International Journal of Cardiology 198 (2015) 66–69

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

A high-sugar and high-fat diet impairs cardiac systolic and diastolic function in mice☆

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ARTICLE INFO

Article history:
Received 2 March 2015
Received in revised form 21 June 2015
Accepted 27 June 2015
Available online 2 July 2015

Keywords:
Western diet
High-fat diet
High-sugar diet
Heart failure preserved ejection fraction
Diastolic dysfunction
Obesity

ABSTRACT

Background: Heart failure (HF) is a clinical syndrome characterized by dyspnea, fatigue, exercise intolerance and cardiac dysfunction. Unhealthy diet has been associated with increased risk of obesity and heart disease, but whether it directly affects cardiac function, and promotes the development and progression of HF is unknown.
Methods: We fed 8-week old male or female CD-1 mice with a standard diet (SD) or a diet rich in saturated fat and sugar, resembling a "Western" diet (WD). Cardiac systolic and diastolic function was measured at baseline and 4 and 8 weeks by Doppler echocardiography, and left ventricular (LV) end-diastolic pressure (EDP) by cardiac catheterization prior to sacrifice. An additional group of mice received WD for 4 weeks followed by SD (wash-out) for 8 weeks.
Results: WD-fed mice experienced a significant decreased in LV ejection fraction (LVEF), reflecting impaired systolic function, and a significant increase in isovolumetric relaxation time (IRT), myocardial performance index (MPI), and LVEDP, showing impaired diastolic function, without any sex-related differences. Switching to a SD after 4 weeks of WD partially reversed the cardiac systolic and diastolic dysfunction.
Conclusions: A diet rich in saturated fat and sugars (WD) impairs cardiac systolic and diastolic function in the mouse. Further studies are required to define the mechanism through which diet affects cardiac function, and whether dietary interventions can be used in patients with, or at risk for, HF.

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1. Introduction

Heart failure (HF) is defined as '*a complex clinical syndrome that results from any structural or functional impairment of ventricular filling and/or ejection of blood*'. About 38 million people worldwide are affected by HF, 5.7 million in the US with 870,000 new HF cases every year [1]. The incidence of HF also appears to be rising. This has been linked to the aging of the population in Western countries, and the epidemic of obesity, diabetes, and hypertension [2].

The association between obesity and HF is explained in part by the association of obesity with hypertension and diabetes, also independent risk factors for HF. Obesity, however, appears to independently confer an increased risk for HF [3]. Changes in diet, with "unhealthy" food rich in sugars and saturated fat (Western diet [WD]) are considered to be causing the obesity epidemic worldwide. The mechanisms by which WD promotes obesity, and whether WD direct impairs cardiac function are not completely understood. The aim of the study was to assess whether a diet rich in sugars and saturated fat, simulating the WD, was sufficient to induce cardiac systolic and diastolic dysfunction in the mouse.

2. Methods

All experiments were conducted in 8-week old male or female CD-1 mice following the NIH guidelines and were approved by the Virginia Commonwealth University Institutional Animal Care and Use Committee. Standard Diet (SD — Teklad LM-485, Harlan) or a diet rich in saturated fat and sugars (WD, TD.88137, Harlan) was given to mice for 8 weeks. Nutritional characteristics of the SD and WD are presented in details in Table 1.

We measured food intake daily, body weight weekly, fasting capillary glucose (at 4 and 8 weeks), and arterial blood pressure through a noninvasive tail-cuff blood pressure analyzer CODA System (Kent Scientific Corporation, Torrington) at 8 weeks. We completed a transthoracic Doppler echocardiography using the Vevo770 imaging system (VisualSonic Inc, Toronto, Ontario and 30-MHz probe), at baseline, 4 and 8 weeks, as previously described [4]. We measured left ventricular (LV) dimensions, mass, ejection fraction (EF), stroke volume (SV), cardiac output (CO), the isovolumetric contraction time (ICT) and relaxation time (IRT), the ejection time (ET), the myocardial performance index (MPI), and heart rate (HR). Prior to sacrifice, we performed a LV catheterization through a retrograde right carotid artery approach (Millar catheter — Millar Inc, Huston,

☆ Disclosure: None applicable.

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http://dx.doi.org/10.1016/j.ijcard.2015.06.136
0167-5273/Published by Elsevier Ireland Ltd.

Table 1
Nutritional facts of "Western" diet.

Components in % calories	Standard diet	"Western diet"
Proteins	25	15.2
Total fat	17	42
Saturated fat	0.8	12.8
Total carbohydrates	58	42.7
Sucrose	0	30
Cholesterol	0	0.2
Sodium	0.3	0.1
Energy density (kcal/g)	3.1	4.5

TX) to measure the LV end-diastolic pressure (LVEDP), as previously described [4]. After sacrifice, the heart was explanted, fixed in formalin, and processed for paraffin embedding and slide preparations. Myocardial fibrosis was assessed with Masson's trichrome (Sigma-Aldrich), evaluated with computer morphometric analysis (Image Pro Plus 6.0 software), and expressed as a percentage of fibrosis staining (blue) over the all section area, as previously described [4].

An additional experiment was performed in a group of male mice fed WD for 4 weeks and then switched back to SD for 8 more weeks (washout).

Values were expressed as the mean and standard error of the mean. The statistical analysis was performed using SPSS 22.0 package for Mac (Chicago, IL). Differences within each group were analyzed using the Student's T test for paired data, whereas differences between groups were assessed using Student's T test for unpaired data. We estimated that a sample size of 6 or more for each group would provide a power >80% ($\alpha = 0.05$) to detect a 'meaningful' difference defined as a difference between means that exceeds the standard deviation in each group. Male and female mice were examined separately.

3. Results

Adult male mice fed with the WD for 8 weeks had an approximate 20% less daily food intake (g) than mice fed with SD group (4.5 ± 0.4 g/day vs 5.4 ± 0.5 g/day, $p = 0.001$), but the daily caloric intake, was higher in the WD vs SD groups by an approximate 20% (20.3 ± 1.8 vs 16.8 ± 1.5 kcal/day, $p = 0.001$), and WD-fed mice gained approximately 21% more weight than SD (Fig. 1). Capillary fasting glucose levels were slightly increased on WD (*data not shown*). Systemic blood pressure at 8 weeks were not statistically different comparing WD to SD (Fig. 2).

Male mice fed with WD experienced a mild but statistically significant reduction in LVEF reflecting impairment in LV systolic function, while there were no changes in LV dimensions, LV mass, and CO (Fig. 3). WD-fed mice also showed increased IRT values leading to greater MPI values (Fig. 3). No significant changes in LVEF, IRT or MPI were seen in the mice fed with SD (*data not shown*). LV catheterization

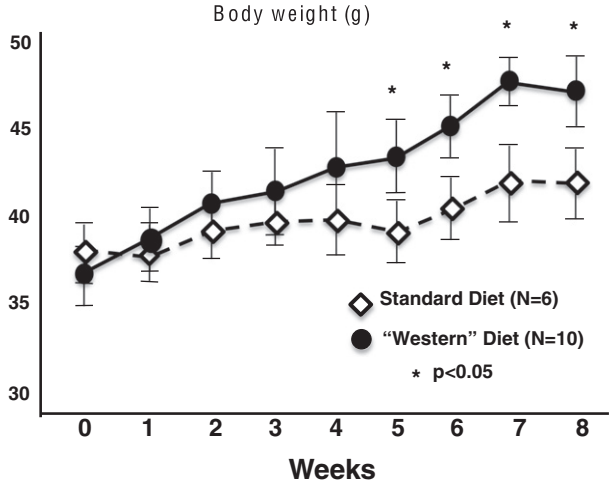

Fig. 1. Weight changes with "Western diet". Male mice fed with a high-sugar and -fat diet ("Western" diet) had greater weight gain vs mice fed with standard diet.

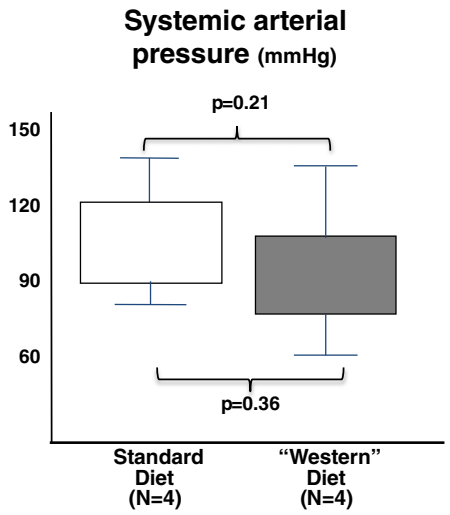

Fig. 2. Non-invasive blood pressure measurement. No significant differences in systolic or diastolic blood pressure were seen between male mice fed with "Western" vs standard diets.

showed significantly higher LVEDP values compared with SD (Fig. 4), reflecting elevated filling pressures. Myocardial fibrosis was mildly increased in the WD vs SD fed mice (Fig. 4).

Similar to what is seen in male mice, female mice experienced a significant reduction in LVEF and an increase in IRT and MPI with WD (Fig. 3), with a magnitude that was similar in females versus males and no significant sex-related differences.

In an additional experiment, male mice who were fed WD for 4 weeks and were switched back to SD (washout) showed a significant recovery in LVEF and improvement in IRT and MPI after 8 weeks of washout (Fig. 5). This was associated with a significantly lower body weight at 4 weeks of washout (40 ± 3 g) vs mice fed WD for 8 weeks ($p < 0.05$).

4. Discussion

This experimental study shows that a diet rich in sugars and saturated fats, resembling the Western diet (WD), induces a significant impairment in LV systolic and diastolic function in mice, in absence of changes in systemic arterial blood pressure and fasting glucose levels.

While the association between diet and the risk of ischemic heart disease is well established, the relationship between diet and HF, however, has not been thoroughly explored [5]. Studies in mice have conventionally used a very 'healthy' diet, virtually devoid of sugars and saturated fat, and when a WD has been used in the experimental setting, it has been to promote atherosclerosis in genetically modified mice [5]. The significant impairment in LV systolic and diastolic function seen within 4 weeks of the initiation of WD suggests a causal link between WD and HF. WD induced a significant impairment in cardiac function, associated with body weight gain, in line with the presence of diastolic dysfunction in the mouse model of morbid obesity and diabetes [6].

Moreover, we show that the diet-induced cardiac dysfunction can be, at least in part, reversed by a return to a 'healthy diet', SD.

The effects of WD on cardiac function appear to be sex-independent, and equally evident in male and female mice, suggesting that sex-related differences in cardiac remodeling, seen after acute myocardial infarction or pressure overload [7], are less important in this context.

The mechanism(s) by which a diet rich in saturated fat and sugars induce cardiac dysfunction in the mouse have not been explored in this study. WD is known to induce a systemic inflammatory response [8]. Saturated fat and sugars bind to the membrane based pattern recognition receptors involved in the innate immune response, the