High-Fat/High-Sugar Diet Causes Metabolic Disorders and Cardiac Dysfunction: a New Model in Primates

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The number and proportion of aged people in the population is increasing. It was reported by World Health Organization (WHO) that the number of people aged 60 years or older was 1 billion in 2019 worldwide, and the number would grow to 1.4 billion by 2030 and 2.1 billion by 2050. With the rapid development of society and great improvement of people's living standard, high-fat/high-sugar diet (HFSD) is common. High-fat/high-sugar diet can lead to the development of obesity and metabolic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, and cognitive decline. However, few studies investigated the effects of HFSD on elderly people.

In a recent study, Zheng et al. identified novel changes in the metabolism, cardiac morphology, and cardiac function of aged *Cynomolgus* monkeys fed a HSFD [1]. The HFSD caused metabolic abnormalities and cardiac contractile dysfunction in aged monkeys. Although the detailed molecular mechanism for the HFSD effects on metabolic disorders and contractile dysfunction remains further investigation, this study provides a powerful model for the HFSD-induced metabolic and cardiac dysfunction.

Comment on: Shuang Zheng[#], Weijiang Tan[#], Xiang Li[#], Binglin Li, Baoyong Gong, W Glen Pyle, Jian Wu, Lei Li, Ting Luo, Yunzeng Zou, Feng Hua Yang^{*}, Peter H Backx^{*}. Aged monkeys fed a high-fat/high-sugar diet recapitulate metabolic disorders and cardiac contractile dysfunction. *J Cardiovasc Transl Res*. 2021 Feb 16. doi: 10.1007/s12265-021-10105-z.

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High fat and high sugar have now become the major constituent of modern diet. However, chronically high consumption of fat and sugar could lead to the occurrence of metabolic and cardiovascular disorders, which has been widely documented. Epidemiological study has highlighted the association between dietary patterns and cognitive decline in elders with average aged 69.3 years, and it is reported that western dietary pattern was associated with higher risk of cognitive decline [2]. Besides, chronic high-fat diet could induce myocardial hypertrophy and fibrosis. Obesity-related cardiac dysfunction epidemic heightened the need to identify a safe and effective therapy that can improve cardiac function and decrease the risk of cardiovascular disease. Large animal model provides a unique tool to study the mechanism of diet-induced cardiac dysfunction. Nonhuman primates (NHPs) are more similar to the human condition in terms of genetics, physiology, and metabolism.

The recent study established an aged monkey model with HFSD feeding, which is characterized with metabolic disorders and cardiac contractile dysfunction [1]. This is similar to that seen in the human condition. Serum metabolites analysis showed that HFSD significantly increased glucose and fatty acid levels. It is reported that the heart primarily consumes fatty acids, and the failing heart consumes more ketones and glutamate and releases more amino acids [3]. Echocardiography showed that the HFSD remodeled the heart and inhibited cardiac function in aged monkeys compared with regular diet (RD). To further explore the molecular signal changes caused by HFSD in aged myocardium, the authors investigated the inflammatory regulation and myofilament-associated phosphorylation signaling in the myocardium. It was showed that both the expression levels of inflammatory genes including IL-1 β , IL-6, IL-8, and IL-10 and the myofilament phosphorylation levels were significantly increased, suggesting activated inflammatory signaling and depressed myofilament contractility.

Taken together, the recent study used the aged *Cynomolgus* monkeys to model HFSD-induced metabolic and cardiac dysfunction, provides a powerful model for the

human condition [1]. It would be interesting to know the role of specific metabolites playing in the progress of the age-related cardio-metabolic disorders, or to identify new biomarkers for metabolic heart diseases in elderly. For example, what's the regulatory role of amino acids in heart failure? Whether and which amino acids can be used as biomarkers of age-related cardiovascular diseases? Further studies should combine the multi-omics, for example, RNAseq, and bioinformatics technology to investigate the molecular mechanism underlying the pathology.

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Declarations

Conflict of Interest The authors declare no competing interests.

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