Role of PARP1-PKM2/inflammation/oxidative DNA damage axis in the pathogenesis of right ventricular failure associated with pulmonary arterial hypertension

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**Background:** Right ventricular failure (RVF) is an independent poor prognostic factor for pulmonary arterial hypertension (PAH) patients. Studies have revealed a metabolic shift from oxidative phosphorylation to glycolysis (Warburg effect) in compensated RV hypertrophy (cRVH). Nuclear pyruvate kinase muscle isozyme M2 (PKM2) promotes Warburg effect and PKM2/PKM1 ratio is established as a marker of glycolysis. Although the DNA damage response protein Poly ADP-ribose polymerase 1 (PARP1) was documented to induce PKM2 nuclear translocation and enhances Warburg effect in cancer, their role in RVF has never been studied. We hypothesized sustained PARP1 activation accounts for nuclear PKM2 localization, contributing to cardiomyocyte dysfunction and thus decompensated RV hypertrophy (dRVH).

**Methods and Results:** We found by Western blot (WB) that PKM2/PKM1 ratio was upregulated in cRVH (Cardiac index >2.2, n=14) and dRVH patients (died with RVF, n=9), compared to control donors (n=14), and correlated with RV hypertrophy and fibrosis. Similar findings were found in three PH rat models (monocrotaline, pulmonary artery banding and Sugen-hypoxia). Interestingly, cardiac inflammation (NF-kappaB, IL-8, CD68), oxidative DNA damage (PARP1, MTH1, 8-oxodG), and apoptosis (TUNEL) were significantly increased in dRVH compared to cRVH despite similar PKM2/PKM1 ratios. Specifically, PARP1 expression inversely correlated with cardiac output and positively correlated with ANP, RV hypertrophy and fibrosis; suggesting that persistent DNA damage repair by PARP1 promotes dRVH. Using neonatal rat RV cardiomyocytes, we confirmed DNA damage promotes nuclear expression of PARP1 and PKM2, leading to inflammation (NF-kappaB), oxidative DNA damage (8-OxoDG) and apoptosis (TUNEL). PARP1 inhibitor (ABT888) prevents nuclear retention of PKM2 and suppresses cardiomyocyte dysfunction (inflammation, oxidative DNA damage, apoptosis). (All p<0.05)

**Conclusions:** We demonstrated for the first time that PARP1-PKM2/inflammation/oxidative DNA damage axis is implicated in the transition from cRVH to dRVH and suppression of PKM2 nuclear function by PARP1 inhibitor may represent a new strategy to improve RV function.

(300/300 words)

**Keyword:** pulmonary hypertension; heart failure; DNA damage; metabolism; inflammation