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Original Article

Effects of intermittent restriction diet and moderate-intensity exercise on the expression of cardiomyocytes in mice with high-glucose loads

[Efecto de la dieta de restricción intermitente y del ejercicio de intensidad moderada en la expresión de los cardiomiocitos de ratones con cargas elevadas de glucosa]

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Abstract

Context: The prevalence of obesity was 8% in 2002 and increased to 11.5% in 2011 in Indonesia. The results of the 2018 Basic Health Research stated that 13.6% of people over the age of 18 were overweight, and 21.8% were obese.

Aims: To analyze the effect of intermittent restriction diet and continuous exercise with moderate intensity on individuals exposed to a high-calorie diet.

Methods: A randomized posttest control group design was used as the research design, with 6 mice in each group as the study subjects. The groups in this study were the control group with a high-calorie diet (CON+), the intermittent restriction diet group (IRD), the moderate-intensity continuous exercise group (MEX), the combined intermittent restriction diet group and the moderate-intensity continuous exercise (HYB) group. The measured variables were cardiomyocyte diameter and brain natriuretic peptide (BNP) expression.

Results: The results of this study were cardiomyocyte diameter CON+ (27.94 ± 5.65 µm), IRD (20.99 ± 11.80 µm), MEX (25.08 ± 9.14 µm), HYB (24.52 ± 5.90 µm) with p=0.578. Expression scores of BNP CON+ (6.00 ± 1.50), IRD (4.67 ± 1.00), MEX (5.42±2.09), HYB (6.27 ± 1.54) with p=0.335. These results showed no significant difference, but the intermittent restriction diet showed the most optimal mean with the lowest mean cardiomyocyte diameter and BNP expression.

Conclusions: There was no effect between the combination of an intermittent restriction diet and moderate-intensity continuous exercise on cardiomyocyte diameter and BNP expression. However, there is a potential that an intermittent restriction diet has the optimal effect in preventing changes in the cardiac structure.

Keywords: cardiomyocyte; diet; exercise; glucose; healthy lifestyle.

Resumen

Contexto: La prevalencia de la obesidad era del 8% en 2002 y aumentó al 11,5% en 2011 en Indonesia. Los resultados de la Investigación Básica de Salud de 2018 afirmaron que el 13,6% de las personas mayores de 18 años tenían sobrepeso y el 21,8% eran obesas.

Objetivos: Analizar el efecto de la dieta de restricción intermitente y el ejercicio continuo con intensidad moderada en individuos expuestos a una dieta alta en calorías.

Métodos: Como diseño de investigación se utilizó un diseño de grupo control postest aleatorizado, con 6 ratones en cada grupo como sujetos de estudio. Los grupos de este estudio fueron el grupo de control con dieta hipercalórica (CON+), el grupo de dieta de restricción intermitente (IRD), el grupo de ejercicio continuo de intensidad moderada (MEX), el grupo de dieta de restricción intermitente combinada y el grupo de ejercicio continuo de intensidad moderada (HYB). Las variables medidas fueron el diámetro de los cardiomiocitos y la expresión del péptido natriurético cerebral (BNP).

Resultados: Los resultados de este estudio fueron diámetro de cardiomiocitos CON+ (27,94 ± 5,65 µm), IRD (20,99 ± 11,80 µm), MEX (25,08 ± 9,14 µm), HYB (24,52 ± 5,90 µm) con p=0,578. Puntuaciones de expresión de BNP CON+ (6,00 ± 1,50), IRD (4,67 ± 1,00), MEX (5,42±2,09), HYB (6,27 ± 1,54) con p=0,335. Estos resultados no mostraron diferencias significativas, pero la dieta de restricción intermitente mostró la media óptima con el diámetro cardiomiocítico medio y la expresión de BNP más bajos.

Conclusiones: No hubo efecto entre la combinación de una dieta de restricción intermitente y el ejercicio continuo de intensidad moderada sobre el diámetro de los cardiomiocitos y la expresión de BNP. Sin embargo, existe la posibilidad de que una dieta de restricción intermitente tenga el efecto más óptimo en la prevención de cambios en la estructura cardiaca.

Palabras Clave: cardiomiocitos; dieta; ejercicio; glucosa; estilo de vida saludable.

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INTRODUCTION

The prevalence of obesity was 8% in 2002 and increased to 11.5% in 2011 in Indonesia (Rachmi et al., 2017). The results of the 2018 Basic Health Research stated that 13.6% of people over the age of 18 were overweight, and 21.8% were obese (Kemenkes, 2018). The prevalence of obesity and overweight is higher in women (15.1%) than men (11.1%) in the world (WHO, 2019). Women (1.6%) have more heart disease and cardiac arrest than men (1.3%) in Indonesia (Kemenkes, 2018). A total of 6,638 women diagnosed with coronary heart disease (CHD) in the world have a normal body mass index (BMI) (27.6%), overweight (35.72%), obese (31.21%) and extremely obese (5.47%) (McTigue et al., 2006). The World Health Organization (WHO) states that 17.9 million people died from cardiovascular disease in 2016, representing 31% of all deaths in the world (WHO, 2017).

Factors that influence the occurrence of cardiovascular disease are hypertension, dyslipidemia, and endothelial dysfunction (Kit et al., 2015), as well as risk factors for metabolic diseases, namely insulin resistance and hyperglycemia (De Jesus, 2011). Lifestyles such as poor diet, lack of physical activity, and smoking can increase the prevalence of hypertension, hyperglycemia, hyperlipidemia, and obesity, which could trigger cardiovascular disease (WHO, 2017).

Cardiac hypertrophy is a sign of cardiac arrest and a strong predictor of cardiovascular disease. The ventricles are also more often hypertrophied than the atria, for example, in left ventricular hypertrophy (LVT), which is also an advanced stage of the disease (Karason et al., 2003). Histological changes in the cardiomyocyte structure of the obese group, namely an increase in interstitial fibrosis compared to the normal weight group in rats (Chen et al., 2014). At physiological concentrations, BNP is a neurohormone that plays a role in body fluid balance and vascular tone, especially secreted by the ventricles of the heart (Tsutamoto and Horie, 2004). Brain natriuretic peptide (BNP) expression increased in the obese group compared to the normal-weight rat group (Chen et al., 2014).

Physical exercise through moderate-intensity swimming done for 20 minutes, 3 times a week can cause the increasing diameter of the heart muscle fibers as an adaptation and homeostasis to the response received (Darsana et al., 2019). Physical exercise has been shown to significantly reduce BNP and N-Terminal pro-brain natriuretic peptide (NT-proBNP) (Smart and Steele, 2010) due to neurohormonal responses during the resting phase (Passino et al., 2006).

The effect of continuous moderate-intensity exercise on cardiomyocyte diameter and BNP expression has been well known. However, the effect of a combination of intermittent restriction diet and moderate-intensity continuous exercise on individuals exposed to a high-calorie diet still becomes an uncovered phenomenon.

Given that uncovered phenomenon, this study continuously took mice exposed to a high-calorie diet for four weeks to analyze the effect of a combination of intermittent restriction diet and moderate-intensity continuous exercise on the cardiomyocyte diameter and BNP expression in their heart muscle.

MATERIAL AND METHODS

Chemicals

Two types of reagents were used in this study. They were hematoxylin-eosin (HE) for staining histology slides of heart muscle tissue and BNP antibody reagent (D-8): sc-271185 Santa-Cruz Bio-Technology, Inc, USA to examine BNP expression through immune histochemistry microscope slides.

Animals

This research was conducted at Universitas Airlangga, Faculty of Veterinary Medicine, Indonesia, from January to February 2020. All procedures for this research have been approved by the Health Research Ethics Committee, Faculty of Medicine, Airlangga University, Surabaya Number 11/EC/KEPK/FKUA/2020. The subjects in this study were 24 mice (*Mus musculus*) strain Balb/c, with the criteria: female sex, body weight ± 20-30 grams, age ± 8 weeks, and no visual and physical defects. Experimental animals were placed in a room with a temperature of 26 ± 2°C and humidity of 50-60%, and the lighting was adjusted to a light-dark cycle with a setting of 12 hours of light and 12 hours of darkness. Before treatment begins, the sample is given a swab test to determine the ovulation period and estrus phase as a starting point for calorie restriction and continuous exercise at moderate intensity.

Study design

The researchers used only a randomized posttest control group as the research design. The study was begun by dividing the mice into four groups randomly, namely positive control (CON+), which was a group with high-calorie diet treatment; Intermittent restriction diet (IRD) was a group with intermittent restriction diet treatment; moderate-intensity exercise (MEX) was the treatment group with a high-calorie diet and moderate-intensity continuous exercise; and a combination of intermittent restriction diet and moderate-intensity exercise or hybrid (HYB) was a group treated with a combination of intermittent restriction diet and moderate-intensity continuous exercise. Furthermore, the mice were acclimatized for a week. The mice were weighed as the initial body weight before treatment and weighed every week to determine the weight of the training load of each mouse. Vaginal swabs of mice were carried out at the beginning to determine the reproductive phase of mice. Before the study, the subjects were in the same condition, namely in the estrus phase (Auta and Hassan, 2016).

Intermittent restriction diet

The intermittent restriction diet in this study was in the form of dietary conditioning given *ad libitum* feed of standard mice and added sonde with D40 solution. Sonde was given at a dose of 3-5% calories (0.013 g BW) or 0.0325 mL/g BW (Herawati, 2018). The frequency of giving a high-calorie diet was three times a week on Tuesdays, Thursdays, and Saturdays at 10 am.

Physical exercise protocol

Physical exercise in the form of moderate-intensity continuous physical exercise in the form of swimming with a loading of 6% of the mice's body weight tied to the base of the tail for a duration of 15 minutes was carried out three times/week (Darsana et al., 2019; Hardjana et al., 2016; Wen et al., 2011) on Mondays, Wednesdays, and Fridays at 15.00 Western Indonesian Time (WIT). Mice swam in a pond with a diameter of 50 cm, a height of 70 cm, and a temperature of about 25°C.

Cardiomyocyte diameter

At the end of the treatment, the animals were anesthetized and sacrificed, and the heart was dissected out. The heart sections were histologically stained with HE and deposited on slides for microscopic observation. The cardiomyocyte diameter began with reading a slide containing a collection of cardiomyocyte cell tissue using an Olympus CX 21 LED (microscope), then an image was taken by photographing it using Optilab Camera Viewer with magnification (400×) in five fields of view and saved using JPEG format, then analyzed (measured and calculated) the number and diameter of cardiomyocytes using the Optilab Image Roaster software application on a computer and the average was taken in each group. The unit of cardiomyocyte diameter was the size of a micrometer (µm) (Darsana et al., 2019).

Brain natriuretic peptide expression

Examination of BNP expression through immune histochemical microscope slide set using BNP antibody reagent (D-8): sc-271185 Santa-Cruz Bio-Technology, Inc, USA was performed. Immune reactive cells that expressed brown color were a binding antigen and BNP antibody. The measurement of immune reactive score (IRS) was carried out using a scoring system, as shown in Table 1, which was multiplied by the results in A by B.

Statistical analysis

Statistical analysis was done by using SPSS software. A normality test was conducted to see the distribution of the data. The homogeneity test and the ANOVA difference test were continued if the data were normally distributed. The Kruskal-Wallis test was performed if the data were not normally distributed. The results were presented as mean ± standard error of the mean (SEM). A significant difference was established if $p<0.05$.

RESULTS

The changes in characteristics of the subjects were observed through the changes of body weight (g), which can be seen in Fig. 1. The lowest weight change in mice was in the combination treatment group with intermittent restriction diet and moderate-intensity continuous exercise (1.17 ± 0.95 g) and the highest in the high-calorie diet treatment group (2.17 ± 1.78 g). From the ANOVA test, $p=0.161$ in the change in body weight of mice was obtained. This showed that there was no significant difference in changes in body weight of mice between the treatment groups (Fig. 2).

Based on the data above, it could be seen that the lowest mean cardiomyocyte diameter of mice was in the intermittent restriction diet treatment group (20.995 ± 4.8170 µm) and the highest in the high-calorie diet treatment group (27.939 ± 2.3046 µm). From the ANOVA test, $p=0.578$ in cardiomyocyte diameter was obtained. It proved that there was no significant difference in the diameter of the cardiomyocytes of mice between the treatment groups (Fig. 3).

Based on the data above, it showed that the lowest mean BNP expression in mice was in the moderate-intensity continuous exercise treatment group (4.7 ± 0.4) and the highest was in the combination treatment group with intermittent restriction diet and moderate-intensity continuous exercise (6.3 ± 0.6). From the ANOVA test, $p=0.335$ in the BNP expression was obtained. This condition proved that there was no significant difference (Figs. 4-5).

Table 1. Semi-quantitative scale of IRS.

A	B
Positive immunoreactive cells	**Color intensity score of immunoreactive cells**
Score 0: 0%	Score 0: no color reaction
Score 1: <10%	Score 1: color intensity low
Score 2: 11-50%	Score 2: color intensity moderate
Score 3: 51-80%	Score 3: color intensity high
Score 4: >80%	Score 4: color intensity very high

Multiply positive immune-reactive cell percentage scores **(A)** with color intensity scores at immune-reactive cells **(B)**. IRS = AxB.

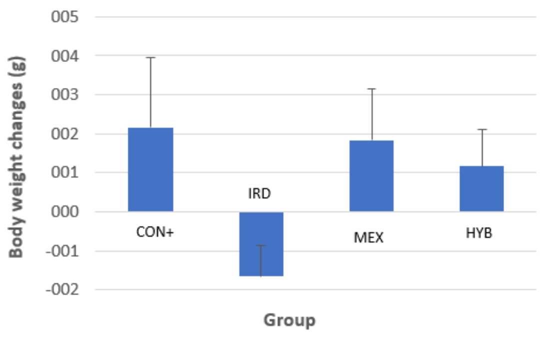

Figure 1. The mean of body weight changes in each group.

The results were expressed as mean ± SEM (n = 24). Statistical analysis used ANOVA. No significant differences among groups (p = 0.161). CON+: Control group with glucose loading; IRD: Intermittent restriction diet; MEX: Moderate-intensity continuous exercise; HYB: Hybrid of intermittent restriction diet and moderate-intensity continuous exercise.

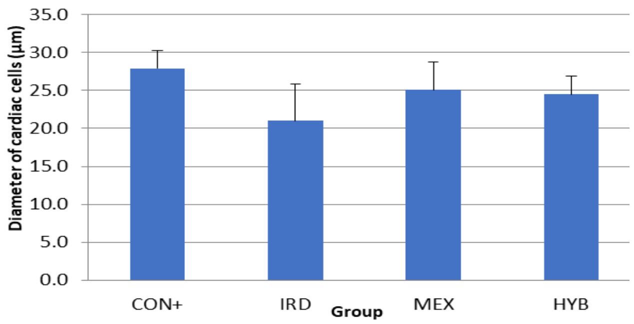

Figure 2. The mean diameter of cardiac cells.

The results were expressed as mean ± SEM (n = 24). Statistical analysis used ANOVA. No significant differences among groups (p = 0.578). CON+: Control group with glucose loading; IRD: Intermittent restriction diet; MEX: Moderate-intensity continuous exercise; HYB: Hybrid of intermittent restriction diet and moderate-intensity continuous exercise).

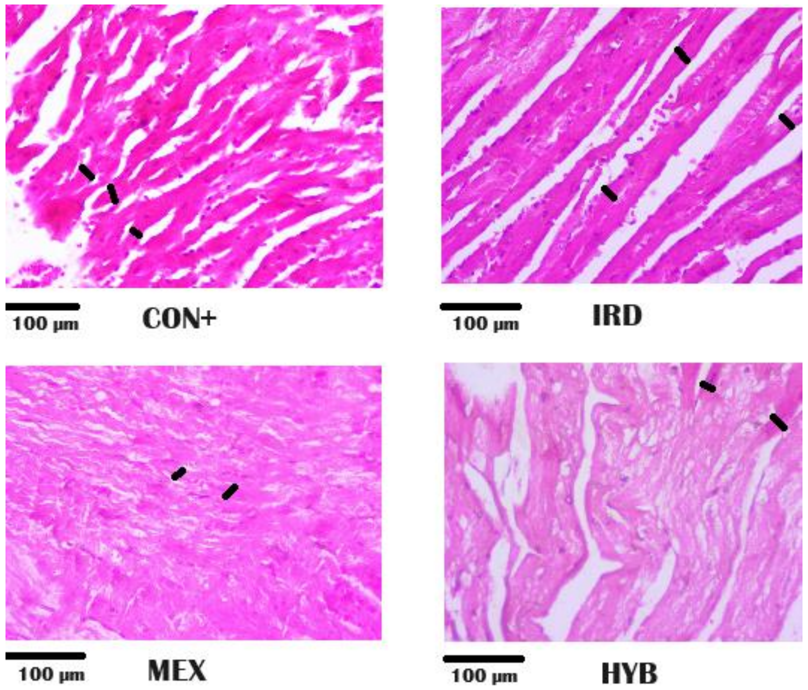

Figure 3. The comparison of heart muscle diameters (arrows).

CON+: Control group with glucose loading; IRD: Intermittent restriction diet; MEX: Moderate-intensity continuous exercise; HYB: Hybrid of intermittent restriction diet and moderate-intensity continuous exercise). Hematoxylin-eosin (HE) staining and 400× magnification.

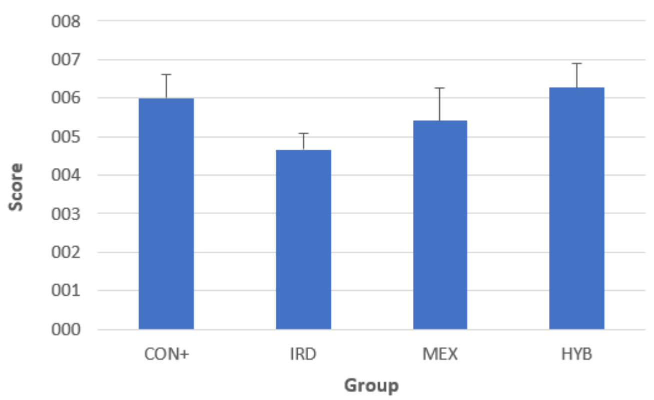

Figure 4. The mean of myocardium BNP score expression.

The results were expressed as mean ± SEM (n = 24). Statistical analyses used ANOVA. No significant differences among groups (p = 0.335). CON+: Control group with glucose loading; IRD: Intermittent restriction diet; MEX: Moderate-intensity continuous exercise; HYB: Hybrid of intermittent restriction diet and moderate-intensity continuous exercise.

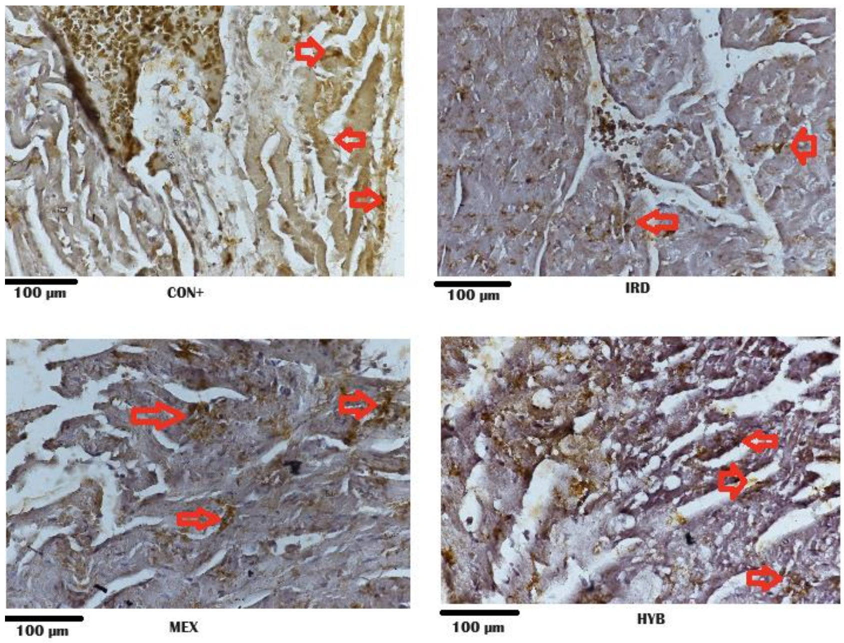

Figure 5. Comparison of BNP expression in cardiac muscle.

BNP expression in cardiac muscle was indicated by the presence of a chromogenic brown color (arrow). CON+: Control group with glucose loading; IRD: Intermittent restriction diet; MEX: Moderate-intensity continuous exercise; HYB: Hybrid of intermittent restriction diet and moderate-intensity continuous exercise). Examination with IHC and 400× magnification.

Table 2. The mean of body weight changes and myocardiums' BNP score expression.

Group	Body weight changes (g)	BNP score	Diameter of cardiac cells (µm)
CON+	2.17 ± 1.78	6.0 ± 0.6	27.939 ± 2.3046
IRD	1.67 ± 0.80	4.7 ± 0.4	20.995 ± 4.8170
MEX	1.83 ± 1.30	5.4 ± 0.9	25.083 ± 3.7303
HYB	1.17 ± 0.95	6.3 ± 0.6	24.522 ± 2.4080

Data was performed in mean ± SE; n = 6 in each group. Statistical analysis used ANOVA. No significant differences among groups (p=0.161). CON+: Control group with glucose loading; IRD: Intermittent restriction diet; MEX: Moderate-intensity continuous exercise; HYB: Hybrid of intermittent restriction diet and moderate-intensity continuous exercise.

The results of the ANOVA test showed that there was no significant difference in cardiomyocyte diameter in the combination treatment group with moderate-intensity continuous exercise and intermittent restriction diet compared to the control group. The control group was one continuous daily high-calorie diet. Although there was no significant difference in the cardiomyocyte diameter test between the two groups, it can be seen in Table 2 and Fig. 1 that the mean cardiomyocyte diameter in the combination treatment group with moderate-intensity continuous exercise and intermittent restriction diet tended to be lower than the control group.

In the previous work conducted by Basilio et al. (2020), old male Wistar rats (aged 30 weeks) who were treated with a combination of intermittent restricted calorie diet and moderate-intensity physical exercise five times per week (ETI) for 12 weeks were compared with the treatment group of moderate-intensity physical exercise five times per week (ET), as well as the intermittent calorie-restricted diet (IF) treatment group. The study showed that the ETI group produced significantly smaller cardiomyocyte diameters compared to the ET and IF groups.

However, in the study conducted by (Okoshi et al., 2019), two-month-old male Wistar rats on an *ad libitum* calorie diet (AL) were compared with an intermittent calorie-restricted diet (IF) for 12 weeks. Cardiac structure and left ventricular function were assessed by transthoracic echocardiogram. The diameter of cardiomyocytes was also measured in this study using the slide method stained with hematoxylin-eosin from left ventricular tissue, then 50 cardiomyocytes were measured in diameter, which is the smallest distance between the edges of myocytes that cross the cell nucleus (nucleus). The results showed that the IF group reduced myocyte hypertrophy and left ventricular dilation (Basilio et al., 2020).

Insulin release was increased in the presence of greater nutrient availability, such as during the postprandial period. A recent study on rats also found improved insulin sensitivity on an intermittent restriction diet. On the other hand, the combination of intermittent restriction diet and physical exercise decreased body adiposity. Physical exercise-induced cardiorespiratory, neural, and hormonal adaptations. In the endocrine context, physical exercise also affects hormone secretion (Basilio et al., 2020). Aerobic exercise for 12 months improved insulin sensitivity, with a 19.4% decrease in the area under the oral glucose tolerance curve in adults (Baumeier et al., 2015).

These results were similar to this study in that in the control group treated with a continuous high-calorie diet, although not significantly different, cardiomyocyte diameter was more enlarged than in the combination group of intermittent restriction diet and moderate-intensity continuous exercise. The combination of intermittent restriction diet and moderate-intensity continuous exercise suppressed the widening of cardiomyocyte diameter through the adiposity suppression pathway (Planer et al., 2012). The results that were not significantly different were probably caused by the adipocyte tissue factor of the subjects not measured in this study.

Moreover, the ANOVA test results showed no significant difference in BNP expression in the combination treatment group with moderate-intensity continuous exercise and intermittent restriction diet compared to the control group. The control group was on a continuous daily high-calorie diet. Although there was no significant difference in the BNP expression test of the two groups, it can be seen in Table 2 that the BNP expression in the combination treatment group of moderate-intensity continuous exercise and intermittent restriction diet tended to be higher than the control group.

The combined effect of metabolic and physiological stress on the cardiac performance of well-trained young adults results in extreme caloric deprivation for four days following moderately intense and prolonged physical activity. This results in changes in left ventricular diastolic function without any effect on left ventricular systolic function and a decrease in BNP expression that correlates with weight loss and decreased sodium levels (Planer et al., 2012).

During conditions of caloric deprivation, myocardial metabolism shifts from glucose to free fatty acid metabolism. It has been shown that in healthy subjects, following three days of a very low-calorie diet resulted in the accumulation of myocardial triglycerides accompanied by diastolic dysfunction (van Der Meer et al., 2007). However, continuous exercise causes right ventricular dysfunction, which is an early sign of exercise-induced cardiac strain (Dávila-Román et al., 1997). Another study stated that continuous exercise did not cause significant changes in right ventricular function or pressure (Planer et al., 2012).

The combination of intermittent restriction diet and moderate-intensity continuous exercise increases BNP expression through the left ventricular metabolic stress pathway, causing impaired left ventricular diastolic function (van Der Meer et al., 2007).

The lack of sample size and supporting evidence literature might be a limitation of this research. Apart from that, several other factors were not examined, such as heart dysfunction, which was also a weakness in this study.

Further research needs to be done to reveal further the long-term effects of more than four weeks and the mechanisms involved.

CONCLUSION

There is no effect of a combination of intermittent restriction diet and moderate-intensity continuous exercise on cardiomyocyte diameter and BNP expression in the heart muscle of subjects with high-calorie intake. However, there is a potential that an intermittent diet has the most optimal effect compared to others in preventing changes in cardiac structure, such as hypertrophy. The underlying mechanism, among others, is through the suppression of body adiposity.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Putri EAC	Vigriawan GE	Setiawan HK	Othman Z	Oktaviano YH	Herawati L
Concepts or ideas	x				x	x
Design	x	x	x			
Definition of intellectual content	x	x			x	x
Literature search			x	x	x	
Experimental studies	x			x	x	x
Data acquisition		x	x			
Data analysis	x	x	x			x
Statistical analysis	x		x			x
Manuscript preparation	x	x	x	x		
Manuscript editing					x	x
Manuscript review	x	x	x	x	x	x

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