

## Ritchie Centre for Baby Health Research



### Acting Centre Director: Dr Philip Berger

The Ritchie Centre has established a world-class reputation in scientific and medical research relating to growth and health of the fetus, infant and child, with a focus on key organs including the brain, heart and lungs.

The Ritchie Centre is one of the few research units that has world-class laboratories, access to patients under clinical care in a major teaching hospital, complemented by a commercial partnership facilitating the transfer of scientific findings to the benefit of patients.

Uniquely the Ritchie Centre brings together scientists, clinicians and engineers in major research programs that seek to develop understanding, diagnosis and treatment of major paediatric cardio-respiratory problems:

- the mechanisms involved with the Sudden Infant Death Syndrome
- novel bed-side tests of brain blood flow and brain function in extremely low birth weight babies,
- physiological and mathematical models of the control of breathing in the newborn
- causes of apnoea and its consequences on oxygen delivery to vital organs (heart and brain)

- causes and treatment of obstructive sleep apnoea in infants, children and adults
- disorders of the heart, circulation and breathing during sleep in preterm infants
- mechanisms leading to chronic lung disease in the preterm infant and potential therapies.

### Novel approaches to assessing cerebral circulation and oxygenation in preterm human infants

**Project Leaders:** Dr Flora Wong, A/Prof Rosemary Horne and Prof Adrian Walker

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#### Project Description:

This project seeks to establish simple, yet reliable, methods based upon NIRS of measuring brain blood flow and brain oxygenation that will be suitable for use in the critically ill newborn. By greater understanding of the basic mechanisms that determine the NIRS measurements, and their correlation with brain blood flow, our project will provide essential information that can be used to enhance the treatment of the more than 5000 babies born each year in Australia that require intensive care for cardio-respiratory dysfunction. By inducing (in newborn lambs) fluctuations in blood pressure, hypoxic-ischaemia and simulated septic shock, we create a model of the most common clinical disturbances in newborn human infants undergoing intensive care. We are then able to evaluate the usefulness of NIRS measurements in these clinical situations of disturbed blood flow and oxygen balance.

## Ritchie Centre for Baby Health Research

### Novel approaches to bedside monitoring of cerebral oxygenation in infants with HIE undergoing therapeutic hypothermia

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#### **Project Description:**

Hypoxic ischaemic encephalopathy (HIE) is a major problem worldwide with significant mortality and morbidity. Based on recent evidence that therapeutic hypothermia is beneficial to term newborns with HIE, neonatal units now offer cooling as recommended therapy. Yet, there are significant unresolved issues in the application of cooling, including uncertainty of appropriate cerebral monitoring during cooling and re-warming, potential side effects with impact on cerebral circulation and oxygenation, and long-term neurodevelopmental outcome.

This project aims to improve and refine the cooling therapy, by using the Tissue Oxygenation Index measured by Near Infrared Spectroscopy (NIRS). We plan to continuously monitor the cerebral oxygenation of HIE infants by NIRS, and relate the measurements to neurodevelopmental outcome. The study will provide bedside information to aid clinical assessments with the potential to guide therapeutic interventions in these critically ill infants.

### Impact of dopamine in the immature brain

**Project Leaders:** Dr Flora Wong and Prof Adrian Walker

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Dopamine is commonly prescribed to preterm babies to raise their blood pressure, but its effect in the immature brain is uncertain.

This project aims to define the effects of dopamine in the immature brain using a preterm lamb model, in order to evaluate the therapeutic potential of dopamine in improving brain oxygenation and reducing brain injury in preterm babies.

Our proposal is based on our preliminary findings in preterm babies that dopamine might promote brain oxygenation to meet metabolic requirement of the brain, thus offering protection against hypoxic-ischaemic injury. We plan to use complementary human-lamb studies: in preterm human infants receiving dopamine therapy, we will monitor their cerebral oxygenation over 3 days using Near Infrared Spectroscopy (NIRS). In preterm fetal lambs receiving dopamine infusion, we plan to correlate changes in cerebral blood flow and metabolism with dopamine dosage and level of dopamine in cerebrospinal fluid.

## Ritchie Centre for Baby Health Research

**Postnatal Consequences of Intrauterine growth restriction on Cardiovascular Control During Sleep in Infants.**

**Project Leader:** A/Prof Rosemary Horne and Dr Stephanie Yiallourou  
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**Project Description:**

Intrauterine growth restriction (IUGR) has been associated with increased risk of cardiovascular disease, high blood pressure, obesity and insulin resistant diabetes later in life. The causes of this increased susceptibility remain unclear. Cardiovascular control undergoes dramatic maturation changes within the first 6 months of life. In the newborn period infants spend approximately 70% of their time asleep and it is during sleep that infants are at increased risk of cardiovascular instabilities. To date there has been no description of the consequences of IUGR on the maturation of cardiovascular control during sleep in human infants. We have previously described normal maturation of both blood pressure (BP) and heart rate (HR) control in both healthy full-term infants and infants born preterm. In these novel studies we will expand our previous studies to examine the effects IUGR on the maturation of BP and HR control during sleep within the first 6 mo of life. This study will provide information on the postnatal consequences of IUGR and aid in understanding any contributing factors that may contribute to increase blood pressure and cardiovascular complications later in life.

**Development of Cardiovascular Control During Sleep in Infants: Effects of prone sleeping and implications for SIDS**

**Project Leader:** A/Prof Rosemary Horne and Dr Flora Wong  
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**Project Description:**

It has been suggested that Sudden Infant Death Syndrome (SIDS) may be due to an inadequate compensatory response to a hypotensive challenge resulting from either a cardiovascular or respiratory event during sleep. Sleeping in the prone position is still a major risk factor for SIDS, and as yet the reason for this is unknown. We, and others, have previously identified that infant autonomic cardiovascular control and arousability from sleep are impaired in the prone position and this is most marked at 2-3 months of age when SIDS risk is highest. Furthermore, preterm infants are at increased risk for SIDS and we have previously identified impaired autonomic cardiovascular control and arousability in preterm infants compared with age matched term infants. The impaired arousability in SIDS may be related to poor regulation of brain blood flow and oxygen level during sleep.

In these novel studies we will expand our previous studies to examine the effects of sleeping position and prematurity on blood pressure (BP) and heart rate (HR) control and cerebral oxygenation using Near Infra Red Spectroscopy (NIRO).

## Ritchie Centre for Baby Health Research

### Protection against Sudden Infant Death Syndrome: Is dummy-sucking the answer?

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**Project Description:**

Epidemiological studies consistently show a protective effect of dummy/pacifier use against Sudden Infant Death Syndrome (SIDS); however the promotion of dummies has been controversial, particularly as the mechanisms responsible for this protection remain unknown. It has been proposed that SIDS may involve an impaired ability to mount an appropriate cardiorespiratory and/or arousal response, to compensate for a threatening situation during sleep. Our laboratory and others have previously demonstrated that both autonomic control and arousability from sleep are impaired by exposure to known risk factors for SIDS, such as the prone position and maternal smoking.

In this project, we will investigate the effects of dummy-sucking, a SIDS protective factor, on infants' sleep patterns, baseline physiology (heart rate, blood pressure, respiration) and arousal processes throughout the first six months of life.

### Postnatal Maturation of Infant Sleep Physiology

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**Project Description:**

It has been suggested that despite appearing well and physiologically normal prior to their deaths, victims of Sudden Infant Death Syndrome (SIDS) may have had a pre-existing abnormality which impaired their ability to arouse from sleep. In support of this hypothesis, we have previously shown that arousal processes are modified by major SIDS risk factors, prone sleeping and maternal smoking. An incomplete progression of sub-cortical to full cortical arousal may provide a marker to identify "at-risk" infants with an increased likelihood of succumbing to SIDS. This may have the potential to minimise the incidence of SIDS by increasing awareness of both parents and medical staff, in association with close monitoring and early intervention; however this would be impossible without normative values for comparison.

This study will examine recordings of undisturbed nocturnal sleep in healthy infants throughout the first 12 months of life. We will compare changes in baseline cardiorespiratory variables and spontaneous arousal processes both between infants and within individual infants across development. In addition, using spectral analysis techniques, we will investigate maturational changes in EEG activity, and on heart rate variability (as a measure of autonomic control).

## Ritchie Centre for Baby Health Research

**Blood pressure changes in preschool children with sleep disordered breathing**

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**Project Description:**

Sleep disordered breathing (SDB) affects up to 34% of children and symptoms can range from primary snoring without obstructed breathing to obstructive sleep apnoea syndrome (OSAS). OSAS is common in childhood occurring in about 2% of the population, with the peak occurrence between 2-8 years of age and the vast majority of cases are associated with adenotonsillar hypertrophy. Frequent arousal from sleep in response to apnoea, results in sleep fragmentation have serious neurobehavioural consequences such as aggressive behaviour, learning disabilities, excessive daytime sleepiness and attention deficit/hyperactivity. In children apnoea is frequently terminated without any changes on the electroencephalograph and so it is difficult to measure the exact severity of sleep fragmentation.

In this study of pre-school children with SDB referred to the Melbourne Children's Sleep Unit for investigation we will measure blood pressure and heart rate during sleep to examine if SDB is associated with increased BP as it is in adults and whether or not this is associated with changes in cardiovascular control.

**Behaviour and neurocognition in pre-school children with sleep disordered breathing.**

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**Project Description:**

Frequent arousal from sleep in response to apnoea, results in sleep fragmentation have serious neurobehavioural consequences such as aggressive behaviour, learning disabilities, excessive daytime sleepiness and attention deficit/hyperactivity. However, few studies have examined a range of severities of clinically defined SDB and how this association is linked with the repeated hypoxic events that occur during sleep and the resultant sleep disruption. This study will examine the effects of a range of severities of SDB on behaviour and neurocognition in 3-5 year old children referred to the Melbourne Children's Sleep Unit for assessment of SDB.

## Ritchie Centre for Baby Health Research

**Effectiveness of treatment for the resolution of Sleep Disordered Breathing, cardiovascular, behavioural and neurocognitive symptoms in primary school children.**

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**Project Description:**

Our previous studies have identified that sleep disordered breathing (SDB) is associated with increased blood pressure and heart rate and also with impaired neurocognition and behaviour. In current clinical practice, only those children with more severe SDB are treated, primarily with adenotonsillectomy (A/T). A/T has been shown to improve sleep quality and neurobehavioural outcomes, however to date there have been no studies on the effects of treatment on the cardiovascular system. Perhaps more importantly, there have been no studies to assess what happens in untreated children with milder symptoms as currently it is believed that children “will grow out of” their SDB. In this study we will follow up the children previously studied to determine the effects of SDB treatment and non treatment on both the cardiovascular system and neurobehavioural outcomes.

**The impact of obstructive sleep apnoea on cardiovascular function: are children with Down syndrome at higher risk.**

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**Project Description:**

Surges in blood pressure and heart rate and increased activation of the sympathetic nervous system occur as a result of obstructive sleep apnoea (OSA) in adults. These responses are part of the protective arousal response to obstructive apnoeas and hypopnoeas, but are also partially responsible for the adverse cardiovascular effects of OSA. Children with Down Syndrome (DS) have reduced autonomic responses during wakefulness and may therefore have a diminished response to obstructive events during sleep, making them more at risk of hypoxia for a given severity of OSA than otherwise healthy children. Children with DS are at greatly increased risk of pulmonary hypertension, and unrecognised hypoxia due to OSA may contribute to this disorder.

In this study we will measure cardiovascular activity and levels of sympathetic activity during sleep in children with DS and otherwise healthy children referred to the Melbourne Children’s Sleep Unit for investigation for sleep disordered breathing.

## Ritchie Centre for Baby Health Research

A clinical tool for the detection of children at high risk of obstructive sleep apnoea.

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**Project Description:**

Obstructive sleep apnoea (OSA) affects 1-3% of children and is a major health issue in childhood, with significant impacts on cognition, behaviour and cardiovascular health. The cardinal symptom of OSA is snoring. Approximately 35% of children snore- over one million children in Australia- but only about 10% of snoring children (1-3% of the population) will have OSA. Formally defining the presence of OSA in a snoring child requires polysomnography, a technically challenging and expensive (about \$1000 each) test only available in paediatric tertiary referral hospitals. Such facilities could never meet the demand if all snoring children were referred. We are developing a clinical scoring tool that will help predict children at highest risk of OSA without the need for polysomnography. The tool involves clinical evaluation of the patient including features such as age, body mass index (BMI), symptoms of OSA (snoring, restless sleep) and clinical findings, plus simple sleep tests that can occur in a patient's home.

Control of Breathing in the Newborn

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**Project Description:**

Artificial surfactant therapy is highly effective in controlling lung disease in the newborn. Nevertheless, many preterm infants develop breathing difficulties that require long periods of costly intensive care. Of major concern to clinicians, and a puzzle to explain in terms of current ideas on the control of breathing, is the appearance of breathing pauses (apneas) lasting up to 30 seconds or more. Long apneas are often associated with profound decreases in blood oxygenation and are therefore life-threatening.

This project examines the physiology of respiratory control with the goal of understanding the genesis of these pauses.

## Ritchie Centre for Baby Health Research

### Switch of GABAergic and glycinergic neurons from excitation to inhibition in early gestation

**Project Leaders:** Dr Philip Berger and Dr Elaine Stockx  
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#### **Project Description:**

During early ontogeny all vertebrate animals exhibit a highly stereotyped and cyclic pattern of activity, involving the simultaneous switching on and off of all the muscles of the body. This behaviour, which is known as cyclic activity, is replaced during gestation with the development of more specific purposive behaviours such as feeding and locomotion. While the timing of this change in behaviour is well known in the chick, mouse, rat and sheep, the mechanisms that bring it about are yet to be established. One possibility is that the neurotransmitters GABA and glycine could be involved in this transition, since they mediate excitation in spinal neurons in early development before their action switches to inhibition in the mature nervous system. This project aims to test this prediction by pharmacologically blocking the action of GABA and glycine at selected gestational ages using the antagonists bicuculline and strychnine in the fetal sheep.

The project will involve fetal surgery, long-term recordings of spontaneous fetal behaviour, and the use of pharmacological agents to establish the involvement of the major neurotransmitters of the central nervous system in fetal behaviour.

### Effect of spinal cord transection of the excitability on somatic and autonomic nervous systems

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#### **Project Description:**

Spinal cord injury (SCI) leads to hyperreflexia, or an over-excitability of spinal circuits, such that stimuli that normally elicit no blood pressure response in healthy people can cause severe hypertension in patients. To assess the effectiveness of pharmacological agents for the treatment of SCI-induced hyperreflexia we will use the fetal sheep with a spinal injury as an animal model of hyperreflexia. In this project fetal sheep aged approximately gestation 80 days (G80) will undergo sterile surgery during which a controlled SCI will be created. Catheters and electrodes will be implanted in the fetus for measurement of blood pressure, heart rate and muscle activity. This model will use distension of the rectum with a balloon catheter as a stimulus to activate spinal reflexes, since this is known to elicit episodic hypertension in animal models of SCI, just as faecal distension of the rectum has this effect in human patients. The effect of pharmacological antagonists of the major neurotransmitter systems of the spinal cord will be screened for their effect on hypertension induced by rectal stimulation.

## Ritchie Centre for Baby Health Research

**Development of serotonergic innervation of the spinal cord of the fetal sheep**

**Project Leaders:** Dr Elaine Stockx and Dr Philip Berger  
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**Project Description:**

The development of motor activity in the fetus is critically dependent upon the establishment of functional inputs from the brain. A key brainstem input that is known to have a major impact on spinal function in the mature animal derives from the neurons of the raphe complex, most of which have serotonin as their principal neurotransmitter.

As part of a larger study this project will adopt two approaches to assessing the physiological roles of the serotonergic innervation of the spinal cord. The first approach will determine, using immunohistochemical techniques, when serotonergic terminals are first found in the gray matter of the spinal cord, to quantify the density of the serotonergic innervation of the spinal cord with gestational age, and to examine the timing of appearance of postsynaptic serotonergic receptors in the spinal cord. The second will involve examining the effect on fetal behaviour of selectively destroying the serotonergic innervation of the spinal cord using pharmacological agents.

**Analysing inflammatory profiles in preterm newborns developing chronic lung disease**

**Project Leaders:** Dr Alex Veldman, Dr Andrew Ramsden and Dr Philip Berger  
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**Project Description:**

Chronic lung disease (CLD) is the most common disease of the preterm infant, with a prevalence that has changed little over the past 30 years despite enormous research efforts. This program will probe the molecular causes, and identify therapeutic strategies, for this major disease. Inflammation is increasingly recognised as the mainstay in the development of CLD. With observations on blood taken from preterm infants on the first day of life, and weekly thereafter until term equivalent age, we will for the first time systematically map the “biochemical fingerprint” of the causative inflammatory process during the postnatal period over which CLD develops. In a prospective, case control observational human study of preterm infants born between 24 and 28 weeks gestation, we will determine the expression profile and the dynamic changes across a comprehensive spectrum of 36 pro- and anti-inflammatory cytokines and proteins in 50 babies. Blood samples will be taken from the cord, in the first 24 hours of life, on days 7 and 14, and at 36 weeks corrected gestational age and analysed using a cytokine profiler to provide semi-quantitative information on the levels of all the candidate cytokines and inflammatory mediators. Total RNA will also be isolated to analyse proteins of the PC pathway not covered by the profiler.

## Ritchie Centre for Baby Health Research

### Testing the anti-inflammatory action of Protein C and IL1Ra in an animal model of chronic lung disease of the preterm infant.

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#### **Project Description:**

Severe chronic lung disease (CLD) of the preterm newborn causes considerable suffering for affected children and families and contributes substantially to health care costs in childhood, being second only to the costs for treating asthma and by far exceeding the cost of treating cystic fibrosis. Inflammation is increasingly being recognised as the mainstay in the development of CLD.

In this study, we will assess the therapeutic potential of PC and IL1Ra in a well-established animal model of neonatal CLD. Newborn mice pups of C57BL/6J mice will be exposed to room air or to a hyperoxic environment (FiO<sub>2</sub> 0.85). Hyperoxia results in an arrest of alveolarisation, increased pro-inflammatory signaling with subsequent apoptosis of pneumocytes and increased alveolar PAI1 and MMP9 concentrations, mimicking the clinical and biochemical profile of human CLD. We predict that animals receiving PC or IL1Ra will show less biochemical markers of lung inflammation, less histological evidence of CLD, improved alveolarisation and vascularisation, and improved respiratory and clinical performance compared to controls.

### Investigating the effects of prenatal stress in cardiovascular and respiratory responses to stress in the newborn

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#### **Project Description:**

Prenatal stress disrupts normal development and results in susceptibility to further complications later in life and to substantial health care costs throughout life. We hypothesise that increased inflammation and reactive oxygen species are implicated in the mechanistic outcomes of stress.

In this study, we will assess the developmental outcomes of prenatal stress in the newborn using a mouse model. Pregnant mice will be exposed to prenatal stress and the pups will be evaluated for their resting cardiovascular and respiratory function. Additionally, their cardiorespiratory responses to physiological challenges will also be evaluated. Small animal echocardiography will be used to assess the cardiovascular function. Respiratory chamber measurements will be used to assess the lung function. Pups will be subjected to stress by pharmacological agents for cardiovascular studies or hypercapnic challenges for respiratory measurements. Various immunohistochemical, biochemical and molecular biology techniques will be used.

We predict that animals born to mothers who were exposed to stress will have poor responses to challenges in the newborn period. Additionally we expect to see increased inflammation and oxidants in these pups. Defining these mechanisms will enable us to identify therapeutic targets and to develop novel therapies in the future.