Cardioprotection by Intermittent Fasting in Rats

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**Background**—Intermittent fasting (IF), a dietary regimen in which food is available only every other day, increases the life span and reduces the incidence of age-associated diseases in rodents. We have reported neuroprotective effects of IF against ischemic injury of the brain. In this study, we examined the effects of IF on ischemic injury of the heart in rats.

**Methods and Results**—After 3 months of IF or regular every-day feeding (control) diets started in 2-month-old rats, myocardial infarction (MI) was induced by coronary artery ligation. Twenty-four hours after MI, its size in the IF group was 2-fold smaller, the number of apoptotic myocytes in the area at risk was 4-fold less, and the inflammatory response was significantly reduced compared with the control diet group. Serial echocardiography revealed that during 10 weeks after MI (with continuation of the IF regimen), the left ventricular (LV) remodeling and MI expansion that were observed in the control diet group were absent in the IF group. In a subgroup of animals with similar MI size at 1 week after MI, further observation revealed less remodeling, better LV function, and no MI expansion in the IF group compared with the control group.

**Conclusions**—IF protects the heart from ischemic injury and attenuates post-MI cardiac remodeling, likely via antiapoptotic and antiinflammatory mechanisms. *(Circulation. 2005;112:3115-3121.)*

**Key Words:** myocardial infarction ▪ diet ▪ remodeling ▪ apoptosis ▪ inflammation

**Clinical Perspective p 3121**

We have previously reported the neuroprotective effect of IF in rodent experimental models. The cellular and molecular mechanisms underlying the beneficial effects of IF are still not fully understood, but they appear to involve the reduction of free-radical production and an improved cellular stress response. Oxidative stress is characterized by overproduction of reactive oxygen species, including free radicals, which induce injuries equally in the cardiovascular and nervous systems and contribute to the development of cardiovascular disease and aging. We hypothesized that the protective effects of IF against ischemic injury observed in the rat brain would also be observed in the cardiovascular system and result in a reduction of myocardial cell death and inflammation in ischemic myocardium. Thus, we examined the effects of IF on acute and chronic cardiac responses to coronary artery ligation in rats.

**Methods**

**Experimental Design**

All animal procedures were approved by the institute’s animal care and use committee. Two-month-old, male Sprague-Dawley rats (N=60) were randomly assigned to be fed either every day (control group) or every other day (IF group) with a standard rat diet ad libitum (NIH-07, Harlan Teklad). After 3 months of these feeding
Regimens, an echocardiographic (echo) assessment of cardiac function was conducted, and all rats underwent either coronary artery ligation or sham surgery. The following 4 groups were created: CL, control ligated (n=25); CS, control sham (n=5); IFL, intermittently fasted and ligated (n=24); and IFS, intermittently fasted and sham (n=5). Twenty-four hours after coronary artery ligation, a subset of randomly selected rats from the CL (n=7) and IFL (n=5) groups was euthanatized for histological evaluation. The remaining rats were assessed by echo at 1 and 10 weeks after surgery and then humanely killed for histological examination. Feeding regimens established before MI surgery were continued during the 10 weeks of post-MI observation.

**Echocardiography**

In rats under light anesthesia with sodium pentobarbital (30 mg/kg IP), a 12-MHz transducer (HP Sonos 5500, Hewlett-Packard Inc) was used to obtain 2D images of the left ventricle (LV) long and short axes. LV mass and LV posterior wall thickness were measured according to a modified Simpson’s rule. LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) were calculated from 2D images according to the LV ejection fraction (EF) was established before MI surgery were continued during the 10 weeks of post-MI observation.

**Generation of MI in Rats**

After baseline echo examination, rats were anesthetized with sodium pentobarbital (50 mg/kg IP), and the left anterior descending coronary artery was ligated as described elsewhere. In sham-operated animals, the suture around the coronary artery was left untied.

**Histological Analyses**

At 24 hours after MI surgery, a subgroup of rats was euthanatized, and their hearts were excised. With use of a 16-gauge tube, 3 mL of 5% Evans blue dye (Sigma) was rapidly injected into the aorta to distinguish the perfused area (blue staining) from the underperfused area (no staining). The atria and great vessels were dissected away from the heart, and the heart was cut transversely into 4 slices from base to apex. A section from the midpapillary muscle level was immediately stored in LN2 for later histological analysis. The other 3 samples were incubated at 37°C with 4% triphenyltetrazolium chloride (TTC, Sigma) for 30 minutes to distinguish the infarct area (unstained) from the area at risk (AAR, brick red staining) in the underperfused area. All images were analyzed with NIH Image software. MI size was expressed as a percentage of the underperfused area. Myocardial sections (5 μm thick) were obtained from the frozen samples and stained with hematoxylin and eosin (H&E, Sigma) and terminal dUTP nick end-labeling (TUNEL; TdT; Promega, Madison, WI). Inflammatory cells (neutrophils and macrophages) were counted and averaged from 5 different fields of the AAR in H&E-stained sections from each heart. Apoptosis was assessed from TUNEL-stained sections of the AAR.

Ten weeks after surgery the remaining rats were euthanatized, and the hearts were isolated and weighed. The heart weight (HW) to BW ratio (HW/BW) was calculated. Myocardial sections (5 μm thick) were obtained from the midpapillary muscle level. MI size was measured in Masson’s trichrome-stained sections as the average of the infarct area of LV epicardial and endocardial lengths divided by LV circumferences and expressed as a percentage of the LV. Myocyte diameters were measured as the shortest distance between borders drawn across the nucleus and averaged from 5 different fields from the LV anterior wall in H&E-stained sections from each heart.

**Statistical Analysis**

All data are expressed as the mean±SEM. The differences in mortality between groups was assessed by the Fisher exact test. Echo-derived indices were compared by 2-way ANOVA for repeated measures. Histological data were assessed by 1-way ANOVA. Group differences at specific time points were tested by Bonferroni’s post hoc test (Prism v3.0, GraphPad Software Inc). *P<0.05* was considered statistically significant.

**Effect of IF on Cardiac Morphology and Function Before MI**

Before the beginning of diet manipulations, the average BW was 366 g and 365 g for control and IF groups, respectively. The average BW of IF rats became significantly (*P*<0.05) less than that of control rats within 1 week of diet initiation. During the 3 months of the different feeding regimens, the BW of IF rats increased by 49±5 g while the BW of control rats increased by 125±5 g, resulting in a significantly (*P*<0.05) lower BW in IF rats (Table 1). Among IF rats, BW was significantly lower on fasting days compared with feeding days. LV mass and LV posterior wall thickness were also significantly lower in the IF group compared with controls. The LV mass and LV posterior wall level was estimated from 2D short-axis LV images at end diastole and expressed as a percentage of the LV endocardial circumference. We have reported a high correlation between echo-estimated MI size and postmortem histologically estimated MI size (see also Figure 1).

**Effect of IF on Postoperative Mortality**

The perioperative mortality (within 24 hours of coronary artery ligation) was similar in both feeding regimens, 33% (8 of 24) in IFL and 36% (9 of 25) in CL animals. However, during the 10-week post-MI observation, there was no mortality in the IFL group while in the CL group, 3 of 9 rats died (33%, *P*<0.05). There was no mortality in sham-operated animals of either group.

**Results**

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TABLE 1. Echo Indices Before and After 1 and 10 Weeks After MI or Sham Surgery

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>1 Week After MI</th>
<th>1 Week After Sham</th>
<th>10 Weeks After MI</th>
<th>10 Weeks After Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=30)</td>
<td>IF (n=29)</td>
<td>CL (n=9)</td>
<td>IFL (n=10)</td>
<td>CS (n=5)</td>
</tr>
<tr>
<td>BW, g</td>
<td>491±6</td>
<td>414±6*</td>
<td>465±14</td>
<td>377±11*</td>
<td>481±14</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>332±7</td>
<td>340±7</td>
<td>349±12</td>
<td>315±15</td>
<td>339±5</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>1.65±0.03</td>
<td>1.48±0.03*</td>
<td>1.22±0.09†</td>
<td>1.41±0.07*</td>
<td>1.60±0.08</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>1.21±0.01</td>
<td>1.10±0.01*</td>
<td>1.20±0.03</td>
<td>1.14±0.02*</td>
<td>1.14±0.05</td>
</tr>
<tr>
<td>LVMi, g/kg</td>
<td>2.48±0.02</td>
<td>2.68±0.03*</td>
<td>2.60±0.11</td>
<td>3.04±0.07†</td>
<td>2.37±0.08</td>
</tr>
<tr>
<td>LVESV, μL</td>
<td>200±7</td>
<td>201±7</td>
<td>449±39†</td>
<td>291±35†</td>
<td>217±24</td>
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<tr>
<td>LVESV, μL/kg</td>
<td>407±13</td>
<td>484±12*</td>
<td>961±68†</td>
<td>769±82†</td>
<td>450±46</td>
</tr>
<tr>
<td>LVEDV, μL</td>
<td>438±13</td>
<td>392±9*</td>
<td>644±50†</td>
<td>485±40†</td>
<td>426±25</td>
</tr>
<tr>
<td>LVEDV/LV</td>
<td>892±24</td>
<td>948±18*</td>
<td>1378±88†</td>
<td>1312±67†</td>
<td>884±41</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.4±0.6</td>
<td>49.3±0.9*</td>
<td>30.8±1.8†</td>
<td>42.3±2.2†</td>
<td>50.5±2.7</td>
</tr>
<tr>
<td>Cardiac index, L/d/sm²</td>
<td>159±6</td>
<td>158±4</td>
<td>145±12†</td>
<td>170±7†</td>
<td>147±3</td>
</tr>
<tr>
<td>MII size, %</td>
<td>0</td>
<td>0</td>
<td>21.1±1.3</td>
<td>15.3±1.4*</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are mean±SEM.

Post hoc test, P<0.05: *between groups at each time point; †compared with before surgery within the group; ‡compared with 1 week after surgery within the group.

Effect of IF on MI Size, Apoptosis, and Inflammation 24 Hours After Coronary Artery Ligation

Representative sections of the hearts subjected to TTC, TUNEL, and H&E staining, as well as the results of measurements of MI size and extent of apoptosis and inflammation in the myocardium, are shown in Figure 2. The total underperfused areas (MI plus AAR) were not different between the 2 dietary regimens (P>0.05, Figure 2A). MI size (expressed as a percentage of the underperfused area), however, was 2.5-fold smaller in the IFL than in the CL group (P<0.05, Figure 2A). The number of cardiomyocytes with TUNEL-positive nuclei in the AAR (per 10⁵ of total cardiomyocytes) was 5.5-fold lower in the IFL than in the CL group (P<0.05, Figure 2B). The number of neutrophils and macrophages (per field at ×200 magnification) in the AAR was significantly lower in the IFL (P<0.05) than in the CL group (Figure 2C).

Effect of IF on Post-MI Cardiac Remodeling During a 10-Week Observation Period

Echo indices before MI (or sham operation) and at 1 and 10 weeks after MI are presented in Table 1. Early (first week) LV remodeling was significantly less pronounced in IFL than in CL animals: at the first week, LVEDV had increased by 47% in CL versus only 26% in IFL rats, LVESV had increased by 124% in CL versus 44% in IFL rats, and LVEF had declined by 43% in CL versus 14% in IFL rats. The posterior wall was significantly thinner in CL compared with
control animals but was not affected by coronary artery ligation in the IFL group.

In the CL group, progressive late cardiac remodeling (between the first and 10th week after coronary artery ligation) consisted of further LV chamber dilation (35% for LVESV and 24% for LVEDV), posterior wall thickening (34%), functional deterioration (25% decrease in LVEF), and further infarct expansion (39% increase of MI size). In contrast, late cardiac remodeling did not occur in the IFL group. In fact, the LVESV and LVEDV were significantly smaller in the IFL than in the CL group at all time points after induction of MI, even after adjustment for BW (in LVEDVI, however, the difference did not reach statistical significance at the first week). LVEF was significantly higher and echo-estimated MI size significantly smaller in IFL rats at both time points.

Postmortem histological analyses showed that the average myocardial cell diameter and HW/BW were significantly lower in IFL than in CL animals (Figure 3). In contrast, these indices were similar in CS and IFS groups. The histologically measured MI size was smaller in IFL than in the CL group (P<0.05).

Effect of IF on Later LV Remodeling (at Equal MI Size)
To exclude the effect of smaller MI size in IF rats at week 1 after ligation on later LV remodeling, 2 subgroups of CL and IFL rats (CLsub and IFLsub) with similar MI and LV chamber sizes were selected after the first-week echo examination. Table 2 summarizes the echo data for these subgroups at 1 and 10 weeks after surgery. The progressive late cardiac remodeling, observed in CLsub during this observation period, consisted of a significant 34% increase in LVEDV, a 54% increase in LVESV, a 28% decline in LVEF, and a 37% thickening of the LV posterior wall. MI in CLsub animals expanded by 49%. In contrast, there was no significant dilation of LV, decline of LVEF, or MI expansion in the IFLsub group. Thickening of the LV posterior wall did occur in IFLsub rats but only to half the extent of that observed in CLsub. These differences in late remodeling between CLsub and IFLsub animals persisted even after adjustment for BW. Less myocardial hypertrophy in IF animals was also indicated by a significantly smaller cardiomyocyte diameter (Table 2) and a lower HW/BW. Histologically measured MI size was smaller in IFLsub compared with CLsub rats.

### Table 2. Effect of IF on Late Cardiac Remodeling of CHF in Subgroups

<table>
<thead>
<tr>
<th></th>
<th>CLsub (n=5)</th>
<th>IFLsub (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 10</td>
</tr>
<tr>
<td>BW, g</td>
<td>441±7</td>
<td>480±7‡</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>361±10</td>
<td>374±10</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>1.30±0.10</td>
<td>1.72±0.15‡</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>1.20±0.04</td>
<td>1.47±0.04‡</td>
</tr>
<tr>
<td>LVESV, μL</td>
<td>384±26</td>
<td>583±43‡</td>
</tr>
<tr>
<td>LVESVI, μL/kg</td>
<td>872±59</td>
<td>1214±85‡</td>
</tr>
<tr>
<td>LVEDV, μL</td>
<td>579±41</td>
<td>769±54‡</td>
</tr>
<tr>
<td>LVEDV, μL/kg</td>
<td>1312±89</td>
<td>1599±104‡</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33.9±1.0</td>
<td>24.0±1.4‡</td>
</tr>
<tr>
<td>Echo MI size, %</td>
<td>19.4±0.8</td>
<td>28.4±1.8¶</td>
</tr>
<tr>
<td>Cardiac index, μL · min⁻¹ · g⁻¹</td>
<td>158±12</td>
<td>143±12‡</td>
</tr>
<tr>
<td>Cell diameter, μm</td>
<td>24.1±0.7</td>
<td>24.1±0.7</td>
</tr>
<tr>
<td>HW/BW</td>
<td>2.89±0.08</td>
<td>2.73±0.03*</td>
</tr>
<tr>
<td>Histology MI size, %</td>
<td>36.2±2.2</td>
<td>36.2±2.2</td>
</tr>
</tbody>
</table>

Data are mean±SEM. There was no difference between CLsub and IFLsub groups at week 1.

Post hoc test P<0.05: *CLsub vs IFLsub at week 10; †comparison of % changes in CLsub and IFLsub; ‡week 1 vs week 10 within the group.
Discussion
IF is known to extend life span and postpone the development of age-associated diseases in animal models.1-7 In humans, reduced-calorie diets are associated with reductions of cardiac-specific risk factors, such as obesity, high blood pressure, and serum lipid levels,11,12 whereas the effects of IF on cardiovascular risk have not been established. The present study is the first experimental evidence that an IF dietary regimen reduces myocardial damage induced by ischemia. Moreover, even with the same degree of early myocardial damage, there were less LV remodeling and functional decline in IF animals than in control ad libitum fed rats.

Effect of IF on the Heart Before Coronary Artery Ligation
Echo evaluation after 3 months of IF before surgery, as well as after surgery in nonligated animals, showed hearts with thinner walls and a lower LVEDV than those of control animals. One explanation for the smaller heart in IF rats is a retardation of growth in young animals experiencing a reduction of caloric intake. Alternatively, the smaller LVEDV might reflect a lower filling pressure because of a lower blood volume associated with an ≈16% lower BW in the IF rats. We have also reported previously a lower blood pressure in IF rats.16 In control rats, the combination of higher blood pressure and a larger LV end-diastolic diameter resulted in a higher wall tension, which increased wall stress.22 The proper response of the cardiac or vascular wall to increased wall stress is to normalize it by increasing wall thickness, i.e., hypertrophy23; hence, the thicker posterior wall in control rats may reflect the physiological hypertrophy response to reduce wall stress. However, these differences are relative, because, when adjusted for BW, LV volumes and mass were actually higher in the IF than control animals before surgery and in sham-operated rats at all time points after surgery. Moreover, the diameter of cardiomyocytes was similar in sham-operated animals on different diets, confirming the lack of "real" hypertrophy in control hearts. A small but statistically significant reduction of LVEF in IF rats owing to a lower LVEDV also had negligible physiological significance, because it did not result in a reduction of cardiac index or cardiac output adjusted for BW.

Cardioprotective Effect of IF Against Ischemic Injury
The possible cardioprotective role of physiological adaptation to IF is not entirely clear. One explanation is related to the established view that the hypertrophied myocardium is more sensitive to ischemic injury24 owing to differences in the levels of oxygen-radical metabolic pathways. However, this appears not to be a major mechanism, because myocardial hypertrophy in ad libitum fed rats was relative and was not confirmed by any actual differences in cardiomyocyte dimensions. Another explanation considers the IF regimen to be a repeated mild stress that induces expression of genes that enhance the ability of cells to cope with more severe stress.25 Ample evidence has been presented that IF induces the expression of protein chaperones, such as glucose regulated protein-78 and heat shock protein-70, and growth factors, such as brain-derived neurotrophic factor in brain cells, which increase the resistance of neurons to oxidative and metabolic stress and stimulate neurogenesis.26-28 In this respect, IF might be similar to ischemic preconditioning, a most potent endogenous cardioprotective mechanism in the myocardium that has been shown to activate signaling pathways that protect against mitochondrial permeability transition and apoptosis.29

The mechanisms whereby an IF regimen protects the myocardium at earlier stages of ischemic damage is not yet clear. We have reported previously30 that IF in rats resulted in a reduction of physical activity both during the fasting and feeding days, especially at night (the active period of the circadian cycle in rats). Furthermore, the overall reduction of physical activity was accompanied by a reduction of heart rate30 and increased heart rate variability (authors’ unpublished observation), indicating an increase in vagal tone that has been shown to be associated with a favorable outcomes in patients with cardiovascular diseases.31,32

At 24 hours after coronary artery ligation, we demonstrated a significant reduction of apoptosis and neutrophil infiltration in the AAR. Although the specific signaling pathways remain to be elucidated, these antiapoptotic and antiinflammatory effects of IF early after induction of MI likely contributed to the observed infarct size reduction. Alternatively, by reducing the amount of myocardial cell damage, IF may reduce cellular loss and inflammation. However, a cardiolic restriction regimen has been shown to have an antiinflammatory effect on the ischemic myocardium.13 This effect involves nuclear factor-κB, cytokines (interleukin-1β and tumor necrosis factor-α), and the antioxidant enzyme manganese superoxide dismutase. Caloric restriction has also been reported to reduce the damage of heart mitochondrial proteins33 and DNA34 induced by oxidative stress in rats. Our data suggest that similar factors play a role in the antiinflammatory and antiapoptotic effects of IF in the present MI model.

In addition to a smaller infarct 24 hours after coronary artery ligation, IF rats had less LV dilatation and less functional decline at the early stage of LV remodeling. One week after coronary artery ligation, the MI in IF rats was smaller and LV dilatation 2- to 3-fold less pronounced compared with those measures in control animals and was correlated with lower levels of apoptosis and inflammation in the AAR 24 hours after surgery.

The cardioprotective effects of IF extended beyond a reduction of myocardial damage at the early stages of MI, resulting in changes throughout the late phase of LV remodeling. During the 10-week post-MI observation period, substantial LV remodeling and functional decline, as well as MI expansion, were observed in rats on the control diet but were absent in IF rats. The most obvious explanation for the lack of late adverse LV remodeling in IF rats is the smaller original MI size and the less-pronounced early LV remodeling. Indeed, MI size and LV chamber size determine wall stress, the main driving factor of cardiac remodeling and cell death.35,36 and thus, a smaller LV chamber and smaller MI in IF rats at week 1 might have resulted in less wall stress and loss of myocytes later. However, additional analyses indicate that this simple explanation is not sufficient. When late
remodeling was examined in subgroups of animals selected on the basis of similar MI and LV size at week 1 (ie, LV wall stress was similar between groups at that time), late remodeling was still observed in rats on the control diet but was absent in rats on the IF diet. It seems that in IF rats, the antiapoptotic and antiinflammatory properties that were observed at earlier stages of MI extended their beneficial effects of protecting myocardial tissue against adverse late remodeling and thus from development of CHF.

Because the IF regimen used in the present study results in an overall reduction in calorie intake and hence, a lower BW, the relative contributions of fasting and caloric restriction components of this diet to improved outcomes after MI are not known. Previous studies suggest 2 general mechanisms by which IF and caloric restriction increase life span and protect neurons against injury. One mechanism involves reduced levels of oxidative stress as the result of reduced mitochondrial oxyradical production, and the other mechanism involves induction of expression of stress resistance genes, such as those that encode protein chaperones and growth factors.\textsuperscript{15,17} Caloric restriction may exert its beneficial effects primarily by reducing oxidative stress, whereas IF may act primarily by a stress resistance mechanism.\textsuperscript{18} Reduced oxidative stress and increased cellular stress resistance therefore likely underlie the cardioprotective effects of IF in the present study.

In conclusion, although behavioral modifications such as exercise and dietary change are well known to reduce risk factors for cardiovascular diseases, this study is the first experimental evidence that modification of the dietary regimen, such as IF, can affect the outcome of actual cardiovascular disease by protecting the myocardium from ischemic damage, preventing postinfarct cardiac remodeling, and impending CHF.

Acknowledgments

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References

Our findings demonstrate cardioprotective actions of an IF dietary regimen in a rat model of MI. Myocardial tissue damage induced by permanent coronary artery ligation was reduced and recovery of cardiovascular function was improved in rats that had been maintained on the IF regimen for 3 months before the coronary artery occlusion event. Histological analysis of myocardial tissue revealed evidence of reduced apoptosis of cardiac myocytes and reduced infiltration of inflammatory leukocytes, suggesting that IF benefits the heart by increasing the resistance of cardiac myocytes to ischemic stress and by suppressing inflammation. Based on previous studies of the effects of IF on other organ systems, it is possible that this type of diet results in cellular and molecular changes in the heart that are similar to those in ischemic preconditioning, resulting in an increased ability of the heart to cope with severe ischemic stress. However, several questions remain to be answered. What are the relative contributions of the fasting component and the calorie-reduction component of IF to the cardioprotective effect of the diet? Will IF be beneficial in improving outcomes when initiated after MI? Nevertheless, if similar beneficial effects of IF occur in humans, then such dietary restriction regimens might be prescribed for subjects at risk for a coronary event based on family history and/or the presence of major risk factors (e.g., obesity, hypertension, diabetes, poor lipid profile, smoking, etc). Finally, IF may not only improve outcome after a coronary event but also reduce the risk for atherosclerosis and coronary events.