

# Effects of Chronic Food Restriction and Exercise Training on the Recovery of Cardiac Function Following Ischemia

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**Clinical and experimental data suggest that exercise training (ET) and food restriction (FR) improve cardiovascular function. However, the effects of long-term FR or FR in combination with ET on the recovery of cardiac function following ischemia have not been determined. Male Wistar rats were assigned to ad libitum-fed, FR, ad libitum-exercise, and FR-exercise groups. Mechanical function of isolated working hearts was assessed in response to increases in afterload resistance and following global no-flow ischemia. At low workload, there was a significant FR effect on aortic flow as well as an interaction between FR and ET on systolic pressure. These effects remained when hearts were subjected to increases in aortic afterload resistance. During reperfusion of ischemic hearts, there was a significant FR effect on aortic flow and systolic pressure and a significant ET effect on diastolic pressure. An interaction between FR and ET on heart rate was also seen during reperfusion. In terms of percent recovery of heart function following ischemia, FR continued to affect aortic flow, and we observed an interaction between FR and ET on aortic flow. Our results clearly indicate that the myocardium from the FR animal or the FR, exercise-trained rat is more resistant to ischemia.**

FOOD restriction (FR) has elicited a great deal of interest because it increases life span and delays the development and severity of age-related diseases (1–3). FR retards the development of cardiomyopathies and, in some cases, prevents the physiological decline of myocardial performance that is normally associated with aging (4,5). The anti-ischemic effects of FR have also been reported, and, as expected, hearts of FR animals are more resistant to anoxic injury (6).

The impact of exercise training (ET) on myocardial performance is also of interest, and the benefits of training on preventing ischemic damage are well documented. Regular exercise reduces the prevalence of heart disease, decreases the development of heart complications, and can prevent the development of non-insulin-dependent diabetes (7–9). ET improves myocardial tolerance to ischemia in various animal models by rapidly restoring high-energy phosphates and by improving hemodynamic function and coronary flow (10,11). The beneficial effects of FR and ET can be explained by similar mechanisms of action. Improved insulin sensitivity (12), enhanced adrenergic sensitivity (13,14), up-regulation of glucose transporter proteins (15,16), and a favorable redistribution of blood lipids have been reported following food restriction as well as ET (17).

To date, few studies have investigated the effects of long-term FR or of ET combined with FR on myocardial performance and recovery of function following ischemia. Although earlier studies have shown that FR increases anoxic tolerance in hearts (6), further studies are needed to confirm this beneficial effect using a model of global ischemia. Further, the effects of FR on recovery following anoxia were

determined in hearts perfused in the absence of fatty acids (6). Blood levels of fatty acids are elevated in patients in the clinical setting of reperfusion and are known to potentiate ischemic injury secondary to an accumulation of intermediates of fatty acid oxidation and by inhibition of glucose metabolism (18,19).

In the present study we examined the effects of FR and ET on the recovery of heart function following ischemia. We showed that FR, or FR combined with ET, improves heart function, particularly following ischemic insult.

## METHODS

### Animals

Male Wistar rats were used in this study. Rats were assigned to four groups: ad libitum-fed (AL), ad libitum-exercise (ALE), FR, and FR-exercise (FRE). Rats were individually housed in standard plastic cages and kept in a holding room on a 12-hour light/dark cycle. The AL and ALE rats were allowed free access to food. Rats in FR conditions were also maintained on ad libitum feed until their body weight reached 400 g. The amount of food provided daily was then reduced to maintain a target weight of  $335 \pm 10$  g. This was achieved by gradually reducing food intake to 45% of the amount consumed by the AL animals. Restricted calorie intake was maintained for a period of 8 months. ET, as described below, was initiated at the onset of weight reduction. All animals used in this study were cared for according to the recommendations in the Canadian Council on Animal Care's Guide to the Care and Use of Experimental Animals.

### *Running Regimen*

Rats in the exercise groups ran in standard activity wheels (Wahmann and Lafayette Instruments Model 86041, Lafayette, IN) that were 35.5 cm in diameter. A microswitch attached to the wheel frame recorded wheel revolutions. Wheels were located in soundproof shells equipped with fans to provide ventilation and to mask extraneous noise. Retractable levers (Med Associates ENV-112, St. Albans, VT) were mounted at the openings of wheels. The levers extended 1.8 cm into the chamber through an opening (7 cm × 9 cm) in the center at the base of the wheel frame. A solenoid-operated brake was attached at the base of the wheel. When the solenoid was operated, a rubber tip attached to a metal shaft contacted the outer rim of the wheel and brought the wheel to an immediate stop. Control of experimental events and data recording were handled by Borland's Turbo Pascal programs on IBM personal computers interfaced to the wheel through the parallel port.

FR rats in the exercise groups were trained under conditions that generated high rates of running. The opportunity to run in a wheel was restricted to 30-second intervals. To obtain these brief opportunities to run, the animals had to press a lever. Initially the animals were given the opportunity to run in a wheel for 30 minutes each day for a period of 10 days. Following this period, we used sucrose reinforcement in standard operant conditioning chambers to train the animals to press a lever for the opportunity to run. Each lever press produced 0.1 ml of a 15% sucrose solution. When rats reliably pressed the lever, reinforcement was shifted from a fixed-ratio schedule to a variable-ratio schedule. This schedule remained in effect for approximately four sessions, with each session terminating when 50 sucrose reinforcers were obtained. After four sessions on the variable-ratio schedule, sessions in the operant conditioning chamber were discontinued. During this period of lever training, the rats continued to run in the wheels for 30 minutes each day in addition to the sessions in the operant conditioning chambers. At this point, the retractable lever in each wheel chamber was extended during the wheel-running sessions, and the opportunity to run for 60 seconds was made contingent upon a single lever press. When the reinforcement requirement was met, the lever would retract and the brake would release, leaving the wheel free to turn for 60 seconds. Once 60 seconds had elapsed, the reinforcement period was terminated by applying the brake and extending the lever. Each session consisted of 30 opportunities to run. The schedule of reinforcement was changed in the following sequence: fixed ratio 1, variable ratio 3, variable ratio 5, variable ratio 9, and variable ratio 15. Subjects remained on each schedule for four sessions before advancing to the next schedule. Following this training regime, sessions were conducted daily over a period of 8 months. Each session consisted of fifty-two 30-second opportunities to run, for a total of 26 minutes of running time. Running rates for these animals average about 30 revolutions for every minute of opportunity to run, which translates into approximately 1800 revolutions per hour.

AL rats had continuous access to rat chow. After rats in the ALE group attained a body weight of 400 g, they were given the opportunity to run in a running wheel for 60 minutes each day. Daily sessions were conducted over an 8-month period.

Running rates in the ALE group were low at approximately 60 revolutions per hour, and for this reason the running regimen was considered voluntary. Rats in the ALE group did not receive the same training as rats in the FRE group because motivation to run in AL rats was insufficient to train the animals to respond for the opportunity to run as a reward.

### *Ischemic Heart Perfusions*

Following FR and ET protocols, animals were anesthetized with sodium pentobarbital. Their hearts were quickly excised, placed in ice-cold buffer, and immediately perfused in the Langendorff mode via the aorta with Krebs-Henseleit buffer containing 11 mM glucose and 2.5 mM  $\text{Ca}^{2+}$  (pH 7.4, gassed with 95%  $\text{O}_2$ -5%  $\text{CO}_2$ ). During this perfusion, the hearts were trimmed of excess tissue and the openings of the left atria were cannulated. Hearts were then switched to the working mode and perfused with Krebs-Henseleit buffer consisting of 11 mM glucose and 1.2 mM palmitate prebound to 3% bovine serum albumin. On the basis of the working mode model, the perfusate enters the heart via this cannulated left atrium, where it is subsequently ejected from the left ventricle through the cannulated aorta. The ejected perfusate enters a compliance chamber and is pumped by the heart against a chosen aortic overflow height. After reaching this height, perfusate overflows back into the perfusion reservoir where it is then recirculated through an oxygenator with a large inner surface area exposed to 95%  $\text{O}_2$ -5%  $\text{CO}_2$ . After oxygenation, the perfusate is delivered to the cannulated left atrium where it enters the left ventricle and is ejected through the aorta.

Hearts were perfused at a constant left atrial filling pressure of 11.5 mm Hg with variable aortic afterload resistances. Following the initial Langendorff perfusion, hearts were perfused at an afterload resistance of 60 mm Hg for 5 minutes. The aortic afterload resistance was then increased to 90 mm Hg and maintained for another 5 minutes. Thereafter, the afterload resistance was reduced to 75 mm Hg while heart function was monitored as baseline pre-ischemic function.

Following a 5-minute period at this afterload resistance, hearts were subjected to 25-minutes of global no-flow ischemia. This was achieved by clamping off both the aortic outflow and left atrial inflow lines, which prevented perfusion of the coronary arteries. Following global ischemia, aortic outflow and left atrial inflow were restored, and hearts were reperfused for 15 minutes. Heart function, measured as heart rate and pressure development, was recorded throughout the normoxic perfusion and at the end of reperfusion using a Harvard research grade pressure transducer in the aortic line interfaced to a flatbed chart recording system (Barnstead, Model 2000, Dubuque, IA). Function was recorded during normoxic and reperfusion conditions at 5-minute intervals over 30 seconds at a chart speed set at 1 cm/s. Aortic flow was measured by time collection of perfusate in the aortic afterload overflow line. Water-jacketed chambers kept the temperature of the buffer at 37°C throughout the perfusion.

### *Measurement of Plasma Metabolites*

Following excision of rat hearts, blood that pooled in the chest cavity was collected in chilled tubes containing hep-

arin and immediately centrifuged. The plasma was collected and later analyzed for cholesterol and triglycerides using commercially available kits from Sigma Diagnostics, Oakville, Ontario, Canada.

### Statistical Analysis

Statistical significance for comparisons among groups was determined using a two-way factorial analysis of variance. A two-way analysis was selected to determine whether significant ET or FR effects were present. This method can also establish if there is an interaction between FR and ET. A value of  $p < .05$  was considered significant. All data are reported as mean  $\pm$  SE.

### RESULTS

The physical characteristics of the animals are presented in Table 1. Significant effects of these variables on plasma lipids were observed, reflecting FR and ET. In fact, there was a significant FR effect on plasma triglycerides and cholesterol as well as an ET effect on plasma triglycerides. However, no significant interactions between FR and ET were seen on the lipid profile. A reduction in body weight was not observed following exercise in the ALE group, which likely reflects the low running rates recorded by this group. Running rates averaged 60 revolutions per hour compared with 1800 revolutions per hour in the FRE group, which had dramatically lower body weights.

FR and ET effects on cardiac performance in response to changes in afterload are shown in Table 2. When hearts were perfused at an aortic afterload resistance of 60 mm Hg, a significant FR effect on aortic flow was observed. There was also an interaction between FR and ET on systolic pressure. At 90 mm Hg aortic resistance, the significant FR effect on aortic flow and the interaction between FR and ET on systolic pressure remained. At this afterload, a training effect as well as an interaction between FR and ET on heart rate were observed.

Following the aortic afterload challenge, the afterload resistance was reduced to 75 mm Hg, and heart function was

Table 2. Effects of ET and FR on Heart Function in Response to Increases in Afterload Resistance

Group	Heart Rate (beats/min)	Systolic Pressure (mm Hg)	Aortic Flow (ml/min)
80 cm H <sub>2</sub> O			
AL	210 $\pm$ 9	102 $\pm$ 5	20 $\pm$ 2
FR	201 $\pm$ 8	80 $\pm$ 3	32 $\pm$ 4
ALE	184 $\pm$ 9	84 $\pm$ 3	20 $\pm$ 2
FRE	193 $\pm$ 9	103 $\pm$ 5	28 $\pm$ 3
<i>F</i> ratios <sup>†</sup>			
FR effect	0.01	0.02	22.55*
Training effect	3.58	0.18	1.98
FR $\times$ training	1.10	24.42*	1.34
120 cm H <sub>2</sub> O			
AL	183 $\pm$ 13	127 $\pm$ 5	12 $\pm$ 3
FR	195 $\pm$ 7	109 $\pm$ 3	32 $\pm$ 3
ALE	178 $\pm$ 8	117 $\pm$ 4	13 $\pm$ 2
FRE	199 $\pm$ 8	135 $\pm$ 5	28 $\pm$ 3
<i>F</i> ratios <sup>†</sup>			
FR effect	0.03	0.01	31.83*
Training effect	5.70*	3.62	2.23
FR $\times$ training	8.56*	17.70*	0.01

Notes: Values are reported as mean  $\pm$  SE for eight to nine hearts for each group. Hearts were initially perfused at an 11.5 mm Hg left atrial filling pressure and 60 mm Hg afterload resistance. Following a 5-min period at this workload, the aortic afterload resistance was then increased to 90 mm Hg. AL = ad libitum-fed; ALE = ad libitum-exercise; FR = food-restriction; FRE = food-restriction-exercise; ET = exercise training.

\*Significant *F* ratios,  $p < .05$ .

<sup>†</sup>*F* ratios of a two-way factorial analysis of variance to determine whether FR and/or exercise training had an effect on heart function.

monitored prior to ischemia. As shown in Table 3, under normoxic conditions, there was a significant FR effect on aortic flow as well as an interaction between FR and ET on heart rate and pressure development. The benefits of FR were clearly shown during the reperfusion of ischemic hearts. Significant FR effects on heart rate, systolic pressure, and aortic flow were seen. In terms of percent recovery following ischemia, significant FR effects were seen on all cardiac parameters, including aortic flow. In addition, an interaction between FR and ET occurred with aortic flow (Table 4).

### DISCUSSION

The main findings of this study clearly indicate that chronic FR, or FR in combination with ET, results in marked adaptations in contractile properties of the heart. These adaptations include the ability of hearts to maintain aortic pump flow in response to increased afterload resistance and improved posts ischemic recovery of heart function during reperfusion following ischemia.

Despite earlier studies demonstrating that FR reduces the incidence of cardiomyopathy, the FR effects on myocardial function and ischemic tolerance has received little attention. Using intact working heart preparations, the literature shows that mechanical function of hearts from FR animals is improved and in some cases even demonstrates a diabetic type of cardiomyopathy (6,20,21). In regards to ischemic tolerance, isolated atrial strips from hearts of FR animals are more resistant to anoxic and reperfusion injury (6). Although our results are consistent with those of Savabi and Kirsch (6), we extend these observations by demonstrating that FR increases ischemic tolerance in hearts perfused in

Table 1. Physical Characteristics of Animals

Group	Body Weight (g)	Triglycerides (mmol/l)	Cholesterol (mmol/l)
AL	617 $\pm$ 35	2.7 $\pm$ 0.3	3.7 $\pm$ 0.1
FR	340 $\pm$ 1	0.7 $\pm$ 0.2	2.8 $\pm$ 0.1
ALE	682 $\pm$ 11	2.8 $\pm$ 0.1	3.8 $\pm$ 0.4
FRE	388 $\pm$ 2	1.3 $\pm$ 0.1	2.5 $\pm$ 0.2
<i>F</i> ratios <sup>†</sup>			
FR effect		83.77*	59.44*
Training effect		4.30*	0.52
FR $\times$ training		1.26	2.34

Notes: Body weight, plasma triglycerides, and cholesterol of rats 8 mo following ET and FR. Values are reported as mean  $\pm$  SE for 8 animals for each group. AL = ad libitum-fed; ALE = ad libitum-exercise; FR = food-restriction; FRE = food restriction-exercise; ET = exercise training.

\*Significant *F* ratios,  $p < .05$ .

<sup>†</sup>*F* ratios of a two-way factorial analysis of variance to determine whether FR and/or ET had an effect on plasma lipids. Analysis of body weight differences were not determined because weight was regulated through food intake for the FR groups but not in the ad libitum groups, leading to heterogeneity of variance in weights between groups.

Table 3. Effects of ET and FR on Heart Function Under Normoxic Conditions and During Reperfusion of Previously Ischemic Hearts

Group	Heart Rate (beats/min)	Pressure		Aortic Flow (ml/min)
		Systolic (mm Hg)	Diastolic (mm Hg)	
Normoxic				
AL	215 ± 6	117 ± 5	52 ± 3	21 ± 3
FR	192 ± 6	102 ± 2	46 ± 2	36 ± 3
ALE	176 ± 8	108 ± 3	43 ± 2	20 ± 2
FRE	199 ± 8	121 ± 5	56 ± 3	30 ± 3
<i>F</i> ratios <sup>†</sup>				
FR effect	0.01	0.13	1.18	22.07*
Training effect	4.69*	2.07	0.02	1.36
FR × training	9.85*	13.31*	13.11*	1.12
At 15 min reperfusion				
AL	183 ± 13	94 ± 11	45 ± 3	6 ± 3
FR	181 ± 9	98 ± 2	48 ± 1	21 ± 4
ALE	128 ± 10	78 ± 11	32 ± 5	1 ± 1
FRE	193 ± 8	116 ± 3	60 ± 4	19 ± 2
<i>F</i> ratios <sup>†</sup>				
FR effect	8.91*	6.31*	0.02	35.12*
Training effect	3.90	0.02	18.35*	1.70
FR × training	10.41*	3.91	0.02	0.24

Notes: Values are reported as mean ± SE for eight to nine hearts for each group. Hearts were perfused at an 11.5 mm Hg left atrial filling pressure and 75 mm Hg aortic afterload and then subjected to 25 min of global no-flow ischemia. Following ischemia, hearts were reperfused for a period of 15 min. AL = ad libitum-fed; FR = food-restriction; ALE = ad libitum-exercise; FRE = food-restriction-exercise; ET = exercise training.

\*Significant *F* ratios, *p* < .05.

<sup>†</sup>*F* ratios of a two-way factorial analysis of variance to determine whether FR and/or ET had an effect on heart function.

the presence of relevant levels of fatty acids. We chose to perfuse hearts with elevated levels of fatty acids, because this is representative of clinical setting of myocardial infarct (18). High levels of fatty acid are also known to contribute to postischemic cardiac dysfunction, secondary to the accumulation of intermediates of fatty acid and by inhibition of

Table 4. Effects of ET and FR on Percent Recovery of Heart Function Following Global No-flow Ischemia

Group	Heart Rate (beats/min)	Pressure		Aortic Flow (ml/min)
		Systolic (mm Hg)	Diastolic (mm Hg)	
AL	85 ± 5	81 ± 9	92 ± 7	27 ± 10
FR	95 ± 4	97 ± 2	105 ± 2	56 ± 7
ALE	73 ± 6	72 ± 10	75 ± 11	6 ± 4
FRE	98 ± 4	96 ± 2	105 ± 3	66 ± 7
<i>F</i> ratios <sup>†</sup>				
FR effect	13.08*	7.83*	9.14*	33.10*
Training effect	0.83	0.40	1.54	0.56
FR × training	2.35	0.26	1.45	4.27

Notes: Values are reported as mean ± SE for 8 to 9 hearts for each group. Hearts were perfused at an 11.5 mm Hg left atrial filling pressure and 75 mm Hg aortic afterload and then subjected to 25 min of global no-flow ischemia. Percent recovery is shown at 15 min reperfusion. AL = ad libitum-fed; FR = food-restriction; ALE = ad libitum-exercise; FRE = food-restriction-exercise.

\*Significant *F* ratios, *p* < .05.

<sup>†</sup>*F* ratios of a two-way factorial analysis of variance to determine whether FR and/or ET had an effect on percent recovery of heart function following ischemia.

glucose metabolism (18,19). Further, unlike in the current study, function following anoxic insult was determined using tissue preparations rather than an intact working heart where reperfusion recovery could be monitored under physiological loading conditions.

The benefits of chronic FR on reperfusion recovery can likely be explained, in part, by a favorable redistribution of lipids and cholesterol. Chronic interventions that lessen plasma lipid levels also favorably alter the reliance of the heart on fatty acid metabolism (12,22,23). In particular, interventions that decrease the supply of lipids to the heart can improve glucose metabolism and exert a protective effect on the heart following ischemia (17,24). In support of these observations, we show that there was a significant effect of chronic FR on plasma levels of cholesterol and triglycerides. This may be of importance where glucose utilization is impaired, such as in the ischemic reperfused heart (25–27).

We can only speculate as to what could be responsible for the interaction between caloric restriction and ET on percent recovery of heart function following ischemia. One possibility is that the benefits of ET and FR on cardiac performance occur through common systemic mechanisms. In support of this, earlier studies have shown that both FR and ET increase the sensitivity of tissues, particularly of the heart, to insulin and adrenergic stimulation (12,14,15). FR and ET attenuate the decrease in myocardial performance associated with aging (5,7). An increase in insulin sensitivity attributable to an up-regulation of glucose transporter proteins and insulin receptor content also occurs in response to training and caloric restriction (15,28). Interestingly, FR inhibits the physiological decline in the levels of glucose transporter proteins associated with aging (29). This may be relevant in our studies because the duration of the protocols was based on heart function following long-term FR and ET in aging rats.

Several physiological and biochemical changes occur in tissues with chronic FR. In the present study, mechanical function of the heart during reperfusion is improved following FR. Although these changes can be attributed in part to an improved lipid profile, other metabolic processes induced by FR that have the potential to enhance the heart's ability to withstand ischemia should not be excluded. In fact, a key to the enhanced longevity in the FR laboratory animal is an increase in mitochondrial antioxidant defenses (4,30). The increase in heart free-radical production and oxidative damage normally associated with aging can be attenuated or even prevented with dietary restriction (31). In rat heart mitochondria, increases in the activity of antioxidant enzymes, including superoxide dismutase and catalase, have been reported with FR (31,32). Antioxidant defense is of important clinical concern, because a burst of oxygen free radicals immediately upon reperfusion can cause dysfunction of the heart (33).

Several studies have sought to assess the functional response of the rat heart to chronic exercise. Although most of these studies have reported cardiac benefits following training, others have not always shown an improvement in cardiac function. These inconsistencies may result from the type of exercise itself, the intensity and duration of the training protocol, or even the sex of the animals. In our study,

heart function of animals from the ALE group was not improved from previous ET, particularly following ischemia, because recovery was compromised. Low running rates recorded in this group could be the reason for this lack of beneficial effect. No benefits on either body weight or circulating plasma lipid levels were reported. In the FRE group, however, cardiac adaptations to ET occurred and cannot be attributed to FR alone. The effects of FR on recovery of heart function following ischemia can be separated from the effects of ET. This is supported by the observation that aortic flow of hearts from FR animals returned to 56% of preischemic function, whereas a 66% recovery of function occurred in hearts from the FRE group.

In summary, we show that chronic FR alone or in combination with ET improved heart function under aerobic conditions and brought about a clear protective effect against ischemia in hearts reperfused with relevant concentrations of fatty acids.

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