



Embracing the Potential of
**YOUNG
INVESTIGATORS**

REBECCA KAMENY, MD

University of California, San Francisco
San Francisco, CA

Translating the natural history of pulmonary vascular disease secondary to congenital heart disease into basic mechanisms and therapeutic targets

INTRODUCTION:

The development of pulmonary vascular disease (PVD) is the most important complication for children with congenital heart defects (CHD) that result in increased pulmonary blood flow and pressure. Although the natural history of the development of PVD is well characterized for differing lesions, the mechanisms for these differences are not understood.

BACKGROUND:

Beginning immediately after birth, the pulmonary vasculature in patients with common CHD, such as large ventricular septal defects, is subjected to pathologic mechanical forces, including increased shear stress and stretch, resulting in early functional abnormalities of the vascular endothelium. These aberrations include impaired nitric oxide (NO) signaling, increased endothelin1 (ET1) expression, and increased oxidative stress. Natural history studies clearly demonstrate that different lesions have differing risks and time frames for the development of PVD. For example, truncus arteriosus, a lesion that results in direct exposure of the pulmonary vasculature to both high blood flow and pressure, has a 100% incidence of developing PVD occurring within the first two years of life. However, pre-tricuspid valve lesions, such as atrial septal defects, expose the pulmonary vasculature to only high flow (without the direct pressure stimulus) and have only ~10-20% incidence of developing PVD, which does not occur until the third-fourth decades of life. Utilizing fetal cardiac surgical techniques, we have previously created an ovine model of CHD that induces postnatal increases in pulmonary blood flow and pressure (aortopulmonary window) which recapitulates human disease including early aberrations in endothelial function. More recently, we have created a model of increased pulmonary blood flow to the right lung with normal pressure (left pulmonary artery ligation). RNA sequencing data comparisons of pulmonary endothelial cells from juvenile lambs with normal flow and pressure, increased flow and pressure, and increased flow and normal pressure, demonstrate novel differences in gene expression related to these differing mechanical forces.

HYPOTHESIS AND OBJECTIVES:

The objective of these studies is to characterize the differential gene expression related to differing mechanical forces and investigate their mechanisms. We hypothesize that increased flow and pressure induce differential changes in gene expression that contribute to the differing risk of developing PVD in CHD.

SPECIFIC AIM 1:

To characterize and compare differential gene expression patterns (RNAseq) in endothelial cells and tissue isolated from juvenile lambs with either: normal flow and pressure, increased flow and pressure, or increased flow and normal pressure.

SPECIFIC AIM 2:

Utilizing an Ibido system, that allows endothelial cells and tissue rings to be exposed to shear stress and/or cyclic stretch, we will investigate the mechanisms for the changes in gene expression demonstrated in Aim 1.