Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats

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ABSTRACT **Dietary restriction (DR) has been shown to increase life span, delay or prevent age-associated diseases, and improve functional and metabolic cardiovascular risk factors in rodents and other species. To investigate the effects of DR on beat-to-beat heart rate and diastolic blood pressure variability (HRV and DPV) in male Sprague-Dawley rats, we implanted telemetric transmitters and animals were maintained on either intermittent fasting (every other day feeding) or calorie-restricted (40% caloric reduction) diets. Using power spectral analysis, we evaluated the temporal profiles of the low- and high-frequency oscillatory components in heart rate and diastolic blood pressure signals to assess cardiac autonomic activity. Body weight, heart rate, and systolic and diastolic blood pressure were all found to decrease in response to DR. Both methods of DR produced decreases in the low-frequency component of DPV spectra, a marker for sympathetic tone, and the high-frequency component of HRV spectra, a marker for parasympathetic activity, was increased. These parameters required at least 1 month to become maximal, but returned toward baseline values rapidly once rats resumed ad libitum diets. These results suggest an additional cardiovascular benefit of DR that merits further studies of this potential effect in humans.—Mager, D. E., Wan, R., Brown, M., Cheng, A., Wareski, P., Abernethy, D. R., Mattson, M. P. Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. *FASEB J.* 20, 631–637 (2006)**

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Prolonged dietary restriction (DR) has been shown to increase life span and delay the occurrence of age-associated pathophysiological changes in several mammalian species (1). Recent findings suggest that caloric restriction (CR) also may increase the life span of nonhuman primates (2). Although most of these effects have been correlated with a reduction in caloric intake, another form of DR termed intermittent fasting (IF; where meals are not limited in calories but consumed with decreased frequency) also extends life span (3). Both forms of DR have been shown to improve functional and metabolic cardiovascular risk factors in rodents (3–6). These effects include enhanced insulin sensitivity, decreased resting heart rate (HR) and blood pressure (BP), and improved cardiovascular stress adaptation. Primary mechanisms by which these anti-aging and cardiovascular protective effects are achieved are still unclear; major hypotheses include reduction in oxidative stress and damage, induction of a mild stress response or hormesis, and modulation of glucose-insulin homeostasis (7). Because an imbalance in autonomic activity has been associated with cardiovascular risk factors improved by DR (8), we hypothesize that DR alters cardiac autonomic activity in ways that may improve cardiovascular function and resilience. The time course of such effects is of particular interest and has not been well described by traditional infrequent sampling schemes (e.g., measurements made on a monthly basis during DR regimens). Thus, using continuous measurements of heart rate and blood pressure, the purpose of this study is to apply spectral analysis to such data in order to ascertain the sympathetic and vagal components of autonomic activity before, during, and after the implementation of DR in rats.

Since the early 1980s, power spectral analysis of inter-beat HR and BP variability time series has been used to assess the interplay between the autonomic nervous system (ANS) and cardiovascular function (9). Frequency domain techniques, such as the fast Fourier transform (FFT), have served to quantitatively evaluate the functioning of various cardiovascular control systems and identify key frequency regions that appear reflective of specific ANS activity. Of importance is the

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recognition that HR variability (HRV) analysis can provide insights into parasympathetic and sympathetic ANS function under various physiological, pharmacological, and pathological conditions. In humans, older age appears to be associated with decreased variance in inter-beat intervals and HR spectral content from 0.04 to 0.32 Hz, largely explained by autonomic influences (10). In addition, reduced HRV as assessed by spectral analysis is associated with risk of coronary heart disease (11). The clinical applications of HRV analysis to other disease states have been reviewed (12), and standards for measurement and interpretation have been reported (13). Studies in rats suggest that the high-frequency (HF=0.75–2.5 Hz) component of the power spectral density of HRV reflects parasympathetic tone, whereas the low-frequency (LF=0.2–0.75 Hz) power of diastolic BP variability (DPV) is a marker for sympathetic activity (14). In this study we show that physiological changes induced by either CR or IF are accompanied by alterations in spectral measures of HRV and DPV in rats.

MATERIALS AND METHODS

Animals and surgical procedures

Twelve Sprague-Dawley rats (Harlan Teklad, Madison, WI, USA) initially 2.5 months of age were maintained under temperature- and light-controlled conditions with access to food and water ad libitum (AL). The photoperiod in the colony and testing rooms was maintained on a 12 h light/dark cycle with lights on from 6:00 AM to 6:00 PM daily. A telemetry system (Data Sciences International, St. Paul, MN, USA) was used to monitor behavioral and physiological parameters, including general activity, HR, and BP (mean, systolic, and diastolic). Surgical implantation of transmitters (TA11PA-C40) was performed in 3-month-old rats under isofluorane anesthesia using a six-station anesthesia system (SurgiVet, Waukesha, WI, USA). For each implant, the catheter tip was inserted upstream into the descending aorta between the renal arteries and iliac bifurcation and secured with tissue adhesive at the insertion point. The body of the implant was inserted into the peritoneal cavity and sutured to the abdominal musculature at the incision site. After completing the implantation procedure, rats were given buprenorphine administered subcutaneously (0.022 mg/kg) and returned to individual cages. Animals were allowed to recover for at least 1 month before the initiation of additional experimental procedures, during which time rats were provided food and water AL.

Diets and experimental procedures

After a 1 month recovery from surgery, baseline physiological and behavioral activities were recorded for 3 wk, during which all rats were maintained on the AL dietary regimen. A scheduled continuous sampling procedure was used whereby waveforms and specific parameters (locomotor activity, systolic and diastolic BP) were digitally recorded (500 Hz) for 2.5 min every 10 min during each 24 h period. DR was introduced after 3 wk of recording baseline conditions. Rats were randomly divided into two groups of 6 animals each. The rats in the first group were fed regular rat chow (NIH-07) on an IF regimen (every other day fasting), and rats in the second group were fed daily but with a 40% reduction in calories (CR). All rats were fed or fasted at 5:00 PM daily and had continuous access to water. The 40% CR regimen was based initially on the amount of food consumed during the AL regimen from the previous week. The body weight of the each rat was monitored weekly. The amount of food to be given each week to rats in the 40% CR group was adjusted weekly by adding 1–3% to the amount consumed during the previous week to ensure that rats maintained their health and continued on a slow and steady growth during the dietary restriction period. All parameters were recorded continuously during the first 8 wk after initiating dietary restriction. Recordings were stopped temporarily by switching off the battery to conserve power for the next phase of the study. All rats were maintained on either IF or CR regimens for an additional 8 wk (total of 16 wk on dietary restriction). Beginning on the 17th wk, all rats resumed an AL feeding regimen. Waveforms and physiological parameters were recorded continuously again using the identical sampling scheme as described previously. The study was terminated 4 wk after all rats were returned to an AL dietary regimen.

Blood samples (2 mL) were withdrawn from the tail vein of each rat into EDTA-containing tubes (BD Vacutainer, Franklin Lakes, NJ, USA) at various times, including: just prior to starting diets, every 2 wk during the first 6 wk after diets were initiated, and 2 wk after AL feeding was resumed. All blood samples were obtained after an overnight fast, where food was withheld on the afternoon of the previous day. During the DR period, blood samples were taken on a fasting day for rats on the IF regimen. Plasma was harvested from blood samples and stored at −80°C until analysis.

Blood chemical assessment

Plasma glucose concentrations were measured using a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA, USA). The concentration of corticosterone in plasma was measured using a commercially available radioimmunoassay kit (ICN Diagnostics, Costa Mesa, CA, USA).

Physiological and behavioral activities

Recordings of baseline activities prior to DR demonstrated stable parameter values that followed a daily circadian rhythm. Although physiological parameters were monitored continuously for 3 wk prior to and 8 wk after initiating diets, the data were extracted from the last day of each week for purposes of analysis and presentation. The data for rats in the IF group were extracted from one of the last two days of each week that corresponded with a fasting day. The data were organized and presented as mean values either during light (6:00 AM to 6:00 PM) or dark periods (6:00 PM to 6:00 AM). Statistical comparisons were usually made in two ways, i.e., the alteration in the same rat in response to different dietary regimens (within group) and the difference between rats in response to different diets during the same period (between groups).

Spectral analysis

Twenty-four hour blocks of inter-beat intervals and diastolic blood pressures were extracted using the Dataquest A.R.T. software at various weekly intervals and processed offline with MATLAB (The Mathworks, Natick, MA, USA) running on a standard Pentium 4 1.80 GHz PC. For each 2.5 min recording, ectopic beats and outliers were replaced by the mean of the previous and next valid measure prior to resampling the signal at 10 Hz (conducted using a spline function) to ensure

equidistant measures. A modified periodogram, which included a discrete FFT and Hamming window to prevent spectral leakage, was used to calculate the power spectral density of each 2.5 min segment. Each spectrum was integrated between 0.2–0.75 and 0.75–2.5 Hz to calculate the power in the LF and HF bands, respectively. To ascertain the time course of these measures, plots of LF and HF power and the LF/HF ratio over the 24 h blocks were constructed, and area under the curve (AUC) values were calculated using the linear trapezoidal rule. These procedures were piece-wise automated with algorithms written in MATLAB.

Statistical analyses

Physiological and behavioral data were analyzed using repeated-measures ANOVA, followed by post hoc assessments with the Student Newman Keuls test. One-way ANOVA, followed by the SNK test or Student's *t* test, was used to compare biochemical measures. Differences in mean LF, HF, and LF/HF AUC values were assessed using nonparametric repeated-measures ANOVA (Friedman test) and Dunn's multiple comparison tests with predietary restriction values.

RESULTS

Body weight and circadian activity

Body weights decreased in response to initiating both IF and CR regimens, with major weight loss occurring during the first 2–3 wk, followed by an adaptation to DR characterized by slow and steady growth over the 16-wk DR period (**Fig. 1**). However, rats in the CR group had consistently lower body weights compared with those in the IF group ($P<0.05$). Body weight gain resumed in all rats as soon as the AL feeding regimen was resumed. Circadian activity, as indicated by recordings of locomotor activity, was reduced in animals on the IF regimen particularly during the dark period (see Fig. 6 in Online Data Supplement), with no activity change associated with the CR regimen.

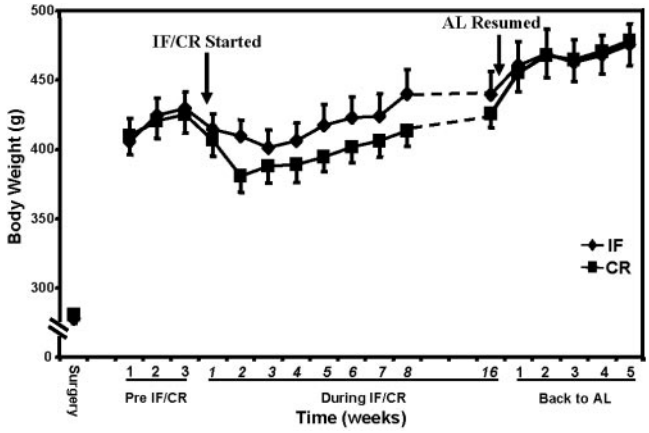

Figure 1. Changes in body weight in rats prior to, during, and after IF and CR feeding regimens. Symbols represent mean values, which were measured weekly, and error bars correspond to SEM (n=6/group).

Heart rate and blood pressure

HR in both groups decreased gradually in response to the initiation of both DR regimens, and although the trend was similar in both periods, the effect appeared more significant during the dark period than in the light period (**Fig. 2*A***). From DR wk 2–8, HR was reduced significantly compared with pre-DR measures in the same rats ($P<0.05$). In addition, HR during DR wk 3–8 was significantly decreased compared with that in wk 1 ($P<0.05$). These results indicate that the IF- and CR-induced reductions in HR reach a maximal effect at 3–4 wk after the diets were initiated in both groups. However, DR-induced reductions in HR were rapidly reversed after food was made available AL. Although HR during wk 1–3 after AL diet resumption was lower than pre-DR in the same group ($P<0.05$), this difference was not significant 4 wk after the AL regimen was resumed. The magnitude of the effects on HR produced by either IF or CR were similar.

Systolic BP gradually decreased for both diets, with the magnitude of the effect greater during the dark period (see Fig. 7 in Online Data Supplement). Compared with pre-DR values, systolic BP was significantly reduced from wk 3 to wk 8 for the IF group and from wk 2 to wk 8 for the CR group, with the plateau reached in both groups at wk 3. Systolic BP returned to pre-DR levels in the first week when the AL regimen was resumed. Systolic BP during the last 2 wk of AL was higher than during DR wk 3 to 8 ($P<0.05$). The magnitude of the effect on systolic BP produced by either IF or CR appeared to be comparable.

Both IF and CR caused a gradual decrease in diastolic BP, with greater reduction during the dark period (Fig. 2*B*). The maximal decrease in diastolic BP was reached by 4 wk in both groups. When AL feeding was resumed, during the dark period, diastolic BP in the IF group approached pre-DR levels during the last 2 AL wk. For the CR group, diastolic BP values during the dark period gradually increased during the AL wk; however, diastolic BP during the entire AL period remained lower compared with pre-DR values. The magnitude of the effect of IF and CR on diastolic BP was similar.

Trends of mean and pulse BP in response to DR were similar to those observed for systolic and diastolic BP (data not shown). During the light period, only the CR regimen produced significant changes in mean BP. Although both IF and CR diets decreased pulse BP during the dark period, only the IF regimen induced significant alterations during the light period.

Biochemical measurements

Plasma glucose concentrations were measured in each rat prior to and 2, 4, and 6 wk after initiating DR, and 2 wk after AL feeding was resumed (**Fig. 3*A***). The CR regimen produced a significant decrease in the plasma glucose concentration within 2 wk ($P<0.05$). The IF

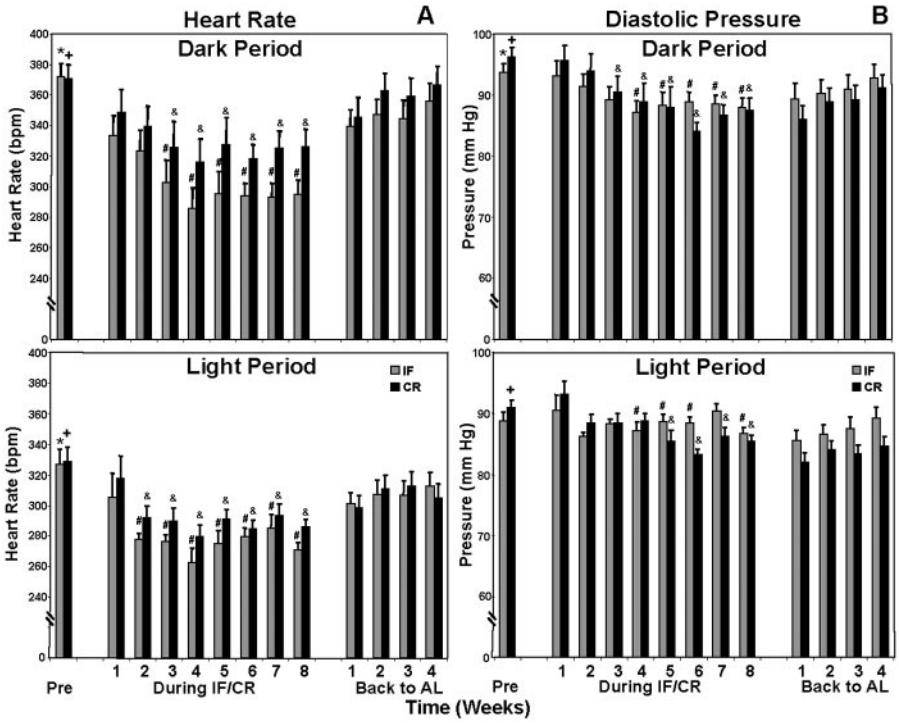

Figure 2. Heart rate (*A*) and diastolic BP (*B*) responses to IF and CR diets. The data are shown as mean values, either during the dark period or light period, and error bars represent SEM (n=6/group). *$P < 0.05$ compared with 2–8 wk post-DR and 1–3 wk post-AL; +$P < 0.05$ compared with 2–8 wk post-DR and 1–3 wk post-AL; #$P < 0.05$ compared with 1–4 wk post-AL; $P < 0.05$ compared with 1–4 wk post-AL.

regimen did not have a significant affect on plasma glucose concentration at any time point examined.

In contrast to glucose, plasma corticosterone concentrations increased for the IF regimen 4 wk after the diet was initiated, and remained as such until after AL feeding was resumed ($P<0.05$) (Fig. 3*B*). Plasma corticosterone concentrations increased more rapidly in response to the CR regimen (starting 2 wk after the diet was implemented), and returned to baseline levels after AL feeding was resumed. These results support the hypothesis that DR is a mild stressor, which increases the activity of the hypothalamic-pituitary-adrenal system (7, 8).

Spectral analysis

Area under the LF, HF, and LF/HF 24 h power time curves (AUC) for HRV and DPV were calculated at baseline, just prior to initiating DR, and at 2, 3, 4, 18, and 19 wk post-DR, where the last two time points reflect 2 and 3 wk after resuming AL feeding schedules. A comparison of AUC values between IF and CR groups under baseline conditions revealed that groups were similar prior to DR (see Fig. 8 in Online Data Supplement).

Rats subjected to the IF regimen exhibited a gradual and significant decrease in the LF power of DPV (**Fig. 4*A***, middle and right panels), whereas the HF component of DPV remained relatively stable. In contrast, changes in the LF band of DPV did not achieve statistical significance in the CR group, although trends in the data were similar between regimens (Fig. 4*B*). All spectral measures following the resumption of the AL regimen were not statistically different from baseline values.

Power in both the LF and HF bands of HRV spectra was significantly increased during the IF and CR diets, and the stable LF/HF ratios suggest that total HRV power was increased (**Fig. 5*A, B***). In agreement with results from the DPV analysis, all spectral measures of HRV were not statistically significant from pre-DR levels once AL feeding was resumed.

DISCUSSION

In this study we have shown that the improvement in parameters seen as human cardiovascular disease risk factors in response to DR in adult rats was accompanied by significant changes in spectral measures of HR and diastolic BP variability. Rats maintained on either the IF or CR dietary regimen exhibited decreased LF power in DPV and increased HF power in HRV, suggesting that DR produces decreased sympathetic ANS activity and augments parasympathetic or vagal tone. Our spectral analysis of DPV confirms earlier studies that have revealed the sympatholytic effects of DR using other measures (15, 16). However, the data presented here are the first to suggest that DR may produce an increase in vagal tone. Given that decreased HRV is a risk factor for the development of coronary heart disease in humans (11), if the opposite is true and increased HRV confers decreased risk, our data suggest an additional cardiovascular benefit of DR and may provide additional insight into the factors contributing to the mechanisms by which IF and CR improve cardiovascular function in animals.

The effects of DR on HR, systolic and diastolic BP, and glucose and corticosterone plasma concentrations confirm and extend prior studies of the hemodynamic

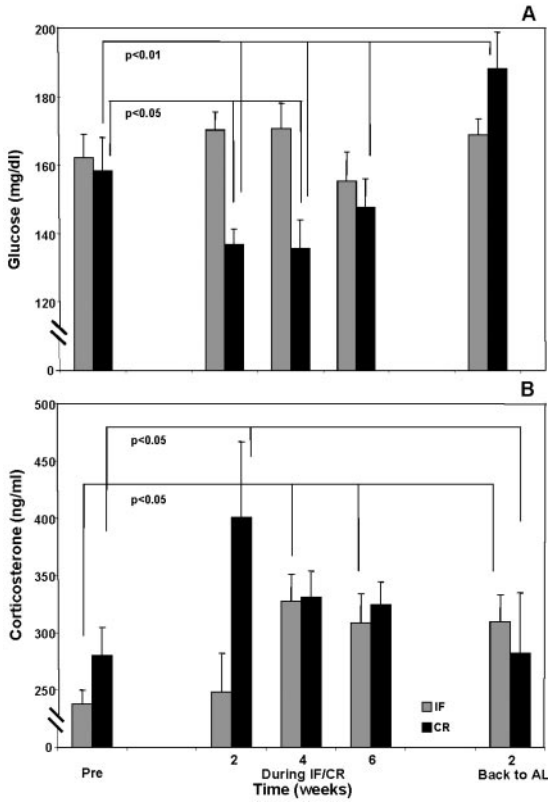

Figure 3. Plasma glucose and costicosterone concentrations prior to, during, and after IF and CR diets measured at selected intervals. Both regimens reduced plasma glucose concentrations (*A*) and increased the concentration of corticosterone (*B*). The values are presented as means (±SEM).

and endocrine effects of IF and CR diets. Whereas many longitudinal studies of DR rely on monthly measurements of cardiovascular and metabolic markers, physiological data in the present analysis were collected in a continuous manner. Such rich sampling provided key insights into the temporal aspects of the effects of the IF and CR regimens. HR and BP profiles show gradual and steady decreases in these values within the first month of imposing DR, and maximal effects are achieved in 4 to 5 wk. Furthermore, values rapidly approach baseline levels once AL feeding is resumed. The significance of these on-off rates has yet to be defined and requires further study. Although less frequently sampled owing to limitations in blood volume, the apparent paradoxical decrease in glucose and increase in corticosterone plasma concentrations in response to IF and CR are consistent with previous studies showing that DR improves insulin sensitivity and may represent a mild stressor (3, 5, 6). Despite the lack of agreement as to the definition, the term hormesis has been used to reflect this phenomenon whereby beneficial effects are achieved from exposure to a low-intensity stressor (7). The mechanisms by which a mild stressor may affect aging and age-related diseases are unknown but may involve the modulation of stress response genes and proteins (7).

The effects of DR on the cardiovascular system in this animal model that would be construed as beneficial in humans appear to be independent of which DR regimen is implemented. The ability of CR to extend life span in mice has been shown to be dependent on the degree of CR, where maximal life span increases with a progressive decrease in caloric intake (1). However, mice maintained on an IF regimen, where total food intake was not restricted, were shown to exhibit improvements in glucose regulation and neuronal resistance to injury that met or exceeded those induced by a CR regimen (3). In this study, rats on the CR diet demonstrated greater weight loss (Fig. 1) and reductions in plasma glucose concentrations (Fig. 3). The lack of effect on glucose concentrations of IF was unexpected, as a previous study revealed significantly

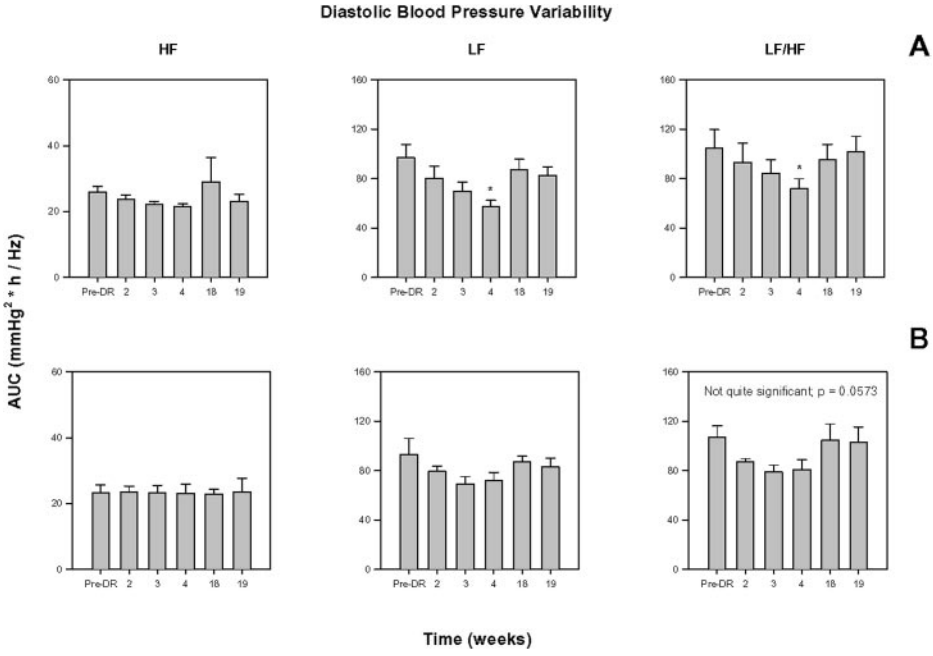

Figure 4. Area under the power 24 h time curves (AUC) for low-frequency (LF), high-frequency (HF), and the LF/HF components to diastolic blood pressure variability in IF (*A*) and CR (*B*) rats at select intervals (wk 18 and 19 are 2 and 3 wk after resumption of AL feeding). Bars represent mean values and the error bars correspond to SEM (n=5 or 6). *$P < 0.05$.

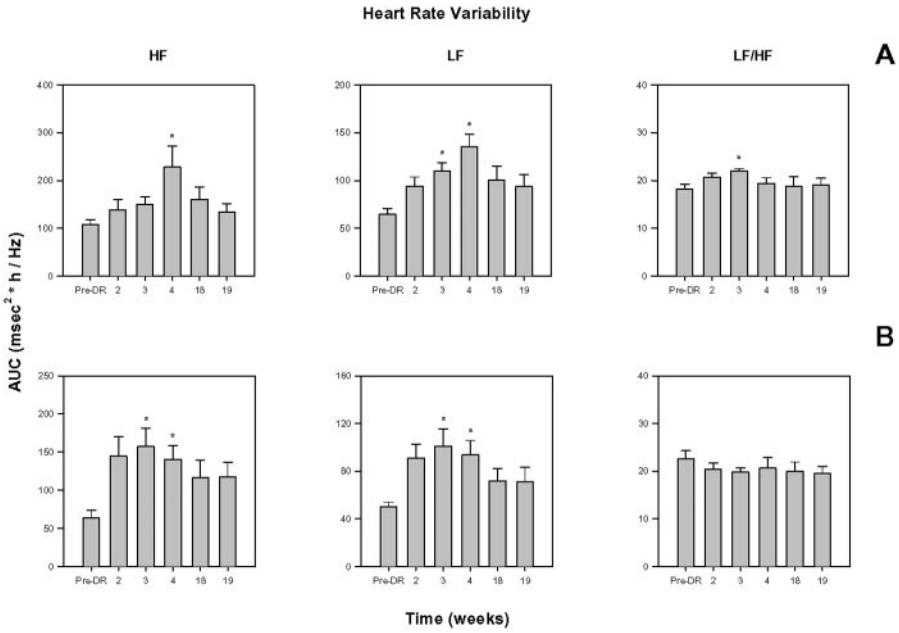

Figure 5. Area under the power 24 h time curves (AUC) for low-frequency (LF), high-frequency (HF), and the LF/HF components to heart rate variability in IF (*A*) and CR (*B*) rats at select intervals (wk 18 and 19 are 2 and 3 wk after resumption of AL feeding). Bars represent mean values and the error bars correspond to SEM (n=5 or 6). *$P < 0.05$.

lower basal concentrations of circulating glucose in IF mice (6); its implications are not clear.

On the other hand, both methods of DR produced comparable changes in hemodynamic parameters and spectral measures of HRV and DPV. The mechanisms linking IF and CR to the observed cardiovascular changes are unknown and need to be elucidated. We hypothesize that neurotrophic factor and neurotransmitter signaling may mediate this effect (8). For example, IF produces increased levels of brain-derived neurotrophic factor (BDNF) in several brain regions in rodents (17). Administration of paroxetine, a serotonin-selective reuptake inhibitor, increases BDNF brain concentrations in mice (18) as well as HRV in patients with panic disorder (19, 20). Although data suggest that BDNF may be responsible for the enhanced insulin sensitivity produced by DR (21, 22), whether BDNF is a contributing or controlling factor in the HRV response to IF and CR diets remains to be determined. The increase in vagal tone may also be implicated in the immunomodulatory effects of DR. The aging process is associated with a decrease in immunologic function (i.e., immunosenescence) and an increase in circulating proinflammatory cytokines (23). Borovikova et al. have demonstrated that direct vagus nerve stimulation attenuates the release of several inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, and IL-18 (24). Several studies show that dietary restriction also inhibits the production of TNF-α, IL-1β, and IL-6 (25–27). In addition, neither DR nor vagus nerve stimulation affect the ant-inflammatory cytokine IL-10 (24, 27). Further research is required to test these links between DR-mediated changes in the autonomic, immunologic, and cardiovascular systems.

In summary, a parasympathomimetic effect of DR has been identified from power spectral analysis of HRV data in rats exposed to IF or CR dietary regimens. Spectral measures of DPV also confirm previous studies revealing that such diets decrease sympathetic ANS activity. The more frequent data sampling scheme used in this study provided insight into the relatively fast rates at which the physiological effects of DR are achieved when diets are initiated and reversed upon returning animals to AL feeding. Although it is unclear whether IF and CR are feasible in humans, preliminary studies report promising results (28, 29) and support ongoing clinical investigations as well as the effort to develop drugs that exhibit CR mimetic properties (30). FJ

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REFERENCES

1. Weindruch, R., and Sohal, R. S. (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. *N. Engl. J. Med.* **337,** 986–994
2. Mattison, J. A., Lane, M. A., Roth, G. S., and Ingram, D. K. (2003) Calorie restriction in rhesus monkeys. *Exp. Gerontol.* **38,** 35–46
3. Anson, R. M., Guo, Z., de Cabo, R., Iyun, T., Rios, M., Hagepanos, A., Ingram, D. K., Lane, M. A., and Mattson, M. P. (2003) Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from caloric intake. *Proc. Natl. Acad. Sci. USA* **100,** 6216–6220
4. Thomas, J., Bertrand, H., Stacy, C., and Herlihy, J. T. (1993) Long-term caloric restriction improves baroreflex sensitivity in aging Fischer 344 rats. *J. Gerontol.* **48,** B151–B155
5. Wan, R., Camandola, S., and Mattson, M. P. (2003) Intermittent fasting and dietary supplementation with 2-deoxy-D-glucose improve functional and metabolic cardiovascular risk factors in rats. *FASEB J.* **17,** 1133–1134

6. Wan, R., Camandola, S., and Mattson, M. P. (2003) Intermittent food deprivation improves cardiovascular and neuroendocrine responses to stress in rats. *J. Nutr.* **133,** 1921–1929
7. Masoro, E. J. (2000) Caloric restriction and aging: an update. *Exp. Gerontol.* **35,** 299–305
8. Mattson, M. P., and Wan, R. (2005) Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. *J. Nutr. Biochem.* **16,** 129–137
9. Akselrod, S., Gordon, D., Ubel, F. A., Shannon, D. C., Berger, A. C., and Cohen, R. J. (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* **213,** 220–222
10. Craft, N., and Schwartz, J. B. (1995) Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans. *Am. J. Physiol.* **268,** H1441–H1452
11. Liao, D., Cai, J., Rosamond, W. D., Barnes, R. W., Hutchinson, R. G., Whitsel, E. A., Rautaharju, P., and Heiss, G. (1997) Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. The ARIC Study. Atherosclerosis Risk in Communities Study. *Am. J. Epidemiol.* **145,** 696–706
12. Malliani, A., Pagani, M., Lombardi, F., and Cerutti, S. (1991) Cardiovascular neural regulation explored in the frequency domain. *Circulation* **84,** 482–492
13. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* **93,** 1043–1065
14. Cerutti, C., Gustin, M. P., Paultre, C. Z., Lo, M., Julien, C., Vincent, M., and Sassard, J. (1991) Autonomic nervous system and cardiovascular variability in rats: a spectral analysis approach. *Am. J. Physiol.* **261,** H1292–H1299
15. Young, J. B., and Landsberg, L. (1977) Suppression of sympathetic nervous system during fasting. *Science* **196,** 1473–1475
16. Young, J. B., and Landsberg, L. (1982) Diet-induced changes in sympathetic nervous system activity: possible implications for obesity and hypertension. *J. Chronic Dis.* **35,** 879–886
17. Duan, W., Guo, Z., and Mattson, M. P. (2001) Brain-derived neurotrophic factor mediates an excitoprotective effect of dietary restriction in mice. *J. Neurochem.* **76,** 619–626
18. Duan, W., Guo, Z., Jiang, H., Ladenheim, B., Cadet, J., and Mattson, M. P. (2004) Paroxetine retards disease onset and progression in huntingtin mutant mice. *Ann. Neurol.* **55,** 590–594
19. Tucker, P., Adamson, P., Miranda, R. J., Scarborough, A., Williams, D., Groff, J., and McLean, H. (1997) Paroxetine increases heart rate variability in panic disorder. *J. Clin. Psychopharmacol.* **17,** 370–376
20. Yeragani, V. K., Jampala, V. C., Sobelewski, E., Kay, J., and Igel, G. (1999) Effects of paroxetine on heart period variability in patients with panic disorder: a study of holter ECG records. *Neuropsychobiology* **40,** 124–128
21. Nakagawa, T., Ono-Kishino, M., Sugaru, E., Yamanaka, M., and Noguchi, H. (2002) Brain-derived neurotrophic factor (BDNF) regulates glucose and energy metabolism in diabetic mice. *Diabetes Metab. Res. Rev.* **18,** 185–191
22. Duan, W., Guo, Z., Jiang, H., Ware, M., and Mattson, M. P. (2003) Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. *Endocrinology* **144,** 2446–2453
23. Pahlavani, M. A. (2000) Caloric restriction and immunosenescence: a current perspective. *Front. Biosci.* **5,** D580–D587
24. Borovikova, L. V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G. I., Watkins, L. R., Wang, H., Abumrad, N., Eaton, J. W., and Tracey, K. J. (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature (London)* **405,** 458–462
25. Spaulding, C. C., Walford, R. L., and Effros, R. B. (1997) Calorie restriction inhibits the age-related dysregulation of the cytokines TNF-alpha and IL-6 in C3B10RF1 mice. *Mech. Ageing Dev.* **93,** 87–94
26. Chung, H. Y., Kim, H. J., Kim, J. W., and Yu, B. P. (2001) The inflammation hypothesis of aging: molecular modulation by calorie restriction. *Ann. N.Y. Acad. Sci. USA* **928,** 327–335
27. Vega, V. L., De Cabo, R., and De Maio, A. (2004) Age and caloric restriction diets are confounding factors that modify the response to lipopolysaccharide by peritoneal macrophages in C57BL/6 mice. *Shock* **22,** 248–253
28. Fontana, L., Meyer, T. E., Klein, S., and Holloszy, J. O. (2004) Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc. Natl. Acad. Sci. USA* **101,** 6659–6663
29. Heilbronn, L. K., Smith, S. R., Martin, C. K., Anton, S. D., and Ravussin, E. (2005) Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. *Am. J. Clin. Nutr.* **81,** 69–73
30. Ingram, D. K., Anson, R. M., de Cabo, R., Mamczarz, J., Zhu, M., Mattison, J., Lane, M. A., and Roth, G. S. (2004) Development of caloric restriction mimetics as a prolongevity strategy. *Ann. N.Y. Acad. Sci. USA* **1019,** 412–423

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