ALTERED PULMONARY ARTERIAL SMOOTH MUSCLE WITH CHRONIC HYPOXIA-INDUCED PULMONARY HYPERTENSION

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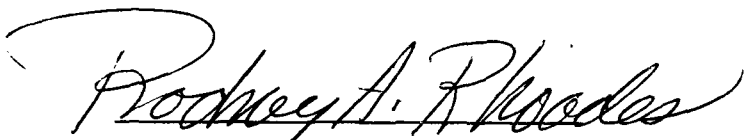

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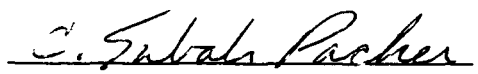

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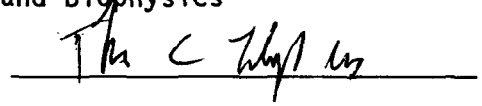

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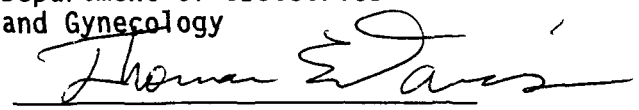

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ABSTRACT

Pulmonary hypertension is a primary event leading to the development of right ventricular failure and respiratory failure. The principal stimulus which evokes pulmonary hypertension is chronic alveolar hypoxia. This results in remodeling of the vessel walls, including an increase in wall thickness by hypertrophy and hyperplasia of the pulmonary arterial smooth muscle (PASM) and an increase in the deposition of connective tissue. At present there is insufficient knowledge regarding the role that the vascular smooth muscle plays in pulmonary hypertension. The hypothesis of the proposed study is that hypoxia alters the biochemical, structural, and contractile properties of PASM. Such alterations may be the underlying mechanisms for the development and/or the maintenance of chronic pulmonary hypertension. Experiments were designed to determine whether or not hypoxia-induced pulmonary hypertension alters: 1) the maximum isometric tension, 2) optimum resting tension, 3) sensitivity and/or reactivity to agonists, 4) structural properties of the pulmonary arterial smooth muscle, and 5) relative amounts of contractile proteins in the pulmonary arterial smooth muscle. To induce pulmonary hypertension, young adult male rats were made hypoxic by experimentally lowering the percent inspired oxygen. Pulmonary arterial segments were isolated from the rat lungs and then assessed for changes in reactivity to agonists by measuring isometric tension development in response to various agonists and

comparing the dose-response curves of the control and hypertensive groups. Gel electrophoresis was used to assess changes in contractile protein isoforms. Histology was used to correlate the structural changes with changes observed in the pharmacology and biochemistry studies. This study provides evidence of decreased isometric tension development relative to the amount of muscle in pulmonary arteries from rats with pulmonary hypertension. This along with the generalized decrease in reactivity to agonists and a trend toward an increase in the non-muscle myosin isoforms, suggests that the mechanism by which hypoxia induced pulmonary hypertension is maintained is likely due to a shift in muscle phenotype to a synthetic, less-contractile phenotype.

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