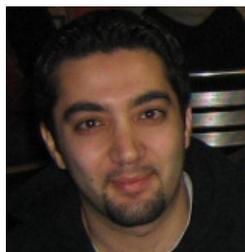




2011 Abstracts



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Vascular Reactivity in Response to Acute Hypoxia: Defining Features and Mechanisms

Exposure to chronic hypoxia is a frequently used model for pulmonary arterial hypertension (PAH). However, it is clear that states of chronic hypoxia such as chronic obstructive pulmonary disease and obstructive sleep apnea, as well as high altitude exposure, do not uniformly lead to the development of PAH. This disparity may be due, in part, to genetic predisposition, yet it remains incompletely defined. The impact of acute hypoxia is even less well defined but may have significant clinical relevance. Increasing evidence suggests that acute and chronic hypoxemia responses may be related. Aldashev (2002) showed that the hyper-responsiveness, defined as 50% increase in pulmonary artery pressure to acute hypoxia at sea level, is predictive of the development of PAH in native highlanders (~3000m above sea level). We propose to systematically study the relationship between the dose-response to acute hypoxia and the development of PAH using a defined rat hemodynamic model created in our laboratory. We hypothesize that the acute hemodynamic response to brief hypoxia can be used as an indicator of the predisposition to develop chronic pulmonary hypertension and as an assay for testing the genetic predilection, mechanisms and new therapies. The aims of this application are: 1) to establish a new assay metric [dose-response] quantifying the acute effects of brief hypoxia (30 seconds) on the vasculature using in vivo recordings of hemodynamic variables; and 2) to define the relationship between acute and chronic hypoxemia in the development of PAH using genetically divergent strains of rats. We will define these differences in dose-response curves with drug intervention [L-NAME: L-Nitro-Arginine



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Methyl Ester) and investigate potential mechanisms through which nitric oxide mediates this acute response. Thorough investigation of the vascular response of both the systemic and pulmonary circulation, as proposed by these studies, will lead to a better understanding of the mechanisms and genetics of hypoxia induced pulmonary hypertension. This work will form the foundation of a potential screening model for drug development in the area of PAH,