Diastolic dysfunction is associated with cardiac small vessel disease in ovariectomized females but not in males

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Introduction: Coronary microvascular disease has been proposed to be responsible for heart failure with preserved ejection fraction (HFpEF) about 10 years ago. However, to date the role and phenotype of the coronary microvasculature has still been poorly considered and investigated in animal models of HFpEF.

Objective: To characterize the phenotype of the coronary microvasculature in male and female mice with diastolic dysfunction.

Method: We assessed cardiac function and characterized the coronary microvasculature in two mouse models of HFpEF: mice fed with a high fat diet (HFD) + L-NAME regimen and Leptin receptor deficient (Leprdb/db) mice. Notably, our study was done in males, females and ovariectomized (OVX) female mice in order to search for possible sexual dimorphisms.

Results: Upon a HFD + L-NAME regimen, both males and OVX females but not non OVX females develop diastolic dysfunction attested by an increased end diastolic pressure. In Leprdb/db mice, both Male and non OVX female mice develop diastolic dysfunction. Notably female mice have reduced estradiol and progesterone level mice mimicking ovariectomy.

We found that both OVX and non OVX females but not males display increased endothelial activation attested by increased ICAM1 expression, endothelium leakage attested by increased Fibrinogen and IgG extravasation and decreased arteriole diameter suggesting vasoconstriction. The same results were found in Leprdb/db mice.

Conclusion: Diastolic dysfunction is not always associated with cardiac small vessel disease since Leprdb/db males and C57BL/6J males fed with a high fat diet (HFD) + L-NAME regimen develop diastolic dysfunction in the absence of endothelial dysfunction. Also endothelial dysfunction may not be sufficient to induce diastolic dysfunction since non OVX female mice fed with a high fat diet (HFD) + L-NAME regimen display endothelial dysfunction while they do not develop diastolic dysfunction.