Thrombosis in the coronary microvasculature may be responsible for impaired cardiac relaxation and diastolic dysfunction

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Introduction: Heart Failure with Preserved Ejection Fraction (HFpEF) is proposed to be caused by endothelial dysfunction in cardiac small vessels. We previously identified Hhipl1 as a gene upregulated in the coronary vasculature of Leptin receptor deficient mice (Leprdb/db) a well-established mouse model of HFpEF. Importantly, Hhipl1 encodes for a decoy receptor of Desert Hedgehog (DHH) which is known to be critical for endothelial integrity.

Objective: Our objective is to investigate the functional consequences of impaired Hedgehog (HH) signaling in the adult heart in order to identify novel mechanisms underlying the development of diastolic dysfunction.

Method: To do so, Cdh5-Cre/ERT2, DhhFlox/Flox (DhhECKO) mice and their control littermates were administered with tamoxifen at 8 weeks of age to induce Dhh KO. Their cardiac function, exercise tolerance, and the phenotype of their coronary vasculature were assessed one month later.

Results: DhhECKO mice presented significantly reduced exercise tolerance, increased end diastolic pressure (EDP) and Tau, with no change in their ejection fraction consistent with diastolic dysfunction. At molecular and cellular level, impaired cardiac relaxation in DhhECKO mice was associated with a significantly decreased phospholamban phosphorylation on Thr17 and an alteration of sarcomeric shortening in ex-vivo. Besides, as expected, DhhECKO mice exhibited phenotypic changes in their coronary vasculature including a prominent pro-thrombotic phenotype (63±6.2 vs 25±5.2 thrombi/mm²; p<0.001) leading to an impaired capillary perfusion and local hypoxia. Notably, anti-aggregant therapies (aspirin and clopidogrel) prevented the occurrence of both diastolic dysfunction and exercise intolerance in DhhECKO mice demonstrating for the first time that thrombosis may promote diastolic dysfunction. Importantly, we confirmed the critical role of thrombosis in Leprdb/db mice which also displayed increased cardiac small vessel thrombosis in comparison to control mice. Alike DhhECKO mice, we found that anti-aggregants decreased EDP (6.3±0.4 mmHg in aspirin-treated vs 11.3±0.79 in control mice; p=0.001) and improved exercise tolerance in Leprdb/db mice (34±2.52 min in aspirin-treated vs 24±3.55 in control mice; p=0.004).

Conclusion: Altogether, these results demonstrate that small vessel thrombosis may participate in the pathophysiology of heart failure with preserved ejection fraction.