Title: Heme oxygenase-1 and inflammation in experimental right ventricular failure on prolonged overcirculation-induced pulmonary hypertension

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Body: Heme oxygenase (HO)-1 is a stress response enzyme which presents with cardiovascular protective and anti-inflammatory properties. Six-month chronic overcirculation-induced pulmonary arterial hypertension (PAH) in piglets has been previously reported as a model of right ventricular (RV) failure related to the RV activation of apoptotic and inflammatory processes. We hypothesized that altered HO-1 signalling could be involved in pulmonary vascular and RV changes. Fifteen growing piglets were assigned to a sham operation (n=8) or to an anastomosis of the left innominate artery to the pulmonary arterial trunk (n=7). Six months later, hemodynamics was evaluated after closure of the shunt. Pulmonary and myocardial tissue was sampled for pathobiological evaluation. Shunting was associated with a tendency to decreased pulmonary gene and protein expressions of HO-1, while pulmonary gene expressions of interleukin (IL)-33, IL-19, intercellular adhesion molecule (ICAM)-1 and -2 were increased. Pulmonary expressions of constitutive HO-2 and pro-inflammatory tumor necrosis factor (TNF)-α remained unchanged. Pulmonary vascular resistance was inversely correlated to pulmonary HO-1 protein and IL-19 gene expressions, and correlated to pulmonary ICAM-1 gene expression. Pulmonary arteriolar medial thickness and PVR were inversely correlated to pulmonary IL-19 expression. RV expression of HO-1 was decreased, while RV gene expressions TNF-α and ICAM-2 were increased. There was a correlation between RV-pulmonary artery coupling and RV HO-1 expression. These results suggest that downregulation of HO-1 contributes to PAH and RV failure in overcirculation-induced PAH.