Coronary artery remodeling a new component of right ventricular failure in PAH

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Background: Right ventricular failure (RVF) in the setting of pulmonary arterial hypertension (PAH) has been associated with impaired metabolism, decreased RV wall perfusion, both contributing to the development of an ischemic state. We recently reported that coronary artery (CA) remodeling (inducer of ischemic lesions in the heart) is significantly increased in both human and experimental PAH models. However, its role in RVF is unknown. We also reported that the epigenetic reader BRD4 is significantly upregulated in remodeled CA in PAH, which may account for the increased expression of the pro-ischemic long non-coding RNA H19 demonstrated to be implicated in CA diseases.

Objective: We hypothesize that the BRD4/H19 axis is implicated in CA remodeling in PAH and promotes RVF.

Methods and results: In both human (n=17) and rats (n=12), we showed that coronary artery wall thickness was significantly increased in PAH versus control (H&E, $p=0.0005$ and 0.0025 respectively). In rats, CA remodeling correlates with RV functions (CO $r= -0.8459$, $p<0.0005$; RVSP $r=0.6393$, $p=0.0252$). In addition, BRD4 expression was significantly increased in RV and CA from PAH patients (WB, $p<0.05$) and In situ hybridization confirmed the upregulation of H19 in remodeled CA in PAH versus control, confirming a possible regulation of H19 by BRD4. Current experiments aim to 1) investigate the role of H19 in coronary artery smooth muscle proliferation and resistance to apoptosis and 2) determine whether the decrease in coronary artery remodeling in response to BRD4 inhibitors is mediated by H19 in PAH rats.

Conclusion: We demonstrated for the first time that CA remodeling is a new clinical component of RV failure in the setting of PAH. The BRD4/H19 epigenetic axis might represent a novel and attractive therapeutic target to improve RV functions.