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Original Article

Glucose loading for heart failure protects the myocardium and improves physical function

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Abstract. [Purpose] The purpose of this study was to investigate the effects of glucose intake on physical function in a heart failure rat model. [Materials and Methods] Five-week-old male Wistar rats were used for this study. Monocrotalin (40 mg/kg) was administered intraperitoneally to rats to induce heart failure. The rats were divided into two groups, control and MCT; the MCT group was further classified according to glucose concentration (0%, 10%, and 50%). [Results] Glucose intake during heart failure prevented the loss of body weight, skeletal muscle, and fat mass. Myocardial metabolism in heart failure was enhanced by hypoxia, which in turn, enhanced the glycolytic system. [Conclusion] Glucose loading suppressed cardiac hypertrophy and improved physical function in the heart failure rat model.

Key words: Heart failure, Myocardium metabolism, Cardiac cachexia

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INTRODUCTION

Heart failure is a progressive disease with a poor prognosis and can lead to deterioration of cardiac and physical function due to exacerbations. Furthermore, approximately 8–42% of patients with heart failure have cachexia, which is a risk factor independent of the severity of heart failure (New York Heart Association [NYHA] cardiac function classification). Cachexia is associated with shorter survival in patients with heart failure[1)]. Therefore, therapeutic intervention for heart failure is very important. One such intervention, nutritional, is easy to apply clinically. In addition, considering the importance of nutritional intervention in daily activities and function is crucial. Physical function and activities of daily living have been shown to improve when nutritional intervention is combined with physical therapy[2)]. Therefore, physical therapists need to be aware of and understand the importance of nutritional intervention. However, most of the recent reports on nutritional intervention have only focused on total caloric intake as a factor of consideration during heart failure, and have not addressed metabolic factors[3, 4)]. Myocardial metabolism is characterized by the fact that 80–90% of the myocardium utilizes fatty acid metabolism and 10% glucose metabolism. Conversely, when the myocardium becomes hypoxic in heart failure, it becomes dependent on glucose. Because glucose metabolism produces less ATP than fatty acid metabolism, oxygen is often administered. However, oxygen administration for heart failure has recently been reported to cause myocardial damage. Fujita et al. reported that overexploitation of fatty acid metabolism during heart failure causes more oxidative stress (reactive oxygen species [ROS])

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in mitochondria than usual, leading to myocardial injury[5]. Glucose loading, which increases glucose metabolism in heart failure, may suppress fatty acid metabolism in mitochondria and exert a protective effect on the myocardium.Therefore, in this study we generated rat models of heart failure to examine the effects of forced turnover of glycolytic metabolism on the myocardium and physical functions. We hypothesized that glucose loading for heart failure may enhance glucose metabolism and protect the myocardium.

MATERIALS AND METHODS

Five-week-old male Wistar rats (SLC, Shizuoka, Japan) were used for this study. Monocrotaline (MCT; sigma-Aldrich, St. Louis, MO, USA) (40 mg/kg) was administered intraperitoneally to the heart failure models[6]. All rats were weighed every 2–3 days, and the weight change from the beginning to the end of the experiment was observed. The study design is shown in Fig. 1. The experiment was conducted continuously for 21 days from the day of MCT administration, using the drinking water glucose tolerance model[7]. The diet used for this study was CE-2 (Nippon Crea Co., Ltd., Tokyo, Japan). Glucose water was prepared by diluting 50% Otsuka sugar solution (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) with distilled water to a glucose concentration of 0%, 10%, and 50%. The rats were divided into two groups; control and MCT; the MCT group was further classified according to glucose concentration (0%, 10%, 50%).

Twenty-one days after the administration of MCT, an endurance test was administered. The treadmill was set at 15 m/min with a 20° incline, and the rats ran continuously until they left the treadmill three times[7]. The maximum exercise duration was 60 minutes. The exercise distance was measured.

After the experiment, the myocardium, lungs, testicular fat, and skeletal muscle were collected and weighed. Bilateral extensor digitorum longus and soleus (SOL) muscle weights were measured, and the total skeletal muscle mass (TSM) was calculated. The collected tissues were stored in a deep freezer at −80 °C until analysis.

Myocardial tissue was divided into the right ventricular wall (RV) and left ventricle and ventricular septum (LVSW) after myocardial weight measurement. To determine the severity of heart failure, the ratio of RV to LVSW was calculated (RV/LVSW). In addition, we calculated the right ventricular hypertrophy index (RVHI)[8, 9].

After the right ventricle was washed with phosphate-buffered saline (PBS), the tip was pelleted with the Power Masher II (Nippi Corporation, Tokyo, Japan) using the Biomasher II (Nippi Corporation, Tokyo, Japan). Protein extraction was then performed using PRO PREP (Intron Biotechnology, Song Nam, Republic of Korea). Each sample was quantified and hypoxia inducible factor-1 alpha (HIF-1 alpha) and lactate production were determined. For HIF-1 alpha, the HIF-1 alpha Sandwich enzyme-linked immunosorbent assay [ELISA] Kit (CELL BIOLABS, INC., San Diego, CA, US) was used according to the provider's protocol. The HIF-1 alpha concentration was calculated from a calibration curve based on the standard. Lactate production was determined using a lactate assay kit (Dojin Chemical Laboratory, Kumamoto, Japan) according to the protocol.

To avoid exposing the animals to significant pain, the endpoints of this experiment were set according to international guidelines, and the experiment was approved by the Animal Experiment Committee of Kio University (Approval No. R02-06).

All data are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was used for body weight change, myocardial weight, lung weight, skeletal muscle weight, fat mass, testicular fat length, and endurance tests. The Bonferroni test was used for comparison among multiple groups. IBM SPSS Statistics software version 26.0 (IBM, Armonk, NY, USA) was used for statistical analysis, and the significance level was set at 5%.

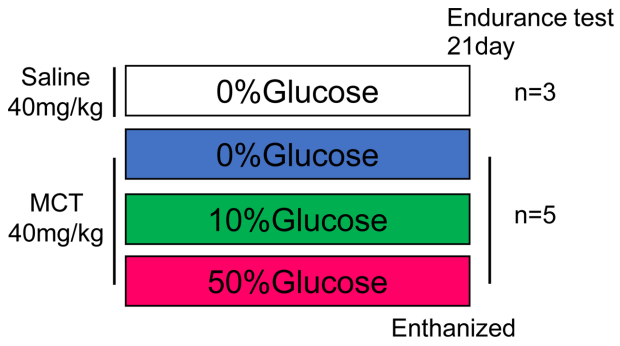

Fig. 1. Research design of this study.
The experimental schematic workflow in this study. The intervention period was 21 days. Saline was administered to CT group, Monocrotaline was administered to MCT group. The CT and MCT groups were divided, and the MCT group was further classified by sugar concentration. After the experiment period, each was measured endurance test of each group. CT: control; MCT: monocrotaline.

RESULTS

Body weight was decreased in the heart failure rat models compared to that in the CT. In addition, body weight loss was suppressed in the heart failure model rats in a glucose concentration-dependent manner. Fat mass, SOL, and TSM were also suppressed in a glucose concentration-dependent manner (Table 1). RVHI, which is associated with RV weight and severity of right heart failure, increased in the MCT group, particularly in the 0% group (Table 2). In the endurance test, the rats in the 0% MCT group showed a significantly shorter walking distance than that in the CT group (Table 3). There was no significant difference between the 10% and 50% MCT groups and the CT group. We also analyzed the effects of different glucose loads on lactate production in heart failure models. Lactate production in the right ventricle was increased in the 0% MCT group and was enhanced in the 10% and 50% MCT groups after glucose loading (Table 4). Since HIF-1 alpha is regarded as a marker of hypoxia[10], we also examined the levels in the RVs. Results confirmed that HIF-1 alpha was increased by MCT administration, regardless of the presence or absence of glucose load (Table 4).

Table 1. Effect of glucose intake on tissue weight in heart failure

Group	Body weight (g)	SOL (g)	EDL (g)	TSM (g)	Fat pad (g)	Lung (g)
CT	241.4 ± 8.19	0.10 ± 0.01	0.10 ± 0.01	0.40 ± 0.02	3.8 ± 0.2	1.14 ± 0.06
0%	192.5 ± 3.44**	0.08 ± 0.01*	0.09 ± 0.00	0.33 ± 0.01*	2.3 ± 0.1**	1.49 ± 0.06**
10%	217.1 ± 6.60*	0.09 ± 0.00	0.09 ± 0.01	0.36 ± 0.01	2.6 ± 0.1**	1.53 ± 0.09**
50%	207.5 ± 10.07*	0.09 ± 0.01	0.09 ± 0.00	0.35 ± 0.00	3.4 ± 0.4	1.47 ± 0.20

Data shown as mean ± standard deviation. Significant difference between CT vs. 0%, 10%, 50%. *vs. CT <0.05, **vs. CT <0.01. CT: Control; SOL: Soleus; EDL, Extensor digitorum longus; TSM: Tatal skeletal muscle.

Table 2. Effect of glucose intake on myocardial hypertrophy

Group	HW (g)	RVW (g)	LVSW (g)	RVHI (RV/LVSW)
CT	0.79 ± 0.03	0.14 ± 0.01	0.63 ± 0.05	0.22 ± 0.03
0%	0.82 ± 0.06	0.26 ± 0.02**	0.57 ± 0.05	0.46 ± 0.00**
10%	0.75 ± 0.03	0.17 ± 0.02*	0.58 ± 0.02	0.30 ± 0.02*
50%	0.67 ± 0.07	0.15 ± 0.03*	0.51 ± 0.07	0.30 ± 0.07*

Data shown as mean ± standard deviation. Significant difference between CT vs. 0%, 10%, 50%. *vs. CT <0.05, **vs. CT <0.01. CT: Control; HW: Heart weight; RVW: Right ventricle weight; LVSW: Left ventricle septum weight; RVHI: Right ventricular hypertrophy index.

Table 3. Effect of glucose loading on exercise tolerance for heart failure

	Walk distance (m)
CT	900.0 ± 0.0
0%	522.5 ± 102.7**
10%	885.0 ± 30
50%	853.5 ± 67.1

Data shown as mean ± standard deviation. Significant difference between CT vs. 0%, 10%, 50%. *vs. CT <0.05, **vs. CT <0.01. CT: control.

Table 4. Effects of oral glucose intake on heart metabolism in RV in right heart failure model rats

Group	Lactate (mmol/L)	HIF-1α (pg/mL)
CT	0.36 ± 0.05	69.6 ± 0.3
0%	1.35 ± 0.75*	67.9 ± 1.9*
10%	2.28 ± 0.20***	73.7 ± 1.1*
50%	2.31 ± 0.76***	73.4 ± 0.5*

In 10% and 50% groups, Lactate production in RV was increased than CT. HIF-1α in RV of 10 and 50% groups was increased than 0% and CT. Error bar was showed standard error. Statistical significance was calculated by Bonferroni test. The significant level was set at <0.05. *p<0.05, **p<0.01. HIF-1α, hypoxia inducible factor-1 alpha. CT: control.

DISCUSSION

In this study, we examined the effects of glucose loading on myocardial protection against heart failure in rats. Our results revealed that glucose loading suppressed heart failure in an MCT-induced right heart failure rat model. In addition, glucose suppressed the decline in skeletal muscle mass, fat mass, and exercise tolerance. These results suggest that glucose may prolong the prognosis of life and prevent the decline of exercise capacity. These findings indicate that glucose loading in heart failure enhances glucose metabolism and is cardioprotective.

The MCT used in this study has been confirmed to cause pulmonary hypertension and right heart failure when administered at 30–60 mg/kg. The dead point for heart failure by MCT is approximately 20–30 days; therefore, we set the dead point at 21 days[11, 12]. The rats in our study also had right heart failure due to increased lung weight, right heart hypertrophy, and RVHI after the administration of MCT.

Glucose loading on the MCT model has been suggested to suppress fat mass reduction in a glucose concentration-dependent manner. Heart failure cachexia leads to an excessive increase in systemic lipid metabolism, a strong decrease in body fat mass, and a marked expression of weight loss[13]. Since fat mass is strongly correlated with the survival curve, cachexia is associated with shorter survival[1]. In addition, maintenance of fat mass after the onset of heart failure has been reported to improve activities of daily living and quality of life[14]. These findings suggest that the maintenance of fat mass is important in heart failure recovery. In the present study, glucose loading may have prevented the utilization of body fat by promoting glycolytic metabolism.

Regarding the effect of heart failure on skeletal muscle, total skeletal muscle mass was decreased in our study, confirming heart failure-induced sarcopenia. Conversely, total skeletal muscle mass was maintained by glucose loading. Normally, skeletal muscle takes up 70–80% of blood glucose for muscle homeostasis and exercise and uses it for ATP production[15]. In addition, many in vitro experiments using mouse myoblasts have shown that an increase in glucose concentration promotes the proliferation and culture of skeletal muscle cells[16]. These results suggest that glucose loading promotes glucose uptake into skeletal muscle and maintains skeletal muscle mass.

In the present study, a nutritional intervention was conducted with consideration of myocardial metabolism in heart failure. The heart has the highest ATP production and consumption of all organs in the body and utilizes many energy substrates including long-chain fatty acids[17]. In a healthy heart, 70–90% of ATP production is dependent on fatty acid oxidation[18]. Most ATP production is derived from mitochondrial oxidative phosphorylation[19]. However, when the myocardium is ischemic (intracellular hypoxia) due to heart failure, fatty acid metabolism decreases and glucose utilization increases[20]. Our results also confirmed that administration of MCT induced heart failure, increased HIF-1 alpha (a marker of hypoxia), increased lactate, and enhanced the glycolytic system. Recent reports showed that excessive utilization of mitochondrial metabolism in the pathogenesis of heart failure induces higher than normal oxidative stress (ROS) and apoptosis[5]. Furthermore, normalized oxygen administration for acute heart failure can increase myocardial necrosis[21]. Therefore, it is important to promote the glycolytic system rather than mitochondrial metabolism during heart failure.

We investigated the effects of glucose loading on the myocardium in MCT models. Glucose loading promoted the glycolytic system and suppressed myocardial hypertrophy in heart failure models. This suggests that the promotion of glycolytic metabolism may have a protective effect on the myocardium in heart failure.

Based on our results, we suggest that glucose loading enhanced glucose uptake in both skeletal and cardiac muscle and suppressed skeletal muscle maintenance and heart failure. As a result, exercise tolerance was maintained.

The limitation of this study is a very small sample size. In addition, mitochondrial metabolism was not analyzed. In the future, we will analyze mitochondrial metabolism and examine the effects of glucose loading in a heart failure model.

Conflict of interest

There is no conflict of interest to disclose in this study.

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