Development of new pre-clinical model of pulmonary hypertension associated with left heart disease.

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Rationale: Heart failure (HF) with preserved ejection fraction (HFP EF) affects over than 50% of all patients with HF. 50% of HFP EF culminates to pulmonary hypertension (PH), which confers poor prognosis. Furthermore, metabolic syndrome (MS), which affects more than 34% of adults in the world, is strongly associated with PH (34.3%) and HFP EF (prevalence of 35%). Taken together, these results suggest that MS and HFP EF, which are two major healthcare challenges in the occidental society, may predispose to PH. Unfortunately; studies supporting this hypothesis remain limited by the lack of good pre-clinical models that preclude extensive investigation. We developed a new animal model for WHO2 PH associating HFP EF and MS.

Methods/Results: Using supra-coronary-aortic-banding, we induced HFP EF in wistar rats characterized by left ventricle (LV) hypertrophy, rise in LVSP, LVEDP, E/E’ ratio and no significant modification of LV ejection fraction, 10 weeks post-surgery. We then induced MS with high fat diet and/or daily injection of olanzapine (4mg/kg/2days) for 9 weeks. Establishment of MS was confirmed by rise of hepatic triglyceride, increase visceral fat and high blood pressure. Compared to healthy and sham surgery, only HFP EF-MS rats displayed PH characterized by significant increase of PAP, RVSP, PAAT and vascular remodelling of distal pulmonary arteries. Interestingly, both mediastinal and visceral fat displayed strong correlation with PH severity (RVSP) suggesting that fat accumulation exacerbates PH associated with HFP EF.

Conclusion: In the present study we 1) developed a new model for WHO2 PH associating HFP EF and SM; 2) demonstrated that MS worsens PH associated with HFP EF.