Beta Receptor Blockade Fails to Recover Ventricular Function Despite Increased Presynaptic Sympathetic Nervous System Function in Experimental Pulmonary Arterial Hypertension.

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Background:

Despite β-blocker's proven efficacy in left-sided heart failure, their use in pulmonary arterial hypertension (PAH) and RV failure is less established. The objectives of the study were twofold, to determine the effects of β-receptor blockade on 1) ventricular function; and 2) myocardial sympathetic nervous system (SNS) function in an animal model of PAH.

Methods: PAH was induced in male Sprague-Dawley rats (n=36) by a single subcutaneous injection of Sugen 5416 (20mg/kg) followed by 3 weeks of hypoxia. At week 5 post-injection, PAH rats were randomized to receive carvedilol (15 mg/kg/day oral; n=18) or vehicle (n=18) for 4 weeks. At 9 weeks, myocardial presynaptic SNS function was assessed with [11C]-meta-hydroxephedrine (HED) positron emission tomography (PET).

Results: Carvedilol did not decrease PAH severity, with no changes in RV systolic pressure compared to vehicle. RV ejection fraction (EF) was significantly lower in both PAH groups compared to healthy control (59.1±7% vs 73.0±5; p<0.05), but this was not further reduced by carvedilol. However, carvedilol, but not vehicle, increased RV ESV (180.4±65 vs 147.7±58uL) and decreased LVEF compared to healthy control (72.8±8.1 vs. 82.4±2.4, respectively; p<0.05). Carvedilol increased pre-synaptic SNS function in the LV with significant increases in the volume of distribution (DV) of HED in the LV (p<0.05) but not RV. With increasing PAH disease severity, immunohistochemistry confirmed selective sympathetic denervation (DBH) within the RV, with parasympathetic nerves (VAchT) being spared. These findings were confirmed on PET with a significant negative relationship between HED DV and RVSP (Figure 1) in the RV (r=-0.68, p<0.05) and septum (r=-0.80, p=0.002) but not LV lateral wall (r=-0.41, p=0.18).
Conclusions: In experimental PAH, carvedilol treatment may worsen ventricular function despite an increased SNS function in the LV observed. Together, these results may caution against the use of β-receptor blockade in patients with PAH induced RV failure.