Cholesterol-lowering gene therapy prevents HFpEF in obese type 2 diabetic mice

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Background: Hypercholesterolemia may be causally related to heart failure with preserved ejection fraction (HFpEF) even in the absence of coronary artery disease.

Purpose: The objectives of this study were to establish a model of HFpEF associated with hypercholesterolemia in obese diabetic mice and to evaluate the preventive effect of cholesterol lowering induced by adeno-associated viral serotype 8 (AAV8)-low-density lipoprotein receptor (LDLr) gene transfer in this model.

Methods: Gene transfer with 5 x 10^{10} genome copies of AAV8-LDLr or with the same dose of AAV8-null was performed in C57BL/6J $LDLr^{-/-}$ mice at the age of 11 weeks. The standard chow (SC) diet was continued in part of the mice whereas the high-sucrose/high-fat (HSHF) diet was initiated at the age of 12 weeks and continued for 16 weeks. All endpoint analyses were performed at the age of 28 weeks.

Results: Body weight in the AAV8-null HSHF diet mice progressively increased and was 1.49-fold ($p<0.001$) higher at 16 weeks after the start of the diet compared to AAV8-null SC diet mice (32.8 $\pm$ 1.0 g versus 22.1 $\pm$ 0.4 g). This weight gain was associated with hyperinsulinemia and type 2 diabetes mellitus. AAV8-LDLr gene transfer significantly ($p<0.001$) decreased plasma cholesterol in SC diet mice (66.8 $\pm$ 2.5 mg/dl versus 213 $\pm$ 12 mg/dl) and in HSHF mice (84.6 $\pm$ 4.4 mg/dl versus 464 $\pm$ 25 mg/dl. The HSHF diet induced cardiac hypertrophy (1.23-fold ($p<0.001$) increase of left ventricular weight) and resulted in pathological remodelling as evidenced by a 21.1% ($p<0.01$) decrease of myocardial capillary density and by increased interstitial ($p<0.001$) and perivascular fibrosis. AAV8-LDLr potently counteracted cardiac hypertrophy and pathological remodelling. Moreover, wet lung weight was 19.0% ($p<0.001$) higher in AAV8-null HSHF diet mice than in AAV8-null SC diet mice whereas no increase of lung weight was present in AAV8-LDLr HSHF diet mice. Pressure-volume loop analysis was consistent with HFpEF in AAV8-null HSHF diet mice as evidenced by a preserved ejection fraction (52.2 $\pm$ 2.5% versus 57.2 $\pm$ 2.1% in AAV8-null SC diet mice), a significant reduction of the end-diastolic volume (25.1 $\pm$ 1.4 μl versus 31.5 $\pm$ 1.5 μl; $p<0.01$), of cardiac output (7.76 $\pm$ 0.46 ml/min versus 10.9 $\pm$ 0.6 ml/min; $p<0.001$), and of the peak filling rate (509 $\pm$ 52 μl/min versus 712 $\pm$ 22 μl/min; $p<0.01$). The slope of the end-diastolic pressure to volume relationship ($p<0.01$), ventriculo-arterial coupling ratio ($p<0.05$), and the time constant of isovolumetric relaxation ($p<0.001$) were significantly higher in in AAV8-null HSHF diet mice than in AAV8-null SC diet mice. AAV8-LDLr HSHF diet mice were characterized by a completely normal cardiac function. Treadmill exercise testing showed that the total distance covered was reduced by 62.0% ($p<0.001$) in AAV8-null HSHF diet mice compared to AAV8-null SC diet mice and was not reduced in AAV8-LDLr HSHF diet mice.

Conclusion: Cholesterol-lowering AAV8-LDLr gene therapy prevents HFpEF.