



2010 Abstracts



Jason Gien, MD

University of Colorado Health
Sciences Center
Aurora, Colorado

*ET-1-Rho-kinase Interactions in the
Pathogenesis of Neonatal Pulmonary
Hypertension*

Treatment with inhaled NO (iNO) is often effective in improving outcomes of many newborns with PPHN; however, some infants fail to respond to iNO, and require ECMO therapy. PPHN associated with poor responsiveness to iNO is often seen in the setting of hypertensive vascular remodeling and impaired vascular growth, e.g., in patients with congenital diaphragmatic hernia. In this setting, there is a critical need for therapies that can prevent vascular remodeling and stimulate angiogenesis. Partial ligation of the ductus arteriosus (DA) in utero in late gestation fetal sheep provides a useful animal model for studying the pathogenesis and treatment of PPHN. This animal model is characterized by iNO unresponsiveness, vascular remodeling and impaired angiogenesis, closely mimicking clinical PPHN and, to date, we have demonstrated altered endothelial cell (PAEC) and smooth muscle cell (PASMC) phenotypes that persist in vitro. The uniqueness of this experimental model, as well as the presence of in vitro PAEC and PASMC phenotypes, makes it innovative and crucial for studying mechanisms responsible for hypertensive vascular remodeling and impaired angiogenesis in PPHN. ET-1 and rho-kinase (ROCK) are present in the fetal lung, and contribute to high PVR, which is necessary for diversion of blood



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from the lungs during fetal life. ET-1 and ROCK are important mediators of vascular remodeling and increased tone in adult models of experimental pulmonary hypertension; however, their role in neonatal PPHN is less well defined. We recently reported a role for ROCK2 in regulating angiogenesis in the developing lung and the finding that high ROCK activity contributes to impaired angiogenesis in PPHN. While the effect of ET-1 on angiogenesis in the developing lung remains unknown, ET-1 is an important regulator of ROCK activity and many of the effects of ROCK parallel those of ET-1. Gaining a better understanding of the mechanisms of ROCK and ET-1 interactions that produce vascular remodeling and impaired angiogenesis in severe neonatal PPHN will lay the foundation for the development of novel therapies that will improve outcomes in this setting.