Coronary Arteries from Mice with Cardiac-Selective Deletion of the Insulin Receptor (CIRKO) are Resistant of Dysfunction Evoked by Pressure-Overload

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Left-ventricular hypertrophy is a clinically relevant problem. To model this condition in mice, a restriction (i.e. a "band") was placed around the aorta (i.e., aortic banding). When the diameter of the aorta is reduced, the left ventricle has to develop greater pressure to open the aortic valve. After several weeks of exposure to this "pressure overload", the left ventricular wall thickness decreased, "hypertrophied" as an adaptive response to normalize wall tension. We are studying the response to pressure-overload in mice with cardiac-selective deletion of the insulin receptor (CIRKO). CIRKO mice are used to model impaired insulin receptor-mediated signal transduction that occurs in individuals with diabetes. This is a clinically relevant topic because patients with diabetes are at greater risk for developing cardiovascular disease.

In a previous study we showed that CIRKO hearts do not respond appropriately to pressure overload hypertrophy. For example, hearts from CIRKO mice exhibit dysfunction that is characterized by left-ventricular dilatation and reduced fractional shortening compared to hearts with intact insulin receptor mediated signal transduction (i.e., wild-type mice: WT). Further, we observed evidence in the subendocardium (i.e., the innermost layer of the myocardial wall) of greater fibrosis or cell death in CIRKO vs WT mice. My project was designed to determine whether subendocardial fibrosis in CIRKO mice is caused by poor blood flow to this area resulting from coronary vascular dysfunction. Specifically, we tested the hypothesis that coronary vascular dysfunction is greater in CIRKO vs WT mice in response to aortic banding. Fourteen days after placing the aortic band, heart weight/body weight (mg/g) was similar between WT (8.03 ± 1.14) and CIRKO (7.70 ± 1.25) mice, indicating that a similar degree of hypertension existed between groups. Endothelial and vascular smooth muscle function were assessed using wire-myo-graphy. Our main endpoint is vasorelaxation via mechanisms that depend upon a functional endothelium.

To assess this, we administered various pharmacologic probes to the isolated vessel and monitored the decrease in vascular tension. Acetylcholine (ACh) causes endothelium-dependent vasorelaxation. Sodium nitroprusside (SNP) causes endothelium-independent vasorelaxation. Dose-response curves to ACh (10-8 M - 10-5 M) and SNP (10-6 M to 10-4 M) were performed on vessels that were precontracted using the thromboxane receptor antagonist U-46619. Each dose-response curve was separated by 30-min. We observed that maximal ACh-evoked vasorelaxation was -15 ± 5% and 30 ± 8% in vessels WT-AB and CIRKO-AB mice, respectively. These data indicate that ACh-evoked vasorelaxation was abolished in WT-AB mice, but remained intact in CIRKO-AB mice. We observed that maximal SNP-evoked relaxation was 62 ± 12% and 72 ± 20% in vessels WT-AB and CIRKO-AB mice, respectively. These data indicate that SNP-evoked vasorelaxation is similar between groups, which shows that WT-AB had intact vascular smooth muscle function. Taken together, these results lead to the conclusion that coronary vessels from CIRKO-AB mice are more resistant to vasodilation after two weeks of pressure overload compared to WT-AB. These results did not support our hypothesis. However, these findings do suggest that CIRKO-AB mice may upregulate another endothelium-dependent vasodilator mechanism (e.g. endothelium derived hyperpolarizing factor), which may warrant further investigation.