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Dapagliflozin triggers left ventricular reverse remodeling in a mouse model of pressure overload-induced hypertrophy

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Background

Regression of left ventricular (LV) hypertrophy due to mechanical unloading e.g. aortic valve replacement is characterized by a marked reduction in left ventricular mass (LVM) and the improvement of cardiac function. Recently, the new antidiabetic drugs, sodium-glucose-cotransporter-2 (SGLT2) inhibitors have shown favorable effects on cardiac function among heart failure patients without diabetes. However, the underlying signaling mechanism and whether SGLT2 inhibition stimulates reverse remodeling upon LV hypertrophy are still unknown.
This study aimed to investigate if the SGLT2 inhibitor Dapagliflozin (DAPA) improves LV function and regression of LV hypertrophy in a mouse model of pressure overload-induced LV hypertrophy.

Methods

Male C57BL/6J mice (body weight 20-25g) were used. LV hypertrophy was induced by transverse aortic constriction (TAC) (Fig. 1).

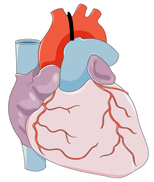

Figure 1: transverse aortic constriction: anatomy of the heart and aortic arch, indicating the postion of the TAC suture (black), modified from [1].

Animal groups (Fig. 2):
1) TAC for 8 weeks
2) TAC and DAPA for 8 weeks
3) TAC for 8 weeks, DAPA only in week 7 and 8
4) Sham (no TAC operation)

Dapagliflozin was provided via drinking water (1mg/kg body weight).
Cardiac function was assessed by echocardiography & invasive LV hemodynamic measurement.

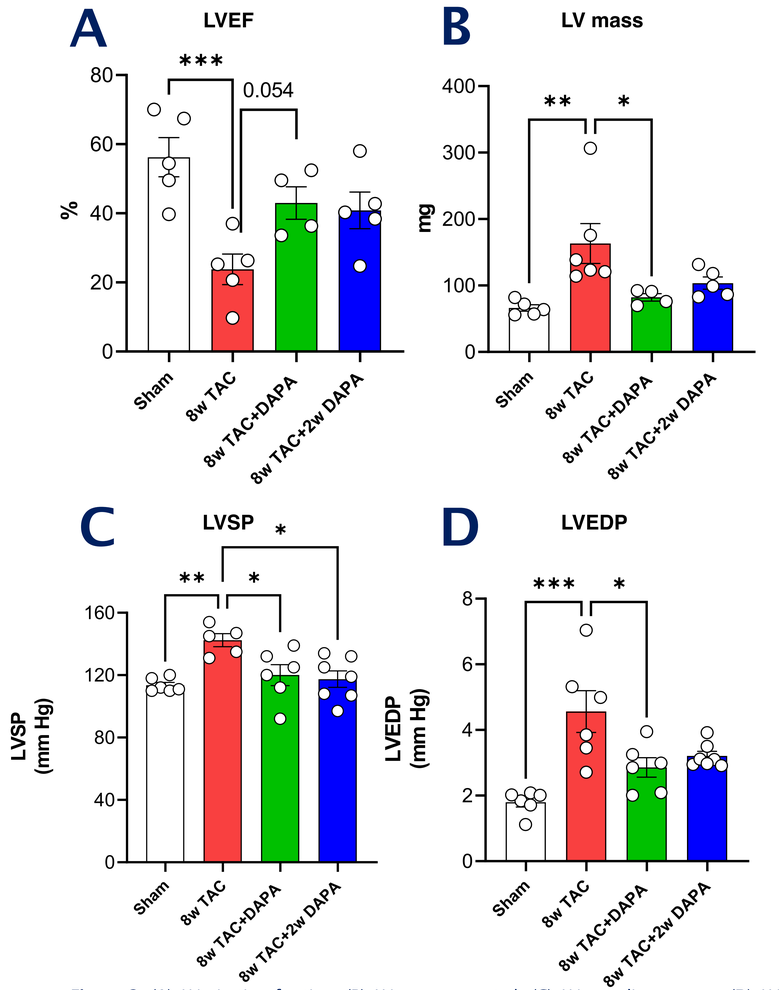

Figure 3. (A) LV ejection fraction. **(B)** LV mass corrected. **(C)** LV systolic pressure. **(D)** LV enddiastolic pressure; all data mean ±SD, n=4-6, *p<0.05, **p<0.01, ***p<0.001.

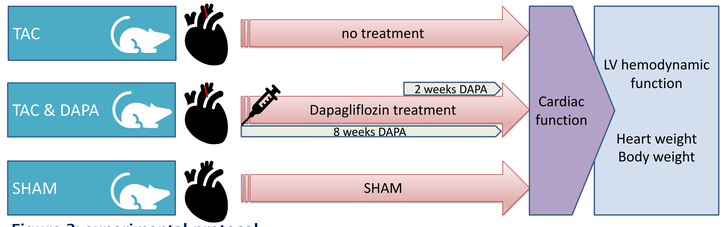

Figure 2: experimental protocol

Results

Eight weeks of TAC resulted in a significant reduction in LV ejection fraction (EF) compared to Sham operated group (LVEF SHAM: 56 ± 12% vs 8 weeks TAC 27 ± 12%, p<0.001). This was associated with a significant increase of LV mass, LV systolic pressure and end-diastolic pressure compared to SHAM (p<0.01). All these functional changes were improved in mice treated with DAPA for 8 weeks. Notably, DAPA treatment only for 2 weeks could effectively improve LVEF and regress LV hypertrophy in comparison with 8 weeks TAC group (LVEF 8 weeks TAC: 27 ± 12% vs 2 weeks DAPA 41 ± 11%.; LV mass: 8 weeks TAC 163 ± 73mg vs 104 ± 20mg).

Conclusion

In our mouse model LV hypertrophy and cardiac dysfunction was markedly improved by the administration of DAPA in a preventive indication. Most important, DAPA treatment in existing LV hypertrophy triggered and resulted in reverse remodeling referring to LV hypertrophy regression and improvement of LV function. Therefore, administration of DAPA in patients with LV hypertrophy and heart failure may be an effective therapeutic approach for boosting LV reverse remodeling.

Funding

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References: [1] https://smart.servier.com