Center for Lung Biology Pulmonary NewsLetter

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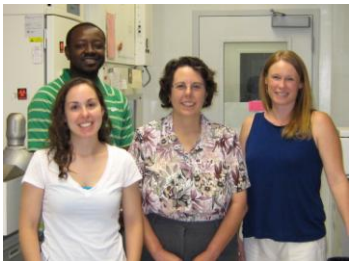
What's New in Pulmonary Science?



Cioffi Lab: Pierre Kadeba (back), Rebekah Morrow, Drs. Donna Cioffi and Audrey Vasausakas

Steroids have been a mainstay anti-inflammatory therapy for many years. Both high- and low-dose steroid therapy have been tested in patients with acute respiratory distress syndrome, yet no consistent improvement in outcomes has been reported. Clinical trials are complicated by the multifactorial causes of ARDS, and by the complex pathophysiology of ARDS as patients first deal with acute, intense inflammation followed by the fibrotic phase of tissue repair. Ongoing work in the Cioffi lab addresses whether steroids may produce an anti-inflammatory benefit in the acute phase of inflammation, by improving pulmonary endothelial cell barrier integrity. Thapsigargin is a plant alkaloid that activates calcium entry through store operated calcium entry channels, a principal class of channels in non-excitable cells such as endothelium. Thapsigargin increases lung permeability due to activation of store operated calcium entry. Cioffi and colleagues now demonstrate that this increase in permeability is inhibited by dexamethasone. Transient receptor potential proteins of the canonical subfamily, TRPC1 and TRPC4, contribute subunits to form a store operated calcium entry channel that is activated by thapsigargin. TRPC4 interacts with large molecular weight immunophilins, FKBP51 and FKBP52. These immunophilins are peptidyl-prolyl isomerases whose interactions with TRPC4 play a role in regulation of channel function. Whereas FKBP52 binding to TRPC4 promotes its activation, FKBP51 binding to TRPC4 inhibits its activation. Emerging data from the Cioffi lab reveals that upregulation of FKBP51 by steroids inhibits calcium permeation through the channel. These exciting new findings not only provide insight into the molecular anatomy of endothelial cell store operated calcium entry channels, they reveal a previously unappreciated mechanism of steroid action. Based upon these new results from Cioffi and her lab, steroids may provide a therapeutic benefit by reducing endothelial cell permeability amidst the acute phase of lung inflammation. Look for forthcoming articles from the Cioffi lab on pubmed.

What's New in Research Training?

The **Running and Walking Club** provides a coordinated mechanism for CLB members to share in their active lifestyles. We run and walk at area-sponsored 5K, 10K, half marathon and marathon events. The list of these events for the 2011-2012 season is shown at **http://www.usahealthsystem.com/RunningandWalkingClub**. Workout schedules are provided online in the Training Schedule section. The workout schedule is adaptable for any individual's goals. In addition, we provide a summary of recent scientific articles that highlight important health issues in our Science for Health section (see below). The schematic shown on the left illustrates our commitment to a life balanced by mind and body. The Latin words *Alio Valetudo* shown in the banner mean personify health; be healthy and enjoy all life has to offer.

Science for Health

Run Forest Run...like your life depends on it. Considerable attention has been paid to the value of daily exercise, including a reduction in susceptibility to cardiovascular disease. In fact, the hemodynamic response to exercise is a predictable determinant of cardiovascular health, and for these reasons, has become increasingly important in documenting health status. Cardiovascular risk is associated with an exaggerated blood pressure response to exercise, and exercise capacity provides an objective assessment tool for cardiovascular reserve. For example, the six-minute walk test is a standard assessment tool for the integrated indices of cardiopulmonary hemodynamic status in pulmonary hypertension patients.

While it is increasingly well known that daily aerobic exercise improves cardiovascular health, the link to longevity has not been systematically tested. This issue was recently addressed by a multi-center group of investigators led by Dr. Koch at the University of Michigan[1]. These researchers took advantage of rats selectively bred into groups with high and low aerobic capacities, capacities that were tested using treadmill running capacity. Cohorts of the rats bred from generations 14, 15, and 17 were tracked for survivability, in relation to cardiovascular fitness, including measurements of maximal oxygen uptake. The mean lifespan of low aerobic capacity rats was as much as 45% shorter than the lifespan of high aerobic capacity rats; 50% survival of low aerobic capacity animals was 24 months, and of high aerobic capacity animals was 36 months. Declines in systolic and diastolic cardiac function were documented as rats aged, and were especially prominent in low aerobic capacity animals. These collective findings reveal that chronic aerobic exercise, and improvements in aerobic capacity, provides a longevity survival advantage. Perhaps we have the fountain of youth at our fingertips after all.

Reference

1. Koch, L.G., et al. Intrinsic aerobic capacity sets a divide for aging and longevity. Circ. Res. 109: 1162-1172, 2011.

What's New in Pulmonary & Critical Care?

In the past several months we have graduated 2 fellows, welcomed 2 new fellows, and continued to expand our research and clinical work. Our graduating fellows will be great ambassadors of our USA training program. Dr. Phil Almalouf will be joining a busy practice in Ocean Springs, MS and Dr. Meshann Fitzgerald will be an Assistant Professor of Medicine at the University of Texas Houston in the Division of Pulmonary and Critical Care Medicine. We continue our efforts to provide the highest quality clinical and research training to our fellows through ongling assessment and restructuring of the program.

Our Pulmonary Clinics continue to be busy and we have recently expanded our clinical services to include endobronchial ultrasound with Dr. Kane Schaphorst. We are the first to have this expertise in our region and will be able to improve diagnostic capabilities in patients with a variety of lung lesions.

Clinical research continues to grow in the Division with investigator and industry developed and sponsored activities. We hope to expand further through submission of translational research proposals to the NIH as well as out ongoing research in the Pulmonary Hypertension Center and the Center for Lung Biology.

Overall, the Division continues to provide outstanding pulmonary and critical care to patients in the northern Gulf Coast with active, productive research and educational programs for the region. We hope to be the major resource for expert clinical care and research in Pulmonary and Critical Care Medicine in the area.

Did You Know…

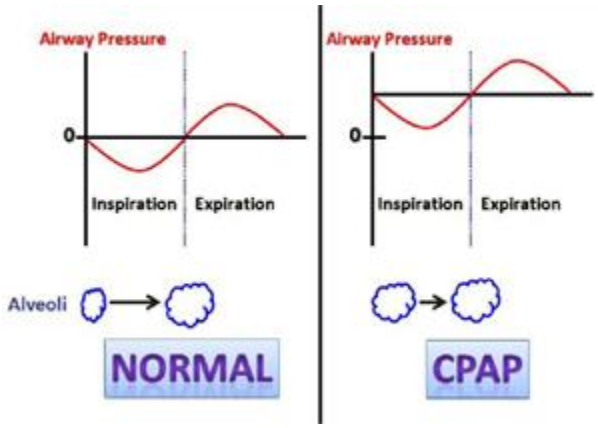


Figure 1. When the alveoli decrease in size during expiration, pressure within the airways increases. Surfactant, which prevents alveolar collapse, is deficient in the preterm lung. Continuous positive airway pressure (CPAP) increases basal airway pressure, holding the alveoli open during expiration and preventing alveolar collapse.

Did you know that improved ventilatory methods have markedly increased survival of preterm infants? Supplemental oxygen delivered by mechanical ventilation is often required for premature infants because the preterm lung exhibits thick saccular walls that limit diffusion of oxygen and carbon dioxide. Current methods for maintaining adequate respiration in infants stem from early methods of resuscitation. In the mid-1700s, the Royal Humane Society recommended mouth-to-mouth resuscitation for infants following the demonstration of this technique by William Smellie.1, 5 However, the obstetrician William Hunter considered this to be a method used by the vulgar, resulting in the recommendation of bellows.5 In 1827, d'Etiolles showed that air blown into the lung through a canula caused pneumothoraces, leading to the abandonment of positive pressure ventilation for a number of years.2, 5 Thirty years later, Wollitz presented data to the Academie de Medicine suggesting that air should be at atmospheric pressure when it enters the lung in order to avoid pneumothoraces.2 He then demonstrated the damaging effects of high pressure on both isolated lungs and animals using early positive pressure ventilators. These developments led to the use of more gentle positive pressure devices that were modified by Braun for use in newborns in 1889.5, 9, 10

In addition to changes in techniques used for resuscitation and ventilation, the supportive treatment of preterm infants was also evolving. In 1914, Julius Hess created a heating bed to keep infants warm, and this bed was used in the first Neonatal Intensive Care Unit (NICU).8 The heating bed was later modified by Hess to allow for the introduction of oxygen, but Haldane cautioned physicians to "make every effort to avert the effects of want of oxygen," recognizing the benefits of keeping inspired O2 as low as possible while supplying sufficient O2 for gas exchange.8 In 1928, Drinker and Shaw successfully ventilated an adult patient using alternating positive and negative pressures, but this method was ineffective in maintaining optimal blood gases in infants. 2, 3, 4, 6, 10 As more gentle methods of ventilation were introduced, infant survival improved. However, with increased survival came altered pathological features in the preterm lung.

While improved short-term survival of infants with respiratory distress came with the changes in treatment strategies, many neonates who survived for the first few days after birth later died of respiratory complications. A glass-like opacity seen in the histological analysis of lungs of preterm infants was termed "hyaline membranes" by Miller and Hamilton, and they proposed that this was a result of injury to the lung.7 Clinical evidence showed damage related to the use of all forms of mechanical ventilation, but this support was required for infant survival. One complication in the preterm infant was alveolar collapse during expiration due to the lack of adequate surfactant production. This problem of alveolar collapse was addressed in 1971, when a clinical trial demonstrated an increase in arterial oxygen tension when infants with respiratory distress were ventilated with continuous positive airway pressure (Figure 1).12 The success of these ventilation techniques in combination with other supportive therapies led to survival of infants who were born at even earlier gestational ages.11 Today, infants who have respiratory distress at birth and require mechanical ventilation have decreased lung injury and increased survival due to advances made in ventilatory methods.

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