nurses of Ontario, was the lead on an RNAO clinical guideline development panel for Decision Support for Adults with Chronic Kidney Disease, and a member of an RNAO clinical guideline development panel for End-of-Life Care. She hopes to become more actively involved with the ORCS now that her degree is completed.

In her free time, Mary Ann enjoys spending time with her husband, sons and best buddy, a geriatric Black Lab who still thinks he’s a puppy.

**Supporting Patients Making Decisions About Place of End-of-Life Care: A Three Phase Mixed Methods Study**

**Introduction**

A paradox exists between where most terminally-ill cancer patients would prefer to receive care as death approaches (home or hospice) and actual place of care (hospital). Patients usually consider several options when deliberating about place of care at the end of life. While patients often need help with decision-making, practitioners generally lack skills and confidence in providing quality decision support.

**Purpose of the Study**

This study aimed to determine whether the quality of clinicians’ decision support can be improved with a brief, framework-based, skills-building intervention.

**Design and Methods**

1. **Systematic Review**: A systematic literature review of primary research studies (January 1997 – January 2007) was undertaken. Studies that investigated place of care or identified place of end-of-life care in relation to outcomes were submitted to screening, critical quality appraisal and bibliographic mapping.

2. **Needs Assessment**: This study identified factors that influence nurses’ provision of decision support. Twenty-two nurses, from three health networks, participated in semi-structured interviews.

3. **Randomized Trial**: A multi-faceted educational program was designed, based on the nurses’ needs and then evaluated.

Participants were assigned randomly to the educational or control condition. Training elements included a: 1) self-directed online auto-tutorial; 2) 3-hour workshop including: performance feedback on participants’ baseline skills, scoring a video contrasting exemplary decision support with traditional patient education, a patient decision aid, and role play; and 3) a follow-up educational outreach call. The Decision Support Analysis Tool was used to rate the quality of audio-taped phone calls with simulated patients before and after training. Participants were also surveyed regarding the acceptability of the training program and intentions to engage in patient decision support.

**Setting of the Needs Assessment and Randomized Trial**

Palliative and oncology practice settings within three Ontario Local Health Integration Networks: Champlain, South East and Toronto Central.

**Results**

1. **Systematic Review**: Of the 735 papers identified, 39 papers representing 33 studies met inclusion criteria. Findings suggest that factors related to the illness, the individual and the care and social environment influence place of end-of-life care for cancer patients. The most commonly identified factors were the patient’s preference, social supports and health care resources. More specifically, stated preference, caregiver presence and contact patterns with health care services influenced place of end-of-life cancer care.

2. **Needs Assessment**: Twenty-two nurses were interviewed. Overall nurses held favourable attitudes towards providing decision support for place of care at end-of-life. Overlap between other professionals’ roles and nurses’ clinical experience impacted nurses’ decision support behaviours. While nurses considered decision support to be an important part of patient-centered care, a lack of skills, confidence and tools were identified as barriers to implementing decision support for place of end-of-life care.

3. **Randomized Control Trial**: The before-

Continued on page 11
after changes in the quality of decision support were greater (p<0.0001) in the intervention group (mean change 3.75, 95%CI: 2.46, 5.03) compared to the control group (mean change -0.667, 95% CI: -1.57, 0.24) at the small expense of time for the intervention group (mean 13.47 minutes, SD 4.70) compared to the control group (10.29 minutes, SD 4.81) (p=0.004). There were no differences in each group’s future intentions to engage in decision support. The intervention group found the components acceptable; however, there was less uptake of the online auto-tutorial.

Conclusions
Terminal cancer patients’ decision making about place of care is complex, with numerous determinants influencing the final choice. Nurses believe they have a role in providing decision support, but lack skills, confidence and tools. These barriers can be addressed with a multi-faceted educational program and a patient decision aid. Practitioners who received training overcame knowledge and skill gaps. Improvements in the quality of decision support can be accomplished by adding an average 3 minutes to the interaction duration. Extra training did not affect intentions to provide decision support, which were already high.

Clinical Relevance
Tools and processes developed from this work may enhance the ability of terminally ill patients to receive care in the most appropriate setting that is commensurate with their informed preferences. Furthermore, implementation of the intervention on a broader scale may help to improve end-of-life care planning which might lead to better quality of life for patients and families, more effective use of health resources and services, and less emergent contact with health care providers (such as after-hours calls to case managers, physicians and emergency room visits and admissions). However, full implementation of the multi-faceted intervention requires consideration of broad system perspectives. To ensure sustainability and responsiveness to patient needs, contextual barriers within practice environments with accompanying macro level policy barriers need to be addressed and patient outcomes evaluated.

Trial registration: NCT00614003

In all other individuals, there were no significant statistical or clinical differences between oxygen and placebo for the CRQ, SGRQ and 5 minute home walk test.

Clinical Relevance
Ambulatory oxygen therapy is routinely prescribed for those who do not meet criteria for mortality reduction, despite the inconsistent evidence regarding its effect. Professional guidelines that recommend ambulatory systems have provided laboratory results of exercise testing as supportive evidence. Domiciliary oxygen is associated not only with cost, but with inconvenience for the patient. These considerations suggest the inadvisability of oxygen use on the basis of laboratory tests. The many home based assessments in this trial cost an estimated $1700.00 per patient. However, this cost is likely considerably less than the cost of providing long-term ambulatory oxygen for patients who do not benefit from it.

Conclusions
This study does not support the general application of ambulatory oxygen therapy for patients with COPD who do not meet criteria for mortality reduction with domiciliary oxygen. The data suggest that only a small proportion of such patients with mild resting hypoxemia and exercise desaturation receive an important benefit from home oxygen.

References

Research Review
Continued from page 1

Thanks to Dr. Nair and colleagues, we are developing new treatments for severe asthematics who are unable to be controlled on conventional asthma therapies such as inhaled steroids and bronchodilators.

Together, these 3 researchers represent the best and brightest that Ontario has to offer. They are truly world-class and they are helping to open up new insights into the pathogenesis and treatment of respiratory diseases. We are proud to feature them in this issue of the Research Review.

The ORCS and OTS research programs contribute significantly to the advancement of knowledge in the field of respiratory health care and to the translation of knowledge from research to clinical practice. This, however, would not be possible without the necessary funding support from the Ontario Lung Association. The success of the OTS and ORCS research programs is due to the shared vision of the Ontario Lung Association and its respiratory societies in building a strong and vibrant research community to sustain excellence and innovation in Ontario.

Additionally, the OTS gratefully acknowledges GlaxoSmithKline (GSK) for their contribution of $180,000 over a 2 year period (2005-2007). Over this time, GSK funded research projects similar to those described within this issue of Research Review. GlaxoSmithKline stepped forward to be “The” corporate sponsor of the OTS research program and by doing so acknowledged its high impact and importance in advancing a knowledge-based economy in medical research for future generations. This success would not have occurred without the vision, hard work and enthusiasm of Ms. Renata Rea, Professional Communications Manager at GSK. Please continue to support us in our mission to bring the best respiratory research to Ontario and the world.

Research Review
Continued from page 1

Mary Ann Murray... Continued from page 10

Mika Nonoyama... Continued from page 4

Continued from page 1
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