Helping immature lungs

Professor Jane Pillow from the Centre of Neonatal Research and Education at the University of Western Australia discusses her ongoing research into the respiratory problems of premature babies, which she hopes will contribute to new and improved future treatments

Professor Jane Pillow with a premature baby, who was treated with high-frequency oscillatory ventilation for lung disease after birth.

Firstly, can you outline the main aims and objectives of your current research project?

The overall aim of the research is to improve understanding of the causes of breathing disorders in premature babies. We seek to develop and investigate new treatment strategies that eliminate or minimise the severity of long-term adverse consequences of premature birth on lifelong respiratory health.

What are the effects of premature birth on the lungs of an infant and can this damage be reversed or repaired?

The lungs of a premature infant are structurally and functionally immature at birth, posing an immediate threat to life and requiring active resuscitation. Whilst some infants develop a milder form of lung disease – hyaline membrane disease – that resolves over a period of days, others develop an insidious chronic lung disease called bronchopulmonary dysplasia.

Until recently, research efforts have focused on minimising the amount of damage to the preterm lung by finding ways to limit the injury and inflammation that occurs after delivery. For infants with very severely damaged lungs, the main option for improving their lung outcome was previously lung transplant. However, emerging treatments such as the development of stem cells are offering hope of both prevention of inflammation and repair of the damaged lung.

Why is clinical research in the extremely low gestational age infants (ELGANs) population particularly challenging?

These babies are extremely small – occasionally as little as 300 g (~11 ounces) at birth – and are consequently very fragile and often very sick. Understandably, their parents are sometimes uncertain about whether or not they should allow their baby to be in a clinical trial testing a new treatment – without a guarantee that it will be of benefit. The time around birth is also an extremely emotional and vulnerable period, and occasionally the mother is also quite unwell, which can make it difficult to approach the family for permission to enrol a baby in a study.

We also know that adverse events in the perinatal period can have lifelong effects; hence we need to be sure that new treatments are thoroughly researched before they are introduced in this population. Another important factor is the low number of ELGANs

born every year. They account for less than 0.5 per cent of total births, so they are a rare and precious resource. Nonetheless, it is very important that we find the best way to treat them and to prevent adverse outcomes following their birth, so that we can help them to enjoy the best possible quality of life as they progress through childhood and adult life.

Can you outline some of the advantages that the ovine model affords your research?

In an ideal research situation, the species chosen for an animal model of preterm birth would reflect the reproductive biology of humans, mimic what occurs clinically in most cases of spontaneous human preterm birth and have foetal maturation characteristics and postnatal physiological behaviours that are similar to those of humans. The preterm lamb has very similar physiology and anatomy to the newborn infant and is of similar size. This is especially true for the development of the respiratory system. These features mean that we can use neonatal equipment to study the lambs, and improves the translation of our pre-clinical research findings to the clinical setting in human infants.

Lastly, have you found ways in which respiratory support technologies can be refined to minimise injury to the lungs?

Much of our research aims at understanding what causes injury in the premature lung, providing evidence for less injurious respiratory support strategies. Examples of this are the optimising of positive end expiratory pressures (PEEP) to stop the lung from collapsing at the end of each breath, and also the importance of avoiding recurrent high breath volumes that cause over-distension of the terminal airspaces and cause injury and inflammation in the lung.

What we have shown recently, however, is that the occasional high breath volume – similar to a sigh – not only promotes recruitment of collapsed areas of the lung and maintenance of a normal lung volume, but also that it achieves this without any increase in lung injury or inflammation. Importantly, variable breathing patterns also appear to enhance the production and secretion of surfactant – a detergent-like substance secreted by cells in the airspaces of the lung that is vital to prevent our lungs from collapsing at the end of each breath.

PROFESSOR JANE PILLOW

Breathing easily

Research underway in Australia is creating a brighter future for vulnerable premature babies, by using preterm lambs to unlock the mysteries surrounding how premature birth impacts on respiration

ALTHOUGH PREMATURE BIRTHS constitute just 8 per cent of all deliveries in Australia, this small proportion of the newborn population is the most dependent on the healthcare system. Without having had sufficient time in the womb to develop to the same level of physical maturity as full-term babies, these infants are highly susceptible to infection and often suffer from severe breathing difficulties. The vulnerability of the premature infant means that it is imperative that all clinical treatments are highly effective. Researchers have found innovative ways to counter these difficulties and are making rapid progress in the treatment of preterm babies.

Less than 1 per cent of infants are born each year before reaching the 26th week of gestation, so there is incredibly limited access to tissues for investigation. As a result, many studies use preterm lambs as a way of learning more about the best way to treat premature infants; the preterm lamb model has proven to be highly successful owing to physiological similarities with the premature human infant. As lambs mature faster than human babies, studies using preterm lambs can produce rapid results and reveal the long-term benefits or harms of potential treatments and technologies. Most importantly, preliminary studies in premature lambs reduce the need for clinical trials on the fragile preterm infant population.

The work of Professor Jane Pillow and her team at the University of Western Australia has contributed a great deal to improving both the quality of healthcare available to premature babies at birth and their long-term health prospects. Pillow's group has made some fascinating discoveries about how and why respiratory systems are affected by premature birth, overcoming many hurdles in the quest to provide a more promising outlook for preterm infants. With funding for a variety of projects from the National Health and Medical Research Council (NHMRC), Pillow has been able to conduct this research in collaboration with scientists on a local, national and international level.

ADVANCING AND ENHANCING

Significant progress has already been made in this field over the last 20 years. For example, before the introduction of exogenous surfactant treatment it was rare for a child born before the 26th week of gestation to survive. The treatment, which compensates for the lack of surfactant in the lungs resulting from underdeveloped epithelial cells in airspaces, has contributed towards a significant drop in mortality rates and a lowered risk of severe illness. Alongside these medical developments, there has been a marked improvement in the efficiency and intelligence of ventilation and monitoring technologies. The ability to synchronise ventilation rhythms with the babies' own breathing efforts, and to limit the volume of air delivered, has reduced incidence of inflammation and injury caused by ventilators overstretching the lungs.

Pillow stresses the importance of these technological developments: "These major advances have significantly enhanced our capacity to care for the extremely low gestational age infant, resulting in improved survival, and reduced frequency and severity of some of the more serious complications of preterm birth".

FIRST BREATHS

Breathing is the most pressing challenge for premature infants at birth, and is the main focus of Pillow's research. Babies with underdeveloped lungs who have been removed from the support of placental circulation often need help from mechanical ventilators and other effective treatments to breathe efficiently. Investigations into existing ventilation equipment and methods as well as the structure and development of the lungs and the diaphragm are deepening understanding of these problems.

The team's findings to date have revealed that some methods of ventilation can actually harm the development of preterm lungs and have spurred on investigations into new technologies. Pillow explains how lung disease can develop: "Bronchopulmonary dysplasia

Preterm infant having a lung function test whilst cradled in the arms of its mother.

OVERCOMING OBSTACLES TO BREATHING AT THE EDGE OF VIABILITY

OBJECTIVES

To improve understanding of the causes of breathing disorders in premature babies and to develop and investigate new treatment strategies that eliminate or minimise the severity of long-term adverse consequences of premature birth on respiratory health.

KEY COLLABORATORS

International:

Professor Kurt Albertine, University of Utah, USA • **Professor Bela Suki**, University of Boston, USA • **Professor Zoltán Hantos**, Szeged University, Hungary • **Professor Alan Jobe**, University of Cincinnati, USA • **Dr Stefan Minocchieri**; **Professor Sven Schulzke**, University of Basel, Switzerland

National:

Dr David Tingay, Murdoch Childrens Research Institute, Melbourne • **Dr Tim Moss**; **Dr Graeme Polglase**, Monash Institut for Medical Research, Melbourne

Local:

Dr Gavin Pinniger; **Associate Professor Tony Bakker**; **Dr Peter Noble**; **Dr Yong Song**, School of Anatomy, Physiology and Human Biology, University of Western Australia (UWA) • **Professor Andrew Bassom**, School of Mathematics and Statistics, UWA • **Adjunct Professor Graham Hall**, Telethon Institute for Child Health Research • **Dr Andrew Wilson**, Department of Respiratory Medicine, Princess Margaret Hospital and School of Paediatrics and Child Health, UWA • **Clinical Associate Professor Andy Gill**, Neonatal Clinical Care Unit, King Edward Memorial Hospital and Centre for Neonatal Research and Education, UWA

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PROFESSOR JANE PILLOW is a clinical academic neonatologist at the King Edward Memorial Hospital and UWA, and Co-Director of the UWA Centre for Neonatal Research and Education. She is acknowledged internationally as an expert in the area of neonatal respiratory physiology and mechanical ventilation.

Miniaturised equipment and masks are needed to measure lung function in premature infants.

is a complex disease with many contributing factors, including: the duration and intensity of mechanical ventilation that may impose direct injury on the airways and the lung; development of inflammation and infection; exposure to high concentrations of oxygen in the airspaces and in the bloodstream; and impaired nutrition, to name but a few". Lung development normally primarily occurs in the last third of pregnancy and during early infancy. Consequently, maximising the growth potential of the premature infant's lung prior to discharge from hospital is paramount to the prevention of breathing difficulties in later life.

Breathing is the most pressing challenge for premature infants at birth, and is the main focus of Pillow's research

A strong diaphragm is essential for efficient respiration. Pillow's group has been looking into how this muscle is affected by premature birth and how it can best be treated. Initial results suggest that steroids administered to mothers at risk of premature delivery aimed at improving lung function after premature birth may be damaging to the diaphragm. Furthermore, exposure of the developing foetus to an inflammatory process whilst they are in the womb (such as might be caused by a womb infection) can cause a condition known as foetal inflammatory response syndrome (FIRS). Pillow and her fellow researchers have shown that this can inhibit development of the diaphragm, reducing the ability of the premature baby to breathe efficiently after birth. Accummulating a thorough understanding of all the factors involved in diaphragm weakness after premature birth will allow researchers to focus on the development of different treatments that reduce inflammation and facilitate the growth of a strong diaphragm. Using this approach, Pillow's group hopes to find new ways to help the premature baby to breath more easily.

A second project funded by the NHMRC is an investigation into how current use of the high-frequency oscillatory ventilator (HFOV) impacts on lung development in preterm babies. Results so far show that traditional use of HFOV to provide small volumes of air at a fast rate prevents stretching of the lungs. On the other hand, Pillow's recent studies reveal that it also has a negative impact on large airways, increasing the likelihood of collapse when mechanical ventilation is removed. Through experimentation with varying frequencies of ventilation, her team is hoping to find an optimal pattern which would allow efficient gas exchange and reduce damage to large airways and lung tissue. Their most recent findings suggest that variable ventilation patterns, which mimic humans' naturally varied breathing patterns, offer the most promising results.

FORWARD THINKING

Some of the studies have now progressed to the translational level, and a group of infants – some with and some without chronic lung disease – is being investigated in collaboration with the Respiratory Medicine Department at Princess Margaret Hospital. By monitoring the change in lung, heart and diaphragm function over time, the collaborators will obtain a broader picture of the mechanics and processes of breathing difficulties following preterm birth. Randomised controlled clinical trials are also now underway to test the effectiveness of new respiratory treatments such as administering exogenous surfactant via nebulisation.

Pillow and her collaborators are ensuring that the challenges faced by preterm infants are thoroughly understood and addressed in the most efficient way. Their work thus far has been invaluable to the development of new and improved technologies and treatments. Future plans will extend their pre-clinical investigations over longer durations to increase potential for translation of their experiments to the clinical setting. This unique collaborative resource will ensure that Pillow and her team remain at the cutting edge of their field. The extended-duration studies will provide opportunities for in-depth evaluation of new ventilation techniques and their effects on developing lungs, as well as hands-on education and training for the next generation of neonatal researchers. The long-term health prospects of premature infants have never looked brighter.