Research Summary

Cardiovascular complications of non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) often clusters with obesity, diabetes and hyperlipidemia. Cardiovascular disease (CVD) is the leading cause of death in patients with NAFLD. Most preclinical models of NAFLD are induced by high-fat diet feeding leading to obesity and diabetes, each promoting CVD independent of changes in hepatic steatosis. To determine the role of hepatic steatosis independent of changes in body weight and insulin sensitivity, we utilized hepatocyte-specific peroxisome proliferator-activated receptor-α (PPARα) knockout ($Ppara^{HepKO}$) mice. On a standard diet, male $Ppara^{HepKO}$ mice exhibited elevated hepatic fat accumulation and increased hepatic triglycerides despite normal body weight, fasting blood glucose and insulin. $Ppara^{HepKO}$ mice had elevated mean arterial blood pressure as well as impaired diastolic function and adverse cardiac remodeling resembling dilated cardiomyopathy. $Ppara^{HepKO}$ mice also displayed alterations in vascular stiffness, including increased pulsatility index, resistive index, and intima-media thickness in the abdominal aorta and carotid artery.

In summary, we have developed a model of hepatic lipid accumulation in $Ppara^{HepKO}$ mice that occurs even in mice fed a standard normal-fat laboratory diet. Our study further demonstrates that increased hepatic fat accumulation in $Ppara^{HepKO}$ mice is associated with cardiovascular dysfunction. This model can represent a useful tool in research for therapeutic targets for CVD especially in patients with lean NAFLD.