The Acute Effect of Fructose on Cardiac Hemodynamic Responses and Infarcted Area in Isolated Rat Heart During Ischemia-Reperfusion

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ABSTRACT

Introduction: This study aimed to investigate the effects of fructose on cardiac hemodynamics and infarct size and the role of the antioxidant mechanism in these effects in isolated rat hearts undergoing ischemiareperfusion.

Patients and Methods: Isolated hearts obtained from female Wistar rats were perfused with Krebs-Henseleit solution containing 12 mM glucose or solution containing 12 mM fructose or 48 mM fructose and underwent lowflow ischemia followed by reperfusion on the Langendorff apparatus. Left ventricular developed pressure (LVDP), timedependent pressure changes (dp/dt max, dp/dt min) and heart rates were recorded at the 1st, 15th and 120th minutes of reperfusion following ischemia, and the percentage of the infarct area and the size of the risk area were determined. At the end of the reperfusion, total oxidant capacity (TOS), malondialdehyde (MDA) and glutathione (GSH) levels were examined in perfusion fluid samples.

Results: Basal dp/dt max values were lower in the high fructose group compared to the glucose group ($p= 0.032$). When the hearts were perfused with 12 mM fructose, a significant increase was observed in the percentage of the ischemic area and risk area compared to equivalent glucose and high fructose ($p< 0.001$ and $p< 0.001$, respectively). MDA, GSH and TOS values were comparable in all groups.

Conclusion: The present study shows that fructose perfusion plays a role in reduced ventricular contractile function relative to glucose in isolated rat hearts. This reduction triggered by fructose appears to be independent of antioxidant mechanisms. Furthermore, fructose perfusion at glucose-equivalent concentration causes a greater increase in infarct area in ischemic hearts, whereas an increase in fructose concentration appears to prevent this effect.

Key Words: Fructose; ischemia; reperfusion; heart

İzole Sıçan Kalbinde İskemi-Reperfüzyon Sırasında Fruktozun Kardiyak Hemodinamik Yanıtlara ve Enfarktüs Alanı Üzerine Akut Etkisi

ÖZET

Giriş: İskemi ve reperfüzyon uygulanan izole kalpte fruktozun kardiyak hemodinami, infarkt alanı büyüklüğü ve antioksidan hasara etkileri tam olarak bilinmemektedir. Çalışmada izole sıçan kalplerinde perfüzyon sıvısında uygulanan iki farklı konsantrasyondaki fruktozun kardiyak hemodinamik parametrelere, enfarktüs boyutuna etkisi ve bu etkilerde antioksidan mekanizmanın rolünün araştırılması amaçlanmıştır.

Hastalar ve Yöntem: Wistar albino türü ve 200-250 g ağırlığında 21 adet dişi sıçan kalbi anesteziyi takiben (100 mg/kg tiyopental, İP) Langendorff düzeneğine yerleştirildi. K grubunda kalpler 12 mM glukoz içeren Krebs-Henseleit (K/H) solüsyonuyla, F grubundaki kalpler glukoza eş değer 12 mM fruktoz ve YF grubundaki kalpler 48 mM yüksek fruktoz ile hazırlanmış solüsyonlarla deney boyunca perfüze edildi. Tüm gruplara 30 dk düşük akımlı iskemi (0.3 mL/dk) ve 120 dk reperfüzyon uygulandı. İnfarkt alan yüzdesi ve risk alanı boyutunu belirlemek için bilgisayarlı planimetri yöntemi kullanıldı. İskemi sonrası reperfüzyonun birinci, beşinci ve 120. dakikalarında sol ventrikül gelişim basıncı (SVGB), zamana bağlı basınç değişim değerleri (dp/dt maks, dp/dt min) ve kalp hızları kaydedildi. Reperfüzyonun sonunda perfüzyon sıvısı örneklerinde total oksidan kapasitesi (TOS), malondialdehit (MDA) ve glutatyon (GSH) düzeyleri incelendi. İstatistiksel karşılaştırmalarda tek yönlü varyans analizi, Kruskal Wallis testi ve Friedman testi kullanıldı.

Bulgular: İskemi öncesinde dp/dt maks değerleri, YF grubunda K grubuna göre anlamlı derecede düşük bulundu ($p= 0.032$). Kalpler 12 mM uygulanan fruktozla perfüze edildiğinde iskemik alan yüzdesi ve risk alanı değerlerinde eş değer düzeydeki glukoz ve yüksek fruktoza göre anlamlı artış görüldü (sırasıyla, $p< 0.001$, $p< 0.001$). MDA, GSH ve TOS değerleri tüm gruplarda benzerdi.

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Sonuç: Bu çalışma, izole sıçan kalbinde fruktoz perfüzyonun, glukoza göre ventrikül kasılma fonksiyonunu azaltıcı rol oynadığını göstermektedir. Fruktoza bağlı oluşan bu azalma, antioksidan mekanizmalardan bağımsız gibi görünmektedir. Ayrıca, glukoza eş değer konsatrasyonda fruktoz perfüzyonu, iskemik kalplerde infakt alanının daha fazla artışına sebep olmakta, fruktoz konsantrasyonundaki artış ise bu durumu önleyici gibi görünmektedir.

Anahtar Kelimeler: Fruktoz; iskemi; reperfüzyon; kalp

INTRODUCTION

Western-style diets of modern life and the widespread use of added sugars in the food industry have substantially increased the intake of fructose ($C_6H_{12}O_6$) in daily life. While approximately 1620 grams of fructose per day used to come from natural sources such as fruits, vegetables and honey in the past, the increasing consumption and availability of industrial food products has raised this amount up to 80150 g/day through the last fifty years[1]. It is suggested that the increase in fructose consumption is alarming and is in parallel with the increased prevalence of metabolic disorders (insulin resistance, metabolic syndrome, type 2 diabetes) and cardiovascular disease[2]. Although there has been major progress in cardiovascular diagnostics and therapeutics, myocardial infarction (MI) still remains a significant morbidity[3]. In this regard, cardiac infarction size is considered an important determinant of post-MI mortality[4]. Restoration of blood flow in the ischemic myocardium results in ischemia and/or reperfusion (I/R) injury. The length of ischemia is one of the primary factors associated with the recovery of cardiac function[5]. In this context, the resulting outcome is termed as cardiac muscle necrosis. For over 30 years, coronary reperfusion therapy has been used to manage myocardial infarction[5]. However, reperfusion itself following prolonged ischemia may lead to I/R injury. Clinical manifestations of such damage include angina, myocardial necrosis, arrhythmia, myocardial stunning, and endothelial dysfunction[6]. Although adenosine triphosphate (ATP) production in cardiomyocytes occurs through a mechanism that relies on fatty acid oxidation, ATP generated by means of glycolysis is also important[7]. Cardiac tissue is insulin-sensitive and dependent on glycolysis[7]. However, when glucose metabolism becomes insufficient or completely suppressed, fructose continues to be used in the glycolysis pathway. Cellular fructose intake is mediated by insulin-independent transporters. In this setting, the myocardium may be sensitive to the detrimental consequences of prolonged fructose intake[7,8].

Although numerous rodent studies have reported that a fructose-rich diet increases blood pressure[9], a great many studies investigating acute fructose ingestion in humans have not indicated increased sympathetic system activity, which is responsible for increased blood pressure[10]. There is no clear evidence from epidemiological studies linking fructose levels in common diets to risk factors for cardiovascular disease. There is only a limited number of experimental studies on this subject matter, and they have reported conflicting results. Some of the studies conducted to date have demonstrated harmful effects of fructose in the damage of myocardial reperfusion[11], while some others have shown a protective role[12,13]. In another study, we observed that fructose had a positive effect on the restoration of left ventricular contractile function after low-flow ischemia when a standard diet was compared to a high-fructose diet despite without any difference in the extent of myocardial infarction. Similar results were obtained in rats fed with fructose and glucose[14]. In addition, oxidative-destructive effects of dietary fructose intake, which suppress antioxidant defensive system and increase the free radical generation, have been demonstrated in rats[15]. In order to better understand the conflicting results reported in earlier studies and the acute cardiac effects of elevated fructose levels during ischemia-reperfusion, the present study aimed to investigate the effects of fructose on cardiac hemodynamic parameters, infarct size and oxidative changes when administered at two different concentrations, i.e. normal and high concentration in perfusion fluid to isolated rat hearts as well as comparing these effects against a control group administered with glucose.

PATIENTS and METHODS

Study Design

This study used 21 female Wistar albino rats weighing 200-250 g and raised under standard conditions (room temperature: 23 ± 1°C, humidity: 60%, 12/12 hours light/dark rhythm) at the Experimental Animals Unit of Trakya University. Rats were stratified into three groups as control (C), fructose (F), and high fructose (HF).

How the Krebs-Henseleit solution was prepared

Krebs-Henseleit (KH) solution was freshly prepared prior to each experiment. The solution (in mM) consisted of sodium chloride (NaCl= 118.5), sodium bicarbonate ($NaHCO_3$= 25), potassium chloride (KCl= 4.8), magnesium sulfate ($MgSO_4$= 1.2), D-glucose ($C_6H_{12}O_6$= 12), potassium dihydrogen phosphate (KH_2PO_4= 1.2), and calcium chloride ($CaCl_2$= 1.7). The hearts included in the control (C) group underwent perfusion with KH solution throughout the experiment. In the study, two different concentrations were used to investigate the cardiac effects of fructose. Group F received fructose instead of the glucose in the KH solution at the same amount of (12 mM).

Group HF received fructose instead of the glucose in the KH solution at a greater amount of (48 mM)[5]. All components were dissolved in distilled water. When adding components, calcium chloride was added after the others in order to prevent precipitation in the perfusion fluid.

Experiment protocol and hemodynamic measurements in isolated heart

All rats were administered 500 U/kg heparin (500 IU/kg: Nevparin Vial, Mustafa Nevzat İlaç Sanayi A.Ş., İstanbul, Türkiye) to prevent coagulation and 100 mg/kg thiopental (Ulagay A.Ş., İstanbul, Türkiye) for anesthesia by intraperitoneal injection[14]. Once anesthesia was induced, the hearts were swiftly excised, placed in Langendorff apparatus and perfused with KH solution previously equilibrated at 37ºC as 95% O_2/5% CO_2 (pH= 7.4). With the hearts placed in the apparatus, a balloon was inserted in the left ventricle to measure hemodynamic parameters.

Left ventricular developed pressure (LVDP= LV systolic pressure – LV diastolic pressure), time-dependent maximum contraction and relaxation values (dp/dt max, dp/dt min), aortic perfusion pressure and heart rate were recorded continuously in the hearts placed in Langendorff apparatus. For all isolated hearts, a 15-minute equilibration period followed by basal perfusion was performed at 15 minutes before ischemia. Basal perfusion was followed by 30 minutes of low-flow ischemia (0.3 mL/min) and 120 minutes of reperfusion (Figure 1)[5].

Evaluation of oxidative parameters

Total oxidant status (TOS), malondialdehyde (MDA) and glutathione (GSH) levels were measured to evaluate the oxidative state in the perfusion fluid collected at 120 minutes of reperfusion. TOS level was determined in line with the protocol recommended by the manufacturer using an ELISA kit (Rel Assay Diagnostic, Türkiye). Concentrations were measured with a spectrophotometer (Shimadzu UV-1700A-Japan) at 412 nm, and data were expressed in mmol H_2O_2 Eq/L[16]. MDA concentration in plasma, an indicator of lipid peroxidation, was analyzed according to the method described by Ohkawa, H et al.[17] using substances that react with thiobarbituric acid. These concentrations were measured spectrophotometrically at 512 nm, and data were expressed in mmol/L. After manual preparation, GSH values were determined by the method described by Ellman, GL et al[18]. GSH concentration was measured spectrophotometrically at 412 nm and the findings were expressed in ng/L.

Measuring the infarct area

After 120 minutes of reperfusion, all isolated hearts were wrapped in cling film and frozen at 20°C. Subsequently, left ventricular tissues were sliced into cross-sections of 12 mm thickness. To identify ischemic areas, these sections were incubated at 37°C in phosphate buffer containing 1% tetrazolium at pH= 7.4 for 15-20 minutes. Fixation was performed in 10% formalin solution. Following the staining process, the sections were dried using filter paper and transferred to a thin glass plate at a distance of 2 mm from each other. A second glass plate was placed over the sections and compressed with two clamps. Necrotic zone margins (tetrazoliumnegative tissue) and the risk zone were drawn on a transparent acetate placed on the glass. Mean of the risk zone/total area percentage (%) and risk area (mm^2) were calculated. All sections obtained from the heart slices were photographed. Necrotic areas were calculated using the computerized planimetric method[19].

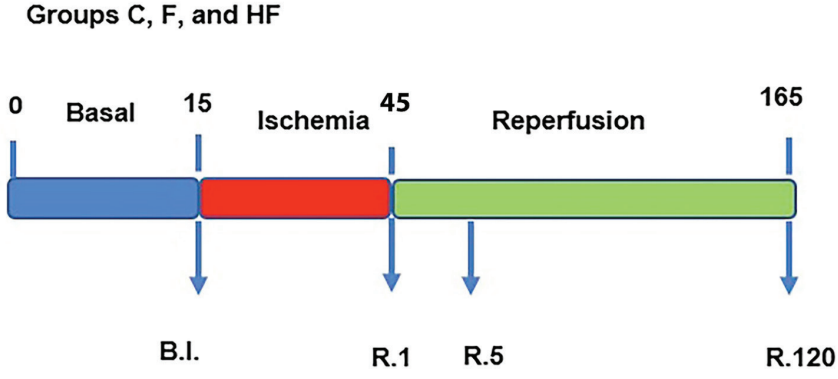

Figure 1. Applied ischemia reperfusion protocol: Fifteen minutes of perfusion, 30 minutes of low-flow ischemia (0.3 mL/min) and 120 minutes of reperfusion were applied to all hearts with appropriate perfusion fluid. The control (C) group was perfused with normal KH solution, the fructose group (F) was perfused with 12 mM fructose instead of glucose, and the hearts in the high fructose (HF) group were perfused with high fructose solutions containing 48 mM fructose instead of glucose. Minute 15 of the experiment, BI (basal measurement before ischemia), minute one (first minute of R1 Reperfusion), minute five (fifth minute of R5 Reperfusion), and minute 120 (120^{th} minute of R120 Reperfusion).

C: Control, F: Fructose, HF: High fructose.

Statistical Analysis

Normality assumption was checked using Shapiro-Wilk's test. Independent groups were compared using one-way ANOVA and Kruskall-Wallis test depending on normality. Dependent groups were compared using Friedman test. Pairwise comparisons were performed using Tukey and Dunn tests. A p-value less than 0.05 was considered statistically significant. All analyzes were conducted using TURCOSA (Turcosa Analytics Ltd Co, Türkiye, www.turcosa.com.tr) statistical software.

RESULTS

Evaluation of hemodynamic parameters during ischemia-reperfusion

In the present study, basal LVDP values before ischemia were similar in groups F and HF compared to group C (p= 0.077). No significant difference was observed between the groups in terms of LVDP levels during 120 minutes of reperfusion following 30 minutes of low-flow ischemia. However, the dp/dt max pressure change values recorded before ischemia were significantly lower in group HF compared to group C (p= 0.037). Before ischemia, dp/dt min and heart rate values at the measurement time points, R1, R5, and R120 during reperfusion were comparable across the three groups (Table 1).

Evaluation of oxidative state

Total oxidant status (TOS), malondialdehyde (MDA) and glutathione (GSH), which were explored to evaluate the oxidative state in perfusion fluid collected at 120 minutes of reperfusion, were not significantly different across the groups (p= 0.959, p= 0.574, p= 0.456, respectively) (Table 2).

Table 1. Hemodynamic values of the groups after ischemia-reperfusion

	C (n= 7)		F (n= 7)	HF (n= 7)	p
LVDP (mmHg)	**BI**	84 (66/102)	47 (14/64)	25 (3/60)	0.077
	R1	75 (19/98)	44 (11/109)	23 (6/116)	0.779
	R5	66 (28/105)	12 (1/50)	16 (5/75)	0.219
	R120	28 (22/30)	17 (1/48)	8 (6/18)	0.390
dp/dt max (mmHg)	**BI**	1293 (738/1642)	535 (141/-1002)	215 (-169/-486)*	0.037
	R1	1000 (192/1550)	175 (-276/-975)	-66 (-196/-1544)	0.309
	R5	882 (401/1957)	-127(-407/-506)	-76 (-208/-1004)	0.167
	R120	539 (274/621)	82 (-138/-408)	16 (-138/-154)	0.050
dp/dt min (mmHg)	**BI**	-1326 (-1660/ -990)	-711 (-1716/-261)	-465 (-691/-228)	0.117
	R1	-859 (-1057/ -207)	-995 (-1304/-239)	-447 (-1396/-329)	0.874
	R5	-988 (-1599/-391)	-567 (-1242/-131)	-281 (-431/-1179)	0.246
	R120	-418 (-426/-364)	-483 (-981/-123)	-221 (-553/-113)	0.584
HR (beat/min)	**BI**	228 (219/249)	216 (197/225)	231 (142/250)	0.551
	R1	166 (92/ 200)	113 (85/147)	113 (48/251)	0.694
	R5	253 (243/328)	191 (169/203)	92 (87/298)	0.116
	R120	224 (208/252)	140 (99/169)	141 (74/224)	0.077

(LVDP: Left ventricular developed pressure, time-dependent maximum contraction and relaxation values (dp/dt max, dp/dt min), HR: Heart rate (beat/minute), BI: Before ischemia, R1: First minute of reperfusion, R5: Fifth minute of reperfusion, R120: 120th minute of reperfusion, C: Control; F: Fructose; HF: High fructose.
(*p< 0.05 compared to the control group). Values are given as median (min/max).

Table 2. Oxidative parameters in the perfusion fluid

	C	F	HF	p
TOS (μmol H_2O_2 Eq/L)	2.41 ± 0.08	2.46 ± 0.08	2.38 ± 0.04	0.959
MDA (mmol/L)	7.25 ± 0.42	8.00 ± 0.54	8.10 ± 0.75	0.574
GSH (ng/L)	777.46 ± 55.39	724.10 ± 32.20	697.47 ± 44.57	0.456

TOS: Total oxidant status; MDA: Malondialdehyde; GSH: Glutathione; C: control; F: Fructose; HF: High fructose. N=7 in each group. Values are given as mean±SEM.

Table 3. Effects of fructose administration (12 and 48 mM) on myocardial infarct size in isolated rat hearts after 30 minutes of low-flow (0.3 mL/min) ischemia followed by 120 minutes of reperfusion

	C (n= 7)	F (n= 7)	HF (n= 7)	p
Infarcted volume $(mm)^3$	72.73 ± 5.43	108.63 ± 5.70***, #	80.50 ± 4.28	<0.001
Infarct size (%)	36.36 ± 2.68	54.33 ± 2.84***, #	40.275 ± 2.14	<0.001

Data are presented as mean ± SEM.
*** p< 0.001 compared to the control group.
#p< 0.01 compared to the HF group.
C: Control; F: Fructose; HF: High fructose.

Evaluation of infarct field

When the effects of fructose on infarct size as percentage and the infarct area in isolated rat hearts were examined, there was a statistically significant difference in mean infarcted myocardial volume (mm^3) between two different doses (12 and 48 mM) of fructose administered after 120 minutes of reperfusion following 30 minutes of low-flow (0.3 mL/min) ischemia (Table 3). The difference resulted from the fact that group F had higher results than both group C and group HF (p< 0.001 and p< 0.001, respectively). When the size of the infarct area was compared between the groups as the mean risk zone/total area percentage, a significant difference was found between the groups. This difference was driven by the higher percentage of infarct area in group F compared to group C and group HF (Table 3) and (Figure 2).

DISCUSSION

The increasing fructose consumption in recent years has been recognized as one of the factors causing cardiometabolic risk associated with obesity, diabetes and metabolic syndrome[20]. Acute MI, one of the leading cardiometabolic risks, is an important cause of mortality in the developed world[21].

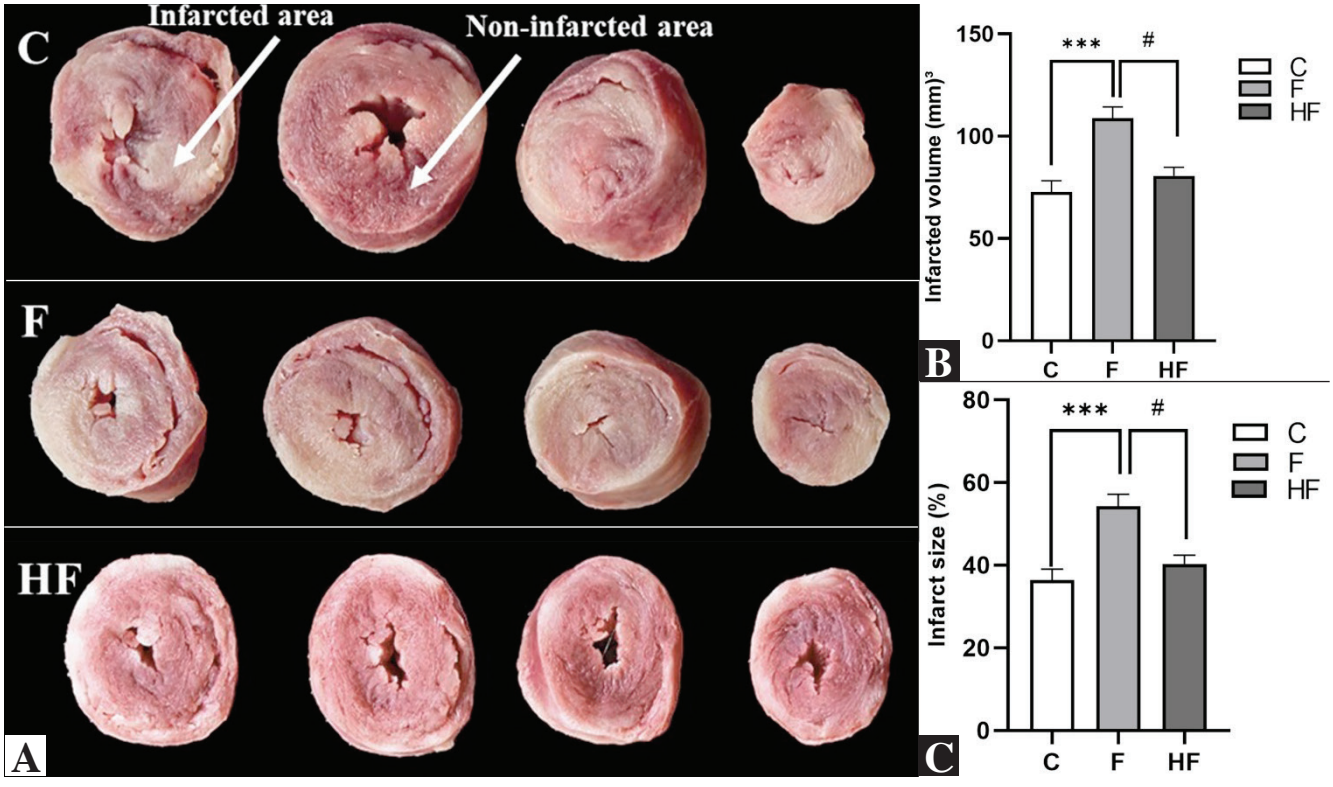

Figure 2. The effects caused by fructose administration on myocardial infarct volume and size in rat hearts after 30 minutes of low flow (0.3 mL/min) ischemia followed by 120 minutes of reperfusion. A: Representative heart sections from groups C, F and HF stained with tetrazolium chloride. Infarcted (dead-IA) and non-infarcted (live-N-IA) areas appear white (pale) and brick red, respectively. B: Infarcted volume (mm^3). C: Infarct size (%).

C: Control, F: Fructose (12 mM) and HF: High fructose (48 mM), KH: Krebs Henseleit solution.

(***: p< 0.001 compared to the control group, #: p< 0.001 compared to group HF).

The reperfusion period following ischemia may have a further lethal effect compared to the effect of ischemia, owing to calcium overload and generation of destructive free radicals. Currently, there are conflicting approaches to the effect of dietary fructose intake on cardiac ischemia. One of these approaches supports the notion that fructose has harmful effects in the damage caused by myocardial reperfusion[11], while the other supports that it may play a protective role in this setting[12].

In the present study, we aimed to investigate the effects caused by fructose at different concentrations on cardiac hemodynamic parameters and infarct size after low-flow I/R in isolated rat hearts. We used two different (i.e. normal and high) concentrations of fructose instead of the glucose administered in the KH solution and evaluated the effects. Our findings showed that high-concentration fructose reduced ventricular contractile function when administered under normal-flow perfusion conditions. We found a statistically significant decrease in dp/dt max levels in group HF (p= 0.032; Table 1). Supporting these findings, we observed that LVDP decreased to a level close to half when normal level of glucose-flow perfusion was applied for 15 minutes; however, the difference was not statistically significant (p= 0.077). Furthermore, the decrease in the dp/dt max level seen across the groups at the end of the reperfusion was close to a statistically significant difference. In addition, according to the findings of dp/dt min levels in this study, fructose did not cause a significant change on ventricular relaxation function.

In this study, we also determined that the administration of fructose at a concentration equivalent to glucose significantly increased the size and volume of the ischemic area. Our results suggest that fructose at a concentration equivalent to the glucose concentration used in the KH solution may not provide sufficient ATP for the normal functioning of the heart, leading to further necrosis and apoptosis of cardiomyocytes during ischemia followed by reperfusion. The findings of this study indicate that glucose has a more effective function than fructose as a source of carbohydrates in the nutrition of the heart muscle.

The effect of fructose on the ischemic area has not been fully elucidated. Contrary to our findings, a previous study, where three different concentrations of fructose have been administered instead of glucose, has reported that fructose reduces the percentage and size of the infarct area at all concentrations[5]. However, the same study has also shown that replacing the glucose used in the KH solution with fructose does not result in a significantly reduced number, shorter duration or less frequent occurrence of hazardous reperfusion arrhythmias, e.g. ventricular tachycardia and fibrillation[5]. Findings of an earlier study have indicated that preconditioning with fructose reduces the size of the infarct area as well as the arrhythmias triggered by ischemia and reperfusion[22]. The findings of our study showed that fructose reduced the percentage and size of the infarct area; however, with the limitation that we could not demonstrate a smaller number, shorter duration or reduced frequency of hazardous reperfusion arrhythmias.

Fructose metabolism is different from glucose metabolism, and the effects of fructose occur by means of an insulin-independent mechanism. Long-term dietary fructose intake may be detrimental for the myocardium as the heart is insulin-responsive[7]. A study in rats fed with a 66% fructose-enriched diet for four weeks has demonstrated decreased tolerance to local ischemia-reperfusion and an increase in infarct size[11]. However, the study by Jordan and colleagues, using a short-term (three-day) fructose-rich diet in rats, have reported that fructose has protective effects against myocardial ischemia/reperfusion injury[12] and as a possible cause of this situation, it has been suggested that dietary fructose intake may directly increase glycogen stores, leading to a higher level of anaerobic energy stored in the myocardium[12]. The data obtained in our study revealed an increase in ischemic area volume and percentage with low fructose concentration; however, the finding that infarct size in the high fructose group was similar to the control group supports this notion only partially. In another study, we have shown that high levels of dietary fructose intake for four weeks can produce favorable hemodynamic effects on left ventricular function without changing the size of myocardial infarct area during reperfusion after low-flow ischemia (0.3 mL/min) in hearts perfused with glucose-containing KH solution[14]. In terms of the factors affecting this finding, a previous study has reported that dietary fructose intake may also facilitate oxidative damage and has harmful effects due to a decrease in antioxidant defense as well as increased production of free radicals[23]. In the present study, TOS, MDA and GSH, which reflect the oxidative state in low-flow ischemia and reperfusion, were found to be similar in all groups.

CONCLUSION

In conclusion, the present study focused on the effects of fructose at different concentrations on cardiac hemodynamic parameters and infarct size after low-flow I/R in isolated rat hearts. At the two concentrations tested in the present study, fructose decreased ventricular contractile function both before low-flow ischemia and at the end of reperfusion while only low-concentration fructose administration increased the ischemic area. These results suggest that fructose at a concentration equivalent to that of glucose may not provide sufficient

ATP for the normal functioning of the heart, leading to necrosis and apoptosis of cardiomyocytes during ischemia/reperfusion. Further studies to elucidate the relevant mechanism may shed light on the acute effects caused by fructose in cardiac I/R.

Ethics Committee Approval: The approval for this study was obtained from Trakya University Local Ethics Committee of Animal Experiments (Decision no: 2021.05.05, Date: 28.05.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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