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## The Unfortunate Tale of Immature Respiratory Control Superimposed on an Immature Lung

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### Personal Perspective

As the humble recipient of the 2018 APS SPR Mary Ellen Avery Neonatal Research Award, I have cause to reflect on life's opportunities, the giant leaps that have occurred in our understanding of neonatal pathophysiology, and the innumerable questions that remain unresolved. My own first exposure to Neonatology comprised relatively futile attempts as an intern to salvage preterm infants in 1970 in the adult intensive care unit of the Royal North Shore Hospital in Sydney, Australia. A real awakening then occurred during residency in the USA and the inspiration of Elizabeth James who had just returned to Columbia, Missouri as one of the early graduates of the University of Colorado Neonatology Program. Meanwhile, Marshall Klaus, one of the true pioneers of the field, was invited to the University of Missouri [Columbia] as a Visiting Professor. I was hooked and immediately researched the whereabouts of Cleveland, Ohio where I have remained to this day! Marshall, who passed away in 2017, had the grand ideas [not always quite right, but always inspiring], Avroy Fanaroff was [and remains] the master clinician and my academic role model, and the late Maureen Hack, with her frankness, was always there to keep me straight.

As a fellow with no research experience whatsoever, I was assigned to explore the mechanisms whereby CPAP decreased the incidence of apnea. This plunged me into a world of developmental respiratory neurobiology which, in those days, was largely physiology based. It took several years and numerous remarkable trainees and colleagues, such as Waldemar Carlo, Martha Miller, and Estelle Gauda for us to establish that there is an upper airway obstructive component to apnea of prematurity which is relieved by continuous positive airway pressure [CPAP]. A concurrent fortuitous breakthrough in Neonatology during the 1970s was the ability to measure blood gas status non-invasively and resultant realization of the remarkable fluctuations in oxygenation that preterm infants exhibit. My ability to contribute to this field was greatly enhanced by a partnership with the late Albert Okken from the Netherlands. Meanwhile, euphoria that the respiratory problems of preterm infants had been resolved by surfactant therapy and novel modes of assisted ventilation was tempered by the realization that persistent respiratory morbidity, as reflected in

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bronchopulmonary dysplasia [BPD], was becoming a real problem. With these new insights there was all the more reason to continue a focus on maturation of respiratory control and apnea of prematurity [Fig 1].

## Does Intermittent Hypoxia Matter?

The multiple episodes of intermittent hypoxia exhibited by preterm infants are consequences of immature respiratory control and ineffective ventilation, superimposed upon immature lungs with a likely contribution from pulmonary hypertension. Most importantly, intermittent hypoxia serves as a potentially powerful link between the developing respiratory system and immature brain. We now recognize the role of intermittent hypoxia in contributing to retinopathy of prematurity [ROP] and its association with adverse outcomes, including mortality and/or impaired neurodevelopment [Fig. 2] [1]. While mechanisms remain largely unexplored, there is an increasing body of data that the intermittent hypoxic, rather than bradycardic, episodes accompanying apnea are the contributors to later morbidity. This has obvious implications as we design optimal strategies for the prolonged monitoring that so often delays discharge of preterm infants. Oxidant stress is a prime candidate for pathophysiology, but it is difficult to separate the fall from the subsequent rise in oxygen saturation in eliciting oxidant injury. Obviously, iatrogenic overshoot during recovery from hypoxia and resultant hyperoxia would aggravate the problem.

There is a wealth of animal, and even human, data in sleep apnea patients relating oxidant stress to adverse proinflammatory pathways. In neonatal rodent models exposed to intermittent hypoxia there are long lasting effects on respiratory control via oxidant mediated mechanisms. Furthermore, pre or postnatal inflammation in neonatal rodents has an adverse effect on respiratory control via both neural and systemic pathways, linking inflammation in the immature lung with the brain [2]. The result is a potential vicious cycle of pre or postnatal inflammation in the lung, impaired respiratory control, and resultant intermittent hypoxia in turn aggravating proinflammatory pathways [Fig. 3]. It, therefore, should not be surprising that BPD and adverse neural development are clearly linked [3].

## What about the Immature Airway?

With encouragement of the late Musa Haxhiu and supported by the NIH, I sought to complement my expertise in ventilatory control with greater understanding of airway smooth muscle regulation. I soon realized that the neural and molecular mechanisms that regulate airway caliber in health and disease represent a very different challenge to studying ventilatory control mechanisms. Despite the very high incidence of wheezing disorders in former preterm infants, including those without BPD, this is a relatively unstudied area. Two issues need emphasis: the first is that despite the widespread switch from invasive to non-invasive ventilatory techniques, the incidence of later respiratory morbidity is almost undiminished. The second challenge is that assessment of later respiratory function in ELBW survivors of neonatal care is largely limited to airway function which may reflect injury to the airway, the developing lung, or both. In neonatal rodent models exposed to low levels of supplemental oxygen, we have documented a delayed, rather than immediate, increase in airway reactivity associated with airway smooth muscle hypertrophy [4]. This is

somewhat analogous to the wheezing in former preterm infants that is not apparent in early postnatal life. Consistent with the role of oxidant stress, we have documented that intermittent hypoxia induces airway hyperreactivity in neonatal rodents only when followed by a so called hyperoxic overshoot [5]. Most recently, my colleague Peter MacFarlane has established a neonatal mouse CPAP model which also seems to induce airway hyperreactivity possibly mediated by effects on the airway extracellular matrix, as has been proposed in mature lung injury models.

## What does the Future Hold?

I have been privileged to give presentations both nationally and internationally, and inevitably I raise more questions than answers. For that I do not apologize. The opportunities for the next generation of investigators are enormous. In my own area of interest there is a need to gain greater insight into the consequences of intermittent hypoxia on neurorespiratory morbidity and underlying mechanisms. As part of the NHLBI sponsored Pre Vent Consortium, and with my long standing colleague Juliann Di Fiore as well as Anna Maria Hibbs, and in collaboration with Máximo Vento [Valencia, Spain], we hope to define specific patterns of intermittent hypoxia in relation to oxidant markers and later morbidity. In collaboration with YS Prakash [Mayo Clinic] we are exploring signaling pathways that predispose the immature airway to a contractile phenotype.

As should be apparent from this commentary, it takes a team to address these pressing issues. I am unbelievably grateful for this prestigious award and to the multitude of collaborators, past and present, named and unnamed, who have given me this opportunity to succeed as a physician/scientist. I also need to acknowledge the late Mary Ellen Avery whom we all associate with surfactant, but who, together with her accomplished colleagues and trainees, recognized the need to investigate neonatal respiratory control mechanisms. This award would not exist without the efforts of Roberta Ballard who also provided me with many academic opportunities. I am blessed with wonderful Neonatology faculty colleagues, led by Michele Walsh, who are so supportive of discovery and innovation, yet always place the well-being of their patients at the forefront. Finally, my receipt of this award would never have happened without the untiring support of Patricia, my life partner over the last 48 years.

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## Biography



Dr. Richard J. Martin

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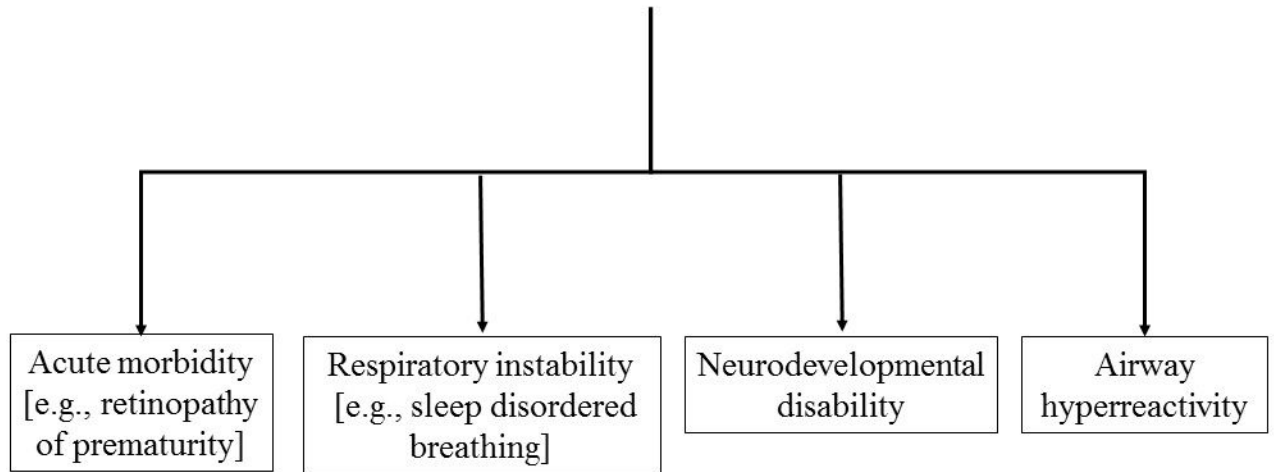
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## Why Apnea of Prematurity Matters!

- Serves as a biologic link between the lung and brain
- May contribute to need for increased respiratory support and resultant pulmonary morbidity
- May contribute to neurodevelopmental morbidity via intermittent hypoxic episodes
- Prolongs hospitalization and cost

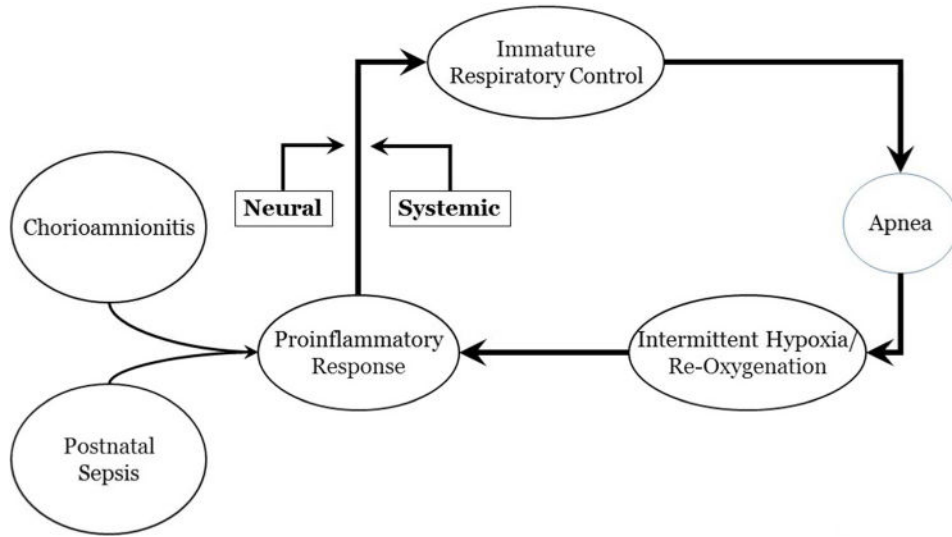
**Figure 1.**  
Why Apnea of Prematurity Matters

## ***Proposed Morbidities of Intermittent Hypoxia/Re-oxygenation***



**Figure 2.**  
Proposed Morbidities of Intermittent Hypoxia/Re oxygenation

### ***Proposed Central Role for Respiratory Control in Mediating Inflammatory Responses***



**Figure 3.**  
Proposed Central Role for Respiratory Control in Mediating Inflammatory Responses

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