

## CIHR New Frontiers Program

*Cardiopulmonary Disorders During Sleep: Mechanisms, Treatment and Public Health Impact  
January 12<sup>th</sup> & 13<sup>th</sup> 2002, Sheraton Gateway Hotel at Toronto airport*

### **Introduction:**

Approximately one-third of the human life span is spent asleep. Sleep is a vital condition inside the daily cycle that contributes importantly to influence the normal physiologic functions of each organ system (e.g. central nervous, respiratory, heart rate, cardiovascular and endocrine systems), as well as immune and inflammatory responses. Accordingly, sleep disturbances (i.e. alteration in sleep duration and/or continuity) will not only alter mood and vigilance, but will adversely affect the function of these organs' system and their interactions. Yet there is remarkably little information on the mechanisms underlying the effects of sleep on important physiological processes, and the consequences of sleep disorders on physiological function and human health. Disorders of sleep affect millions of North Americans, and commonly occur in children, adults and the aging population and are more prevalent than other common and serious chronic disorders such as asthma and diabetes (National Commission on Sleep Disorders Research, 1993). Numerous conditions are associated with sleep disturbances and the role of sleep and circadian rhythms in health and disease has assumed greater importance with the advent of global economy and the round clock working schedules. The importance of such sleep disturbances has been emphasized in a dedicated workshop supported by the New Frontiers Program (Halifax, Nova Scotia, December 2001). Sleep-related breathing disorders (SRBD) represent a major but reversible cause of sleep and circadian rhythm disturbance as well as contributing to significant morbidity and mortality risks (hypersomnolence, impaired neurocognitive development in children, car crashes, hypertension, cerebrovascular and cardiovascular events).

In order to put the conclusions and recommendations of this New Frontiers Program (NFP) workshops in context, we will first briefly review the present state of knowledge on the epidemiological and clinical significance of SRBD.

### **Background:**

*Definition of Sleep-Related Breathing Disorders:* SRBD refers to the occurrence of repetitive episodes of complete or partial cessation of airflow during sleep (apnea and hypopnea, respectively). Hypoxemia and hypercapnia occur during apnea and hypopnea and provoke arousal from sleep and sleep disruption. The combination of asphyxia and arousal from sleep activate the sympathetic nervous system causing abrupt surges in blood pressure and heart rate at the termination of each event. A sleep apnea-hypopnea syndrome related to SRBD is said to occur when recurrent apnea and hypopnea, arterial oxygen desaturations and arousal from sleep are associated with symptoms of habitual snoring, restless sleep and excessive daytime sleepiness. These symptoms constitute the usual indications for treating SRBD. However, in recent large population studies, SRBD has been identified as independent risk factor for the development of hypertension, coronary ischaemic events, stroke, and congestive heart failure (Shahar E et al, 2001). Most of the subjects found to have SRBD in these studies had no

complaint about symptoms of sleep apnea hypopnea syndrome. Therefore, these findings suggest that we may have to reconcile the indication of therapy for SRBD to include asymptomatic subjects with coexisting cardiovascular diseases. There are two major forms of SRBD: obstructive and central sleep apnea (OSA and CSA, respectively). In OSA, reduced airflow is due to sleep-induced narrowing of the pharynx producing partial or complete airway closure. However, central respiratory rhythm persists, leading to continuing breathing efforts against the closed airway. In contrast, reduced airflow in CSA is due to a primary reduction in central respiratory drive to the respiratory muscles leading to the absence of breathing efforts. In an otherwise healthy population, OSA predominates (Young et al., 1993), while CSA more commonly occurs in patients with co-existing medical illnesses, especially congestive heart failure (Sin et al., 1999). Sleep apnea is a disorder that occurs predominantly in males, although the apparent “protective” effect of the female gender is to come extent post-menopausally.

*Public Health Impact of Sleep-Related Breathing Disorders:* The prevalence of obstructive sleep apnea hypopnea syndrome, defined as > 15 apnea and hypopnea per hour of sleep, is approximately 9% in men and 4% in women (Young et al., 1993). Prevalence of OSA in children is 2 – 4 %. Thus, OSA alone occurs as frequently as other common chronic and serious illnesses such as asthma and diabetes (National Heart Lung and Blood Institute, 1994). Obesity, a growing problem in children as well as adults, is a strong independent risk factor for OSA. Because repetitive apneas and hypopneas cause disrupted sleeping patterns, impaired alertness and excessive daytime sleepiness, there are significantly increased work-related and motor vehicle accidents associated with sleep apnea (National Commission on Sleep Disorders Research, 1993). School performance and growth in children are improved with treatment of SRBD (National Commission on Sleep Disorders Research, 1993). In addition, OSA plays a role in the development of cardiovascular diseases, which are the commonest causes of morbidity and mortality in the developed world. Indeed, the U.S. National Commission on Sleep Disorders Research (1993) estimated that the economic impact of sleep-disordered breathing on traffic and work-related accidents, poor job performance and associated medical illnesses in the U.S. alone ranged up to \$40 billion per year. Compared to the general population, health care expenses due to physician services and hospitalizations are twice as high in patients with OSA during the 10 years preceding the diagnosis (Ronald J et al 1999). There is also evidence that SRBD contribute to premature death. Studies have reported higher mortality rates mainly in the 4<sup>th</sup> and 5<sup>th</sup> decades in OSA patients with deaths due predominantly to cardiovascular diseases (He at al, 1988). In patients with congestive heart failure, approximately 25-40% have CSA. The presence of CSA constitutes a powerful and independent predictor of mortality (Sin et al., 1999). Despite these alarming statistics, surprisingly little attention has been paid this disorder, either in undergraduate, postgraduate or continuing medical education or in the formulation of public health policy (Rosen, 1993). This is likely because of the relative recent discovery of the prevalence and importance of such disorders, and the multidisciplinary approaches required in research clinical medicine, and physician and patient education. Therefore, attempts to rectify this problem require targeted initiatives for research, physician education and public awareness (National Heart Lung and Blood Institute, 1994). This problem requires urgent attention since it has been estimated from large epidemiological studies (Young et al., 1993) it has been estimated that ~90-95% of existing people with SRBD are currently undiagnosed and untreated.

Overall, these observations indicate that SRBD are a major public health problem with serious clinical, social and economic consequences (Phillipson, 1993) that are not only relevant to the ICRH but also to a majority of the other institutes of the CIHR. These epidemiological and clinical facts led us to focus our NFP application on *Cardiopulmonary Disorders During Sleep: Mechanisms, Treatment and Public Health Impact*

### **Rationale of the NFP:**

Canadian investigators have an international reputation in basic, physiological, and clinical research in SRBD. The purpose of our NFP application was to take advantage of this Canadian expertise and expand upon the Canada-wide research links that have already been established to form a Canadian Investigation Group for SRBD that would enhance the innovative nature of Canadian investigation and the effectiveness of research investments in SRBD. Many different factors strongly supported the rationale for such development:

- The strong link that is known to exist between SRBD and obesity,
- The progressive increase in the incidence of obesity both in adults and children (30% increase in the last 3 years), and the increasing impact of obesity/SRBD on the health care system over time.
- The strong but under-recognized association between SRBD and cardiovascular disease.
- The small proportion of patients with SRBD who are diagnosed and appropriately treated.
- The paucity of effective therapeutic options for SRBD.

In view of these factors, three workshops were organized aimed to 1. Further develop current links between Canadian investigators in SRBD, 2. Identify priority areas and further develop multi-level (cellular, molecular, physiologic) investigations of disease mechanisms in areas with key clinical relevance, 3. Promote the conduct of multi-center randomized clinical trials in SRBD, 4. Develop collaborations among respiratory and cardiovascular investigators and researchers from other CIHR Institutes, 5. Establish partnerships with industry in support of clinical trials and development of other new therapeutic modalities.

- **Organization of the workshops:**

The research themes covered by workshops were:

- Cardiovascular/sleep apnea interaction; aims: to define fundamental fields of high priority research for basic and clinical investigation into cardiovascular/sleep apnea interactions for the Canadian Investigation Network for Disorders of Sleep (CINDIS).
- Obesity/sleep apnea interaction; aims: to provide an overview of the present knowledge on obesity/sleep apnea metabolic and endocrine features, on the link between obesity and sleep apnea from childhood to adulthood, and on the pharmaceutical and non-pharmaceutical developments in the field of weight loss and obesity prevention.
- Development of new treatment modalities for sleep-related breathing disorders; aims: to define research priorities for the development of new treatments for SRBD and integrate them into the organization of the CINDIS.

Thirty participants attended the workshops that were held in Toronto on January 12th and 13th, 2002 in three successive half-day sessions. In addition to the CIHR grant, the FRSQ respiratory network and Sanofi Synthelabo laboratories financially supported the organization of these workshops. Attendees came from Canadian universities from coast to coast (the Universities of British Columbia, Calgary, Dalhousie, Western, Laval, Montreal, Ontario, Queen's, Sherbrooke and Toronto) and several experts from the United States. Many participants had research expertise in SRBD in animal models and humans (MD, Ph.D.), while others brought expertise from other related research fields including cardiology, obesity/metabolism and the molecular and cellular physiology of circadian rhythms. Each workshop consisted of 6 pre-determined research topics, which were introduced by a brief featured presentation followed by 30 minutes of open discussion. The participants, speakers and workshops' coordinators can be found in the appendix (I – III) of this report describing the detailed workshops' program.

### **Individual workshops reports:**

In all three workshops, it was clearly stated that these areas of research involve the four pillars of the CIHR: biomedical, clinical, health services, and population health research. Speakers emphasized the implication of SRBD as a major public health problem with serious clinical, social, and economic consequences. In view of the high prevalence of such disorders in children, adults and the elderly, and their links to obesity, the health care system faces a potentially enormous burden in managing this disorder. Unfortunately, it does so in the absence of definitive evidence of the major factors involved in the causation and consequences of SRBD. This is likely because of the multidisciplinary approach required to determine underlying causes and the multifaceted consequences of this common disorder.

Although each workshop had its specific research issues, common concerns were raised during the three sessions as a consequence of the interaction of important factors such as obesity, metabolic disturbances, and cardiovascular disorders on research in sleep disorders.

Medical research in SRBD is in its relative infancy due to the recent identification and recognition as a major clinical problem. If major advances in the field are to be made, a more comprehensive and integrative approach must be brought to bear on these disorders. This will require the integration of the basic, physiologic (animal and human models), and clinical research approaches on the causes and consequences of SRBD as well as the forging of interactions with non-respiratory medical disciplines that may not be aware of the implication of SRBD as major risk factor in a wide variety of numerous neurological, cardiovascular, and metabolic disorders.

*Integration of the different facets of SRBD research expertise.* The role of genetic determinants in the development of SRBD and its consequences is a fundamental question that needs to be evaluated; animal models, in which genetic susceptibilities can be manipulated, could also be utilized for this purpose. Such models are essential for the evaluation of the interaction among neurotransmitter release, upper airway mechanical properties, and the effects of sleep and its disruption as well as circadian rhythms on organ systems homeostasis. Animal models would also be a unique way to study the natural history of untreated SRBD from early childhood to adulthood. More relevant and sophisticated animal models are required to test the cardiovascular

consequences of SRBD and the mechanisms involved in organ dysfunction and damage. Such models could also be used to develop new therapeutic strategies for SRBD. The results obtained with these models could provide insight into human pathophysiology, and hopefully, be rapidly applied to human physiological and clinical research. Despite the relatively small number of sleep laboratories and clinical investigators in the field of SRBD in Canada, Canadian investigators are well placed to undertake multicenter trials. A clinical trial was recently completed that compared different obstructive sleep apnea treatment strategies (continuous positive airway pressure vs. anterior mandibular prosthesis). This study was supported by the National Center of Excellence and involved 3 center and randomized 101 patients. A large multicenter trial is presently underway in 9 centers across Canada that investigates the effects of CPAP therapy on mortality and transplantation rates in patients with heart failure and CSA (Canadian Positive Airway Pressure Trial for Therapy of Heart Failure and Central Sleep Apnea /CANPAP Trial). CIHR and industry through the UI program jointly support this study. This trial brings together 20 investigators and is aimed to recruit 400 patients during its 5 year duration (Bradley et al, 2001). Other multicenter studies also are on their way such as in Quebec province where two trials are supported by industry (Mallinkrodt, Medigas) to investigate the accuracy and indication for autoCPAP therapy at home in the treatment of OSA. Furthermore, a pilot project supported by FRSQ respiratory Network has been designed to evaluate the effects of CPAP therapy on bronchial hyperactivity in patients suffering from OSA and asthma. These 3 projects are conducted in 4 different sleep research centers of Quebec province and are aimed to recruit a total of 120 patients. A letter of intent has been sent to the CIHR for a proposal that will be conducted simultaneously in Canada and UK through the UI program to investigate the effects of treating OSA with CPAP on nocturnal and diurnal blood pressure. (Appendix IV). Therefore, some infrastructure has already been developed to support a team of investigators across the country that could be used as a platform upon which to build a more extensive and sophisticated clinical trials network and make it viable for future studies as they arise. This is an ideal setting for CIHR partnerships with other granting agencies such as the Heart and Stroke Foundation of Canada and the Canadian Lung Association, as well as with industry partners. Participants felt that CINDIS priorities should focus on specific research questions with case control study designs rather than large cohort studies such as those that are presently conducted in the United States.

*Need for a multidisciplinary approach of SRBD research.* During this workshop several discussants from diverse backgrounds including psychology/circadian rhythms, obesity/metabolism, pediatrics, respirology, cardiology neurology and neuroscience outlined important unresolved questions that might direct future research initiatives in this area. Recent studies have shown that 30% of the variation in SRBD frequency is explained by familial factors. Racial differences contribute to the development of SRBD by the influence of obesity, craniofacial factors and age of onset. Obstructive SRBD in children differs in symptoms (failure to thrive, learning and behavioral disorders, and pulmonary hypertension), pathophysiology and treatment from the condition in adults. Adenotonsillar hypertrophy is the more prevalent etiological factor, but obese children are at increased risk to develop SRBD. The natural history and long term prognosis of SRBD in childhood is not known. Furthermore it is not known whether childhood OSA is a precursor of the disease in adult and a cause of increased morbidity later during lifetime. However, these questions will remain unanswered as long as sleep investigations will not be more accessible in children. As with adults the gold standard for

diagnosing OSA in children is full polysomnography, but there are only four centers in Canada able to perform this test. The development of children research investigation and collaboration between pediatricians and adult respirologists would need an increase in the ability to perform sleep recordings across Canada as well as the use of less complex diagnostic techniques that could be more widely available particularly in children.

Hormonal factors may be involved in OSA pathophysiology but its profile (testosterone, estrogen/progesterone, cortisol, thyroxin, and growth hormone) may also be altered by the disease and change with treatment. Patients with OSA are at increased risk to develop diabetes mellitus and treatment may improve insulin sensitivity. These patients also demonstrate coagulation disorders (increase in platelet aggregability, and an increase in soluble adhesion factors), and a rise in circulatory inflammatory markers that are reversible with an effective treatment. Sleep apnea has been identified, through epidemiological studies, to be an independent risk factor for hypertension, coronary artery disease, congestive heart failure and stroke. These are the commonest serious medical conditions with the highest rates of morbidity and mortality in industrialized societies. Obesity is either directly or indirectly via OSA a major cause of cardiovascular disease (15% of Canadians are obese with a body mass index of over 30 kg/m<sup>2</sup>). Leptin may play a key role in determining the complex association between OSA, obesity and cardiovascular disease (myocardial infarction and cerebro-vascular disease) by affecting control of body weight, energy expenditure and sympathetic activity. Obesity should remain the primary target for intervention for OSA, but conventional weight loss strategies have been found to have had limited success in these patients due to their inability to lose weight. There is a need to develop new strategies to promote and maintain weight loss in these patients. It was emphasized that OSA may represent a heterogeneous disease with sub-groups at increased risk because of sex hormones, stress hormones and insulin sensitivity. Therefore, a component of OSAHS may be part of a “metabolic” or “vascular” syndrome. These observations have important research and public health implications that involve all four pillars of the CIHR. However, it is clear that many of these potential research initiatives would be crosscutting and involve more than one of the pillars. They clearly demonstrate that SRBD research activities require a systematic multidisciplinary approach. Therefore, as indicated in the above review, SRBD represent a common research theme for many Institutes of the CIHR i.e. Institutes of Ageing, Gender and Health, Genetics, Child and Youth Health, Neuroscience, Mental Health and Addiction, Nutrition, Metabolism and Diabetes, Population and Public Health, in addition to Circulatory and Respiratory Health. Research activities in SRBD therefore have a unique position to establish and strengthen the links inside and across institutes to develop multidisciplinary research initiatives.

*Structural development in SRBD research.* It is important to emphasize that the number of investigators and research staff (master and doctoral students, fellows, medical students) involved in SDBR research in any one university in Canada is presently. Therefore, it may be necessary to involve Canadian experts from different universities to tackle complex research questions in SRBD. Accordingly, there is a need to develop a Canada-wide sleep disorders research program that would increase exposure to the different research expertise and further develop the links between the existing laboratories and to foster the development of future laboratories in the future. This research program should be multi-disciplinary and be coupled with a national clinical training program. Such clinical and research structure would attract the

highest caliber trainees into the field. It would promote the development of clinical investigations that are presently poorly accessible in many centers across Canada and could promote interactions between pediatric and adult researchers in SRBD as well as with all disciplines in which sleep disorders are involved.

*Identification of research priorities.*

(a) To determine the role of genetic, environmental and intrinsic determinants for the onset and progression of SRBD as well as their consequences, and to assess whether these determinants are the same in children, adults and the aging population, and to identify modifiable risk factors.

(b) To determine the molecular, cellular and neurobiological mechanisms underlying the effects of sleep and its disruption, and of hypoxemia on modulation of upper airway neuromuscular control, cerebral, cardio-respiratory and endocrine functions, metabolism and on fetal development and placental function, and to use this information to develop new treatments.

(c) To develop a Canadian multi-center clinical trials structure via the **Canadian Investigation Network for Disorders of Sleep** aimed to evaluate the efficacy of new diagnostic techniques, elaborate strategies for use in the community to reach the large numbers of currently undiagnosed patients with sleep disordered breathing, and assess the effects of treatments on physiological and clinical outcomes, and the development of common clinical and sleep laboratory standards across the country. To develop strategies and methodologies to identify and treat sleep and breathing disorders in the community settings.

**Specific recommendations and/or comments to funding institutes and organizations for future directions.**

One of the main outcomes of this New Frontiers program was a need to inform the research community within institutes (biomedical, clinical science, health systems, population), and across institutes, of the prevalence of sleep-disordered breathing and other sleep disorders and their relevance (clinical, social and economic) to the health of individuals and the population as a whole. The multifaceted nature of sleep, its disorders and consequences require a multidisciplinary research approach that can be reached in different complementary ways aimed at 1) linking basic, clinical, and population based researchers of different institutes to enhance research activity and promote interactions between Canadian experts, 2) developing a national training program for health-care professionals and researchers to disseminate research in these areas and implement this knowledge into policies and practices to improve health and safety. This has been developed in 3 specific recommendations:

a) First, research developments should be favored to approach the above-mentioned targeted proposals by taking advantages of the extensive discussions between scientists with very different expertise and incorporating the conclusions of fruitful brainstorming sessions that directly resulted from the NFP. This can be reached by promoting group grants that would be structured in dedicated meetings supported by CIHR as a direct continuation of the NFP and to be held in the next year. The development of these group grants will of course not be limited to the participants to the NFP workshops but the principal and co-investigators should prioritize the

involvement of cross-institutes collaborations. Such collaborative development would be best achieved by addressing RFA topics that should be addressed to and supported by all the concerned institutes of the CIHR. An RFA entitled: Genetic, environmental and physiological interactions of SRBD and the cardiovascular system would represent an innovative research domain in this issue.

b) Second, a mechanism should be set-up with which to inform the research community within institutes (biomedical, clinical science, health systems, and population), and across institutes, of the relevance and prevalence of sleep and its disorders to individual and population health. At the very least this could involve representation on Institute Advisory Boards by recognized sleep experts. This recommendation was also made from the Halifax meeting. Indeed, following the findings of a commission initiated in the US as to the role of sleep to the health of Americans (National Commission on Sleep Disorders Research, 1993), the NIH set-up a *National Center for Sleep Disorders Research* (<http://www.nhlbi.nih.gov/about/ncsdr/index.htm>) which is part of the *National Heart Lung and Blood Institute*. The mandate of this National Center is to "coordinate government-funded sleep research, training and education" to improve public health of Americans. Representation of sleep at the CIHR would provide a mechanism to coordinate the breadth and depth of talent that currently exists in Canada via "Requests for Applications" relevant to sleep but that cross-traditional boundaries within and between institutes.

c) Third, a national training program to link researchers and current students in the field should be considered as a high priority. Development of such a network would increase collaborations across disciplines within and between participating centers, and would attract high quality personnel into the field and provide an infrastructure to retain them in Canada. Given the high prominence of sleep research in the US and Europe, much Canadian talent is currently lost. In parallel, a mechanism to improve the quality of Canadian sleep medicine education nationwide should be linked with the above research training program. A similar program in the US (*Sleep Academic Award*) encourages curricular development and research in medical schools to increase the knowledge and skills of medical professionals, to develop and evaluate the impact of sleep curricular models that can be adapted and institutionalized by medical schools nationwide, and to promote an institutional environment that encourages appropriate sleep medical care with increasing knowledge of sleep disorders. Such needs are currently not met in Canada.

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# Appendix I

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# Appendix III

## Workshops program

### CIHR New Frontiers Program

*Cardiopulmonary Disorders During Sleep: Mechanisms, Treatment and Public Health Impact*

*January 12<sup>th</sup> & 13<sup>th</sup> 2002, Sheraton Gateway Hotel at Toronto airport*

January 11<sup>th</sup>, arrival, diner (unformal)

January 12<sup>th</sup>, 2002

- 7:30 – 8:20 inscription & breakfast room Lausanne
- 8:20 – 8:30 introduction, F Sériès md
- 8:30 – 12:15 Workshop: Mechanisms and New Treatments for Sleep Apnea
- 12:15 – 2:00 pm Lunch room Lausanne
- 2:00 – 5:45 pm Workshop: obesity/metabolic features of sleep disordered breathing from childhood to adulthood
- 07:00 pm dinner Mahogany Grill

January 13<sup>th</sup>, 2002

- 7:15 – 8:15 breakfast room Zermatt
- 8:15 – 12:30 Workshop: Sleep apnea – cardiovascular interactions
- 12:30 – 2:00 pm Lunch room Zermatt
- 2:00 – 4:00 pm Conclusions and main lines of the final report, room Zermatt

# CIHR New Frontiers Program

*Cardiopulmonary Disorders During Sleep: Mechanisms, Treatment and Public Health Impact*

**Workshop: Mechanisms and New Treatments for Sleep Apnea**  
**January 12<sup>th</sup>, 2002 8h30 – 12h15**

*Coordinating Group:*

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*Location:* Sheraton Gateway Hotel, Toronto, room Lausanne

**08:30-08:45**

**1. Introduction and Overview (15 min)**

*Speaker:* John Remmers, MD

*Emphasis to facilitate further discussion:* (1) Sleep apnea: nature of the clinical problem, prevalence and public health impact. (2) State of the field regarding research fronts both basic and clinical that pertain to the area. (3) Major unknowns.

**08:45-12:15**

**2. Discussion and Identification of Research Priorities**

30 min discussions (25 min each following a 5 min introduction from the facilitator. At the end of each discussion the facilitator makes a ~2 min summary of the main points.)

**08:45-09:15**

**A. Strategies to improve research infrastructure and technological transfer from animal models to human physiology and clinical trials**

For example, discussion of Canadian infrastructure to attract, train and maintain highly qualified basic and clinical scientists in the field of sleep and breathing. Is there a need for a CIHR funded multicentre training program in sleep and its disorders? Identification of potential links with industry and partnership programs.

**Facilitator:** Eliot Phillipson, M.D.

**09:15-09:45**

**B. Mechanisms of upper airway motor control and impact of sleep systems – relevance to development of new treatments for sleep apnea**

What we know, what we do not know, and implications. For example, potential neuropharmacological treatments for OSA may develop from understanding basic neurobiology of sleep, relevant neurotransmitters and upper airway motor control.

**Facilitator:** Richard L. Horner Ph.D.

**09:45-10:15**

C Mechanisms of natural history of OSA in adults and strategies for preventative treatment

What we know, what we do not know, and implications. For example, what is the evidence that a proportion of today's large population of snorers will become tomorrow's OSA patients, and what is the potential public health impact of that progression? Identification of predisposing factors for sleep apnea and development of suitable preventative treatment strategies. What is the role in the natural history of OSA of obesity, age, anatomical factors, abnormalities in the airway mucosa and sensory regulation of upper airway motor tone. What role, if any, do conventional treatments have in individuals who are likely to develop OSA but have no clinical symptoms?

**Facilitator:** John Kimoff, M.D.

**10:15-10:45. Break**

**10:45-11:15**

D Respiratory control mechanisms and relationship to sleep apnea

What we know, what we do not know, and implications. For example, discussion of control system instabilities in central and obstructive sleep apnea and the implications. Are these abnormalities inherent to these patients, or a consequence of normal ageing, disturbed sleep or breathing? Discussion of strategies for investigation and treatment.

**Facilitator:** Magdy Younes, M.D.

**11:15-11:45**

E Treatments for sleep apnea – what makes a scientifically rigorous study or trial and what should be tested and how do we assess outcomes?

For example, discussion of current standards in the field of sleep and breathing. What can and should be improved? What infrastructure exists for scientifically and statistically rigorous trials, and what needs to be implemented locally or via a network? What outcome measures would indicate clinically successful treatment of sleep apnea and standards for their measurement? What old, current and future treatment strategies are high priority for development and testing?

**Facilitator:** Frédéric Sériès, M.D.

**11:45-12:15**

**3. Overall Summary and Identification of Links Across CIHR Institutes (30 min)**

For example, discussion on what strategies and links can be employed to increase understanding and appreciation for sleep and its disorders to the research mandates of other institutes. To be concluded with an overall summary.

**Chair:** John Remmers, MD with help from each facilitator.

# CIHR New Frontiers Program

*Cardiopulmonary Disorders During Sleep: Mechanisms, Treatment and Public Health Impact*

**Workshop: obesity/metabolic features of sleep disordered breathing from childhood to adulthood, January 12<sup>th</sup>, 2002 2:00 – 5:45**

*Coordinating Group:*

John Fleetham MD, University of British Columbia, fleetham@interchange.ubc.ca

Jean-Paul Praud MD University of Sherbrooke, jp.praud@courrier.usherb.ca

Paul Poirier MD, University of Laval, Paul.Poirier@crhl.ulaval.ca

Angelo Tremblay MD University of Laval, Angelo.tremblay@kin.msp.ulaval.ca

*Location:* Sheraton Gateway Hotel, Toronto, room Lausanne

**2:00-2:15pm**

**1. Introduction and Overview**

*Speaker:* Kingman Strohl MD

*Emphasis to facilitate further discussion:* Sleep disordered breathing a) childhood to adulthood b) hormonal and metabolic features c) obesity and abnormal leptin secretion as a contributing cause d) vascular risk factors

**2:15-5:45pm**

**2. Discussion and Identification of Research Priorities**

30 min discussions (25 min each following a 5 min introduction from the facilitator. At the end of each discussion the facilitator makes a ~2 min summary of the main points.)

**2:15-2:45pm**

**A Sleep disordered breathing in children**

What do we know about sleep disordered breathing in children For example, is sleep disordered breathing in children the same disorder as in adults. What are the similarities and differences. What is the impact of puberty on sleep disordered, the consequences (neuropsychological, cardiovascular) of sleep apnea identical in the two populations. What are the predictive factors for an obese child to develop obstructive sleep apnea as an adult. What is the course of the disease in childhood and what would prevent its development (worsening?) during adulthood. Is an animal model available to study the natural history of sleep disordered breathing from early childhood to adulthood

**Facilitator:** Valérie Kirk MD

**2:45-3:15pm**

**B** Sleep disordered breathing and endocrine disease

What do we know about the influence of hormonal status and disease on sleep disordered breathing. What do we know about how sleep disordered breathing and/or obesity alters endocrine function. What is the impact of puberty and menopause on sleep disordered breathing. What is the effect of hormone replacement on sleep disordered breathing and what insights does it provide for other potential pharmacologic therapy.

**Facilitator:** Kingman Strohl M.D.

**3:15-3:45pm Break**

**3:45-4:15pm**

**C** Sleep disordered breathing and obesity

How does obesity contribute to the development of sleep disordered breathing in childhood and adulthood. Is the effect different between children and adults, and men and women. Is there a link between obesity-related systemic inflammation and obstructive sleep apnea. Do sleep apnea contribute to metabolic cascade abnormalities associated with obesity. What is the relationship between leptin secretion, obesity and sleep disordered breathing. What insights do the effects of obesity and abnormal leptin secretion provide for future therapy

**Facilitators:** M Fitzpatrick MD, A Tremblay PhD

**4:15-4:45pm**

**D** Consequences of Sleep disordered breathing and obesity

**Do sleep disordered breathing and obesity act congruently to influence vascular risk factors (such as systemic blood pressure, glucose metabolism, lipids and platelet function) and psychological performances (hypersomnia) and what is the potential impact of effective treatment on the consequences.**

**Facilitators:** *J Fleetham MD*

**4:45-5:15pm**

**E** Strategies to improve collaboration between pediatric and adult research in sleep disordered breathing

For example, discussion of potential opportunities to increase interaction between researchers involved in pediatric and adult sleep disordered breathing. Identification of potential links with other CIHR institutes and industry

**Facilitators:** J.P. Praud MD, F. Sériès MD

**5:15-5:45pm**

3. **Overall Summary and Identification of Links Across CIHR Institutes** (30 min)

**Facilitator:** Kingman Strohl MD with help from each facilitator.

# CIHR New Frontiers Program

*Cardiopulmonary Disorders During Sleep: Mechanisms, Treatment and Public Health Impact*

**Workshop: Cardiovascular Implications of Sleep Apnea**  
**January 13<sup>th</sup>, 2002 8h15 – 12h30**

*Coordinating Group:*

Douglas Bradley, University of Toronto, douglas.bradley@utoronto.ca  
John Floras, MD, University of Toronto, john.floras@utoronto.ca

*Location:* Sheraton Gateway Hotel, Toronto, room Zermatt

**08:15-08:30**

1. **Introduction and Overview**

*Speaker:* Douglas Bradley

*Emphasis to facilitate further discussion:* 1. What is the evidence that sleep apnea can contribute to the development and progression of cardiovascular diseases? 2. What are the major gaps in our knowledge? 3. What are the broad types of research that can be brought to bear on these issues that relate to the four pillars of the CIHR (i.e. Biomedical, Clinical, Health Services/System and Society, Culture, Environments and Health of populations research)?

**08:30-12:30**

2. **Discussion and Identification of Research Priorities**

30 minute discussions (5 minute introduction from facilitator followed by 25 minutes of free discussion, then approximately 2 minute summary of main points by facilitator).

**08:30-09:00**

A. **What are the health and cardiovascular implications of sleep apnea? (8:45-9:15)**

What sleep/circadian aspects of sleep apnea potentially contribute to cardiovascular morbidity and mortality? For example: sleep disruption, disturbances in circadian rhythm/clock, sleep/wake schedules etc.

**Facilitator:** Martin Ralph

**09:00-09:30**

B. **What are unresolved issues in sleep apnea and cardiovascular disease?**

What is the evidence that sleep apnea causes or aggravates cardiovascular diseases? What are the important unanswered questions regarding possible links between sleep apnea and cardiovascular diseases? What research strategies are required to answer these questions?

**Facilitator:** Virend Somers

**09:30-10:00**

C. Integrative physiology/animal models.

What can animal models tell us about the acute and chronic effects of sleep apnea on the cardiovascular system? What types of questions are best answered by animal models? What is the role of whole organism (human and animal) research in determining mechanisms of disease?

**Facilitator:** Eliot Phillipson

**10:00-10:30. Break**

**10:30-11:00**

D. Susceptibilities to cardiovascular diseases in sleep apneics.

Why do some patients with sleep apnea develop cardiovascular diseases and others do not? Is there a need for genomics-related research to identify genetic/molecular susceptibilities to cardiovascular diseases in sleep apneics?

**Facilitator:** John Floras

**11:00-11:30**

E. Epidemiology/Population health implications.

What are the public health implications of the identification of sleep apnea in cardiovascular diseases? Among patients with cardiovascular diseases, who should be tested for sleep apnea? Is full polysomnography necessary or the best way to identify sleep apnea in this population? Could ambulatory monitoring devices be a cost-effective way to screen for sleep apnea in cardiovascular populations? What are the resource implications of widespread screening of cardiovascular populations for sleep apnea?

**Facilitator:** Douglas Bradley

**11:30-12:00**

F. Clinical trials.

What large-scale clinical trials should be undertaken to determine whether therapy for sleep apnea can improve cardiovascular outcomes? Can we build on the CANPAP Trial Network to develop such trials? What type of infrastructure support would be required to build an effective clinical trials network across Canada? How do we encourage cardiovascular, respiratory, sleep and clinical trials experts together to facilitate such trials?

**Facilitator:** Sonny Belenkie

**12:00-12:30**

3. **Summary**

Summary and synthesis of major points. Suggestions for broad research initiatives and potential linkages with other CIHR institutes.

**Facilitator:** Douglas Bradley, with help from each facilitator.

## Appendix IV

Letter of intent addressed to CIHR on Feb 21, 2002 on a multicenter clinical project entitled:  
Multicentre Interventional Trial in Mild-Moderate Obstructive Sleep Apnea.

PI: John A. Fleetham, \$699,825

Obstructive sleep apnea (OSA) is due to repetitive collapse of the pharynx at sleep onset. It is the second commonest respiratory disorder after asthma. Mild variants of this disorder are detectable in 4-6% of adult men randomly selected from the normal community. Treatment of severe OSA (affecting about 0.5% of adult men) with nasal continuous positive airway pressure (nCPAP) produces substantial improvements in excessive daytime sleepiness, and hence both driving performance and 'quality of life' (1-3). It also reduces blood pressure, particularly at night, which is likely to reduce vascular risk (4-5). In patients with severe disease, the size of the therapeutic benefits are large and the 'number needed to treat' figures are small. The improvements in 'quality of life' indices are some of the largest ever reported and only 1.4 patients need to be treated to return one subject to a normal level of daytime sleepiness (1). Small studies have suggested qualitatively similar benefits in patients with milder disease (6), but there are no adequately powered studies to confirm such benefits, nor to describe how these change across the disease severity spectrum. Despite the absence of evidence to substantiate its treatment, nCPAP for mild OSA is advocated by influential authorities in the US (7) and such therapy is creeping into practice in Canada. This view is still highly contentious in Canada which provides a window of opportunity to assess this treatment's efficacy in mild disease. Such data is important since the financial consequences of treating all mild sleep apnoea are substantial. It would cost \$300 million to treat half the Canadian adult men with mild OSA. This trial randomizes 800 patients with sleep apnea, which is below the severity where therapy is currently established, to therapeutic and sub-therapeutic (control) nCPAP for four months. At one, two and four months post randomization, the main outcomes of interest in OSA will be quantified using instruments which have been validated in the setting of OSA in previous studies. The end points examined will be; ambulatory blood pressure subjective and objective excessive daytime sleepiness, self reported health status ('quality of life'), health care costs/benefits, nCPAP compliance, cognitive function, driving simulator performance, and self reported road accident rate. Since most of these end points are influenced by placebo effects in previous trials, the therapeutic intervention will be compared with the most robust form of control therapy, sub-therapeutic nCPAP. Comparison of the outcomes will establish whether nCPAP is effective in mild OSA, how large this benefit is and how the benefits vary with disease severity. This data will allow rational decision making about nCPAP therapy in OSA, ensuring that subjects likely to achieve large benefits from therapy receive it, while also ensuring that health care resources are used appropriately.

This randomized clinical trial intends to build on the collaboration which has developed during two previous Canadian clinical trials in sleep disordered breathing. A randomized clinical trial of nCPAP vs. oral appliances in patients with OSA (Calgary, London, Vancouver) was funded by the Respiratory Center of Excellence (1997-2000). A randomized clinical trial of nCPAP vs. best therapy in patients with heart failure and Cheyne-Stokes breathing (Vancouver, Calgary, Edmonton, Winnipeg, London, Toronto, Montreal, Quebec City, Halifax) is funded by CIHR 1998-2004. In addition to at least 5 confirmed Canadian centres this trial will

also involve at least one UK centre (Oxford) who have pioneered subtherapeutic NCPAP in randomized clinical trials. Additional UK centres (Edinburgh, Leeds, Liverpool, Newcastle) will be involved if research grants submitted in the UK are also funded. ResMed one of the 3 major international manufacturers of NCPAP machines has committed to provide the trial with 330 Autoset T NCPAP machines with tubing and masks at a total cost of \$607200.