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Pulmonary vascular remodeling in transgenic Ren 2 rats

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Angiotensin II is a vasoconstrictor that causes endothelial dysfunction, vascular remodeling, and hypertension. Statins improve vascular endothelial cell function and inhibit vascular endothelial and smooth muscle cell proliferation. In this study, we examined the pulmonary vasculature of Ren-2 transgenic rats (TGR(mREN-2)²⁷) that exhibit tissue level overexpression of the mouse renin gene, a precursor to Angiotensin II. We hypothesized that Ren-2 rats exhibit pulmonary hypertension (PH) similar to humans, i.e. increases in pulmonary vascular resistance, vascular remodeling, and right ventricular hypertrophy. We also hypothesized that the severity of PH in Ren-2 rats may be reduced by the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, rosuvastatin. Male Sprague-Dawley rats and Ren-2 rats were randomly assigned to one of four treatment groups: Sprague-Dawley untreated (n=13), Ren-2 untreated (n=10), Sprague-Dawley Statin treated (n=6), Ren-2 Statin treated (n=9). Rosuvastatin was administered daily by IP injection in 10mg/kg and 20mg/kg doses (no difference was found between dose groups). Three weeks after treatment began lung tissues were harvested for analysis. Morphometric analysis showed significant vascular remodeling of the pulmonary arterioles in the Ren-2 untreated groups; a decrease in area of the lumen and an increase in area of the media. Right ventricular hypertrophy, a symptom of PH, was not found. eNOS (endothelial nitric oxide synthase) levels were elevated in untreated Ren-2 rats compared to Sprague-Dawley untreated; NO levels in the lung were similar between the two groups indicating a possible compensatory mechanism. These data suggest that young Ren-2 rats are at risk for developing pulmonary hypertension. Further studies are needed in older Ren-2 rats in order to determine the stage and severity at which pulmonary hypertension develops. Finally, statin treatment prevents or reverses vascular remodeling in Ren-2 rats and could reduce risk of developing PH.