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Intrauterine Hemodynamic Stress Mechanisms of Fetal Pulmonary Vascular Injury

Biomechanical forces are essential for normal fetal pulmonary vascular growth and development, but increased hemodynamic stress in utero contributes to the pathogenesis of neonatal pulmonary hypertension (PPHN). Impaired endothelial function results from high pulmonary vascular resistance in PPHN, but mechanisms through which hemodynamic stress causes the PPHN remain uncertain. At birth, rapid physiologic adaptation is required for the lung to assume its essential postnatal role of gas exchange. The normal transition of the pulmonary circulation includes hemodynamic changes of immediate and progressive fall in pulmonary vascular resistance (PVR) allowing an eight-fold increase in pulmonary blood flow. Increased oxygen tension, ventilation, and shear stress are factors that contribute to the fall in PVR at birth, largely through the release of endothelium-derived vasodilators, including nitric oxide (NO) and prostacyclin, and decreased production of vasoconstrictors, such as endothelin-1 (ET-1). Failure to develop or sustain this drop in PVR at birth leads to hypoxemia and constitutes clinical syndrome of PPHN. Successful transition of the pulmonary circulation from prenatal to postnatal life requires precise and highly responsive vascular adaptation to changes in hemodynamics as well as diverse growth factors and signaling. Previous models of PPHN from our laboratory have shown that chronic hemodynamic stress alters endothelial cell phenotype as characterized by abnormal vascular tone, growth, and structure, with decreased NO production and up-regulation of ET-1. In addition, fetal pulmonary artery endothelial cells (PAEC) from PPHN sheep have persistent abnormalities of growth, angiogenesis and production of vasoactive mediators. However, biomechanical mechanisms that disrupt normal vascular development and contribute to the pathogenesis of PPHN are incompletely understood.

- 1) Normal fetal PAECs will exhibit a phenotype similar to PPHN PAECs in vitro—increased vasoconstriction ET-1 but reduced vasodilator NO—in pathologic shear stress environment.
- 2) Hypoxia will augment the adverse effect of hemodynamic stress to increase production of increased vasoconstrictors but decreased vasodilators.
- 3) ET-1 blockade through SiRNA or Bosentan will preserve fetal PAEC phenotype in hemodynamic stress and hypoxia.