



Intermittent Dietary Restriction Modulates Pressor Response and Vascular Reactivity in Young Normotensive Adults

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SUMMARY

Keywords:
Sympathetic activation, Ramadan, blood pressure, fasting, cold pressor test, hyperreactivity

Objective: The effect of dietary restriction on blood pressure (BP) changes to acute sympathetic activation has not been adequately evaluated. This study was designed to evaluate the effect of the Ramadan model of intermittent dietary restriction (IDR) on BP changes to acute sympathetic activation.

Method: Seventy healthy volunteers, mean age 25 ± 1 years, participated in the study after giving written informed consent. Ethical approval was obtained from LASUCOM Ethical and Research Grant Committee. Experiments were carried out one week before (1BF) and in the 4th week (4WF) of Ramadan. Sympathetic activation was carried out using the Cold Pressor Test (CPT) with the subjects inserting their left feet for 1 minute in ice slurry maintained at 4°C . Blood pressure was measured before and after CPT. Subjects were considered hyperreactive if CPT caused $\Delta\text{BP} \geq +15\text{mmHg}$, systolic or diastolic and normoreactive if $<15\text{mmHg}$, systolic or diastolic. Differences in means were calculated and compared with the student t test using GraphPad Prism version 5.01 for Windows. Data are expressed as mean \pm SEM and level of significance set at $p=0.05$.

Results: Pressor response to the CPT was blunted by IDR (ΔSBP $19.93 \pm 1.57\%$ at 1BF versus $15.30 \pm 1.62\%$ at 4WF, $p = 0.006$) and (ΔDBP $21.93 \pm 1.98\%$ at 1BF versus $17.12 \pm 1.83\%$ at 4WF, $p = 0.032$). Vascular reactivity was also reduced by IDR though systolic hyperreactivity was higher than diastolic hyperreactivity at 1BF (60% versus 46%) and 4WF (47% versus 36%).

Conclusion: We conclude that 4 weeks' intermittent dietary restriction modulated blood pressure responses to acute sympathetic activation.

INTRODUCTION

Dietary restriction (DR) is the reduction of particular or total nutrient intake without causing malnutrition. It includes caloric restriction[1] and temporal variation of food intake.[2] It has been reported that caloric restriction protects against stress in many model organisms such as mice and rats.[3] Indeed, long-term caloric restriction in rats has been reported to improve autonomic function. Experiments have shown a decreased sympathetic activity while parasympathetic activity was augmented in such rats.[4] In humans, similar long-term caloric restriction has been shown to protect against insulin resistance, obesity and hypertension amongst other benefits.[5-7] Many religions advocate some form of fasting, either time-bound abstinence from food and drinks or total abstinence from some particular food items for all time or for a period of time.[1] These nutritional modifications, based on the beliefs of individuals, are largely taken for granted with very few studies being carried out on the health-benefits of such practice. Ramadan fasting provides a model for investigating dietary restriction because of its tolerability and availability of large pool of subjects.[8]

It has been suggested that Ramadan fasting is a form of Alternate Day Fasting (ADF), a subgroup of dietary restriction.[1] In ADF, there are 24-hour alternation periods between fasting and feasting; during the "fast period", food consumption is restricted or there is total halt in consumption while during the "feast period", the individuals can eat as much as they wish; water being allowed during both period.[1] The Ramadan fast incorporates the feast period and a fast period but in a 12-hour length for both instead of the 24-hour for ADF and the fasters are not allowed water or other fluids.[1] Some of the available studies from other climes have documented physiological effects of the Ramadan fast such as weight loss, fat-free reduction of body mass, reduced systolic blood pressure and reduced cholesterol.[9-10]

The autonomic nervous system (ANS) is an important regulator of both the cardiovascular system and energy balance.[11-12] An increase in the ratio between the two components of the ANS, the sympathetic nervous system (SNS), and the parasympathetic nervous system (PNS) is an independent risk factor of cardiovascular disease.[12] The sympathetic nervous system plays a role in arterial blood

pressure regulation and increase in its activity has been associated with hypertension.[13] Obesity is associated with an imbalance between the PNS and the SNS but weight loss and exercise normalize this.[14-15] The cold pressor test is an acute stress test used to evaluate the sympathetic nervous system. It evokes an increment in blood pressure in both normotensive and hypertensive patients.[16-19] It has also been recorded that hyperreactivity to this test indicates future development of hypertension.[20-23] It is believed that sympathetic nervous activity is reduced in the obese compared to non-obese persons. The effect of intermittent dietary restriction such as that afforded by the Ramadan fast on the blood pressure response to the cold pressor test has not been documented. The aim of this study is therefore to evaluate the effect of intermittent dietary restriction on blood pressure changes induced by acute sympathetic activation in healthy young volunteers.

MATERIALS AND METHODS

This study was carried out in the month of Ramadan, 2015 at the Lagos State University College of Medicine, (LASUCOM) Ikeja, Lagos. Ethical approval was obtained from Lagos State University College of Medicine Research and Ethics Committee and written informed consent was obtained from the 70 healthy volunteers (40Male:30Female) who participated in the study. The medical history of all volunteers was obtained by means of a structured questionnaire. The study was carried out in accordance with the Helsinki Declaration.[24] The experiments were well tolerated by the subjects.

Inclusion criteria

To be included in this study, subjects must be within the age of 18 - 50years. They must be normotensive (SBP <140 mmHg and DBP < 90 mmHg[25]), non-diabetic and must neither drink alcohol nor smoke cigarette or use tobacco in any form. They must not be on medication that may influence the autonomic nervous system and must have been fasting regularly in previous months of Ramadan.

Exclusion criteria

Female subjects who were pregnant or lactating or who could be pregnant were excluded from the study. Also, individuals who were not willing to undergo the cold pressor test were excluded.

Experiments

The experiments were carried out in the Physiology Laboratory of LASUCOM one week before the 2015 Ramadan fast and in the 4th week of fasting. To avoid errors due to diurnal variation in physiological parameters, all studies were carried out between 16:30 - 18:30 hours with the laboratory temperature maintained at 22°C to prevent temperature variation while performing the tests. Subjects were asked to avoid alcoholic drinks, cigarette smoking, coffee and/or tea as well as exercise before the experiments.[26]

Procedure

On arrival in the laboratory, all subjects were asked to sit quietly and rest for 10 minutes before the experiments. Subjects' weights (kg) was measured to the nearest 0.1kg using an Omron digital weight scale while the height (m) was measured to the nearest 0.1cm using a stable stadiometer (Seca 217). Body mass index (kg/m^2) was thereafter calculated as w/h^2 (m^2). Baseline brachial blood pressure was measured using the standardized protocol developed by the International Collaborative Study.[27] Briefly, using the auscultative method, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded to the nearest 2 mmHg as the first and fifth Korotkoff phases respectively. All blood pressure (mmHg) observations were carried out after allowing a 10-minute period of rest after the measurement of each subject's height. Pulse pressure and Mean Arterial Blood Pressure (MABP) were calculated using standard formulae.

Cold Pressor Test

While still seated comfortably and after a rest period of 30 minutes, blood pressure (mmHg) was determined as described above, at 10min intervals until three almost identical blood pressures were obtained. The last of these three BP measured was taken to be the Basal Blood Pressure (mmHg).[19,28] The subjects were then asked to immerse the right foot up to the ankle, in ice slurry maintained at 4°C for one minute.[19,29-30] Three blood pressure measurements were taken rapidly and serially at the end of the minute with the foot still immersed. The highest of these three blood pressure readings was recorded as the Peak Blood Pressure.[19,28] These tests were carried out one week before the fasting (1BF) and in the fourth week of fasting (4WF). Subjects were considered hyperreactive if Peak BP minus Basal BP was +15mmHg or more whether systolic blood pressure (SBP) or diastolic blood pressure (DBP).[19,31] Subjects who had a difference that was < 15 mmHg SBP or DBP were considered normoreactive.[19,31] Magnitude of the subjects' pressor response to the cold pressor test was calculated as percentage change ($\% \Delta \text{BP}$) from the baseline.

Data Analyses

Data was analysed by means of the Student t test using the GraphPad Prism version 5.01 for Windows, GraphPad Software, California, USA; and Z Score for comparison of proportions. Results were expressed as mean \pm SEM and level of significance set as $p = 0.05$

RESULTS

Baseline characteristics of the 70 volunteers aged 18 to 50 years is as shown in Table 1. Following exposure to the cold pressor test, both systolic (Figure 1) and diastolic (Figure 2) blood pressures increased significantly ($p < 0.0001$) from the resting levels. As shown in Table 2, systolic hyperreactivity was recorded in 42(60%) of the subjects while diastolic hyperreactivity was recorded in 32(46%). Interestingly, 26(37%) displayed both systolic and diastolic

hyperreactivity to the cold pressor test before intermittent dietary restriction (Table 2). Also, both pulse pressure (PP) and mean arterial blood pressure (MABP) increased significantly from the resting values following one minute of autonomic stimulation by the cold pressor test (Table 3).

By the fourth week of fasting, the weight of the subjects had fallen significantly ($p < 0.001$) from $64.39 \pm 1.13\%$ kg to $62.60 \pm 1.07\%$ (Table 4). Similarly, BMI of the subjects had reduced significantly ($p < 0.0001$) from 22.9 ± 0.34 (kg/m^2) to 22.3 ± 0.35 (kg/m^2) (Table 4). There was slight reduction in the resting systolic and diastolic blood pressures following 4 weeks of intermittent dietary restriction as shown in Table 5. However, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly increased ($p < 0.0001$) by exposure to the CPT after dietary restriction (Figure 1, Figure 2). On the other hand, vascular reactivity reduced following the four weeks of fasting as 47% now

exhibited systolic hyperreactivity while only 36% of the subjects exhibited diastolic hyperreactivity and 33% were positive for both systolic and diastolic hyper-reactivity to the CPT (Table 2). The pressor response shown in the calculated measures, pulse pressure and MABP were also reduced (Table 6). Similarly, there was significant reduction in the magnitude of both the systolic and diastolic blood pressure responses to the CPT in the fourth week of fasting compared to that before fasting (Table 7).

Table 1: Baseline characteristics of subjects

	X ± SEM
Age (y)	24.81 ± 0.84
Weight (kg)	64.39 ± 1.13
Height (m)	1.68 ± 0.01
BMI (kg/m^2)	22.92 ± 0.34
SBP (mmHg)	108 ± 2
DBP (mmHg)	77 ± 1
PP (mmHg)	31 ± 1
MABP (mmHg)	87 ± 1

Key: BMI = Body Mass Index; SBP= systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MABP = mean arterial blood pressure

Table 2: Vascular reactivity status of subjects before and after dietary restriction

	SHP	DHP	SHP + DHP
1BF	42 (60%)	32 (46%)	26 (37%)
4WF	33 (47%)	25 (36%)	23 (33%)
p	0.14	0.24	0.60

Key: SHP = Systolic hyperreactivity; DHP = Diastolic hyperreactivity; 1BF = One week before fasting; 4WF = 4th week of fasting

Table 3: Effect of Cold Pressor Test on Blood Pressure Before Dietary Restriction

	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MABP (mmHg)
Before CPT	108 ± 2	77 ± 1	31 ± 1	88 ± 1
After CPT	130 ± 2	93 ± 2	38 ± 1	105 ± 2
p value	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Key: SBP= systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MABP = mean arterial blood pressure; CPT = cold pressor test

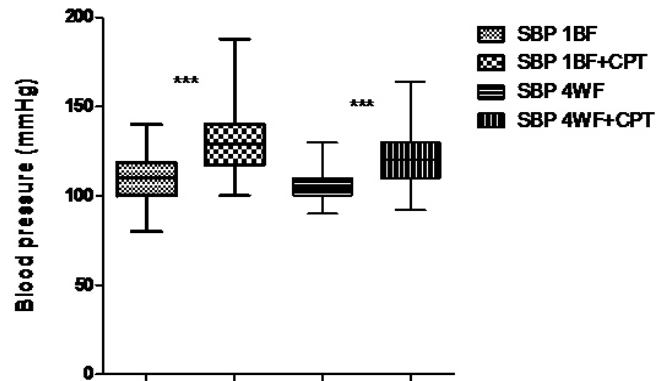


Figure 1: Systolic blood pressure response to the cold pressor test before and after dietary restriction

*** - $p < 0.0001$

SBP = systolic blood pressure, CPT - cold pressor test, 1BF = 1 week before fasting; 4WF = 4th week of fasting

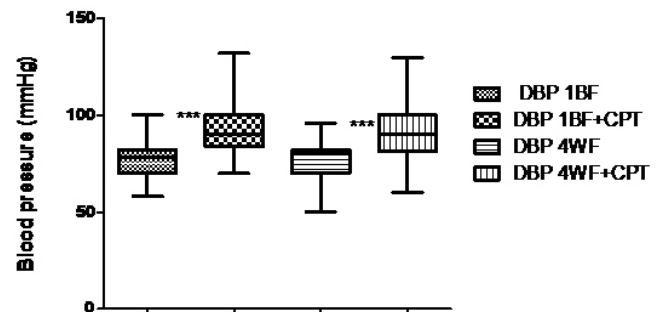


Figure 2: Diastolic blood pressure response to the cold pressor test before and after dietary restriction

*** = $p < 0.0001$

DBP = diastolic blood pressure, CPT - cold pressor test, 1BF = 1 week before fasting; 4WF = 4th week of fasting

Table 4: Effect of 4 weeks' intermittent dietary restriction on weight and body mass index

	1BF	4WF	p
Weight (Kg)	64.39 ± 1.13	62.60 ± 1.07	<0.0001 (CI= 1.319 – 2.252)
BMI (Kg/m ²)	22.92 ± 0.34	22.31 ± 0.35	<0.0001 (CI=0.458 – 0.774)

Key: 1BF = One week before fasting; 4WF = 4th week of fasting; BMI = body mass index; CI= confidence interval

Table 5: Comparison of resting blood pressures before and after dietary restriction

	1BF	4WF	p
SBP(mmHg)	108 ± 2	106 ± 1	0.09
DBP(mmHg)	77 ± 1	77 ± 1	0.98
PP(mmHg)	31 ± 1	29 ± 1	0.10
MABP(mmHg)	88 ± 1	87 ± 1	0.43

Key: 1BF = one week before fasting; 4WF = in the 4th week of fasting; SBP= systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MABP = mean arterial blood pressure

Table 6: Effect of the cold pressor test on blood pressure after dietary restriction

	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MABP (mmHg)
Before CPT	106 ± 1	77 ± 1	29 ± 1	87 ± 14
After CPT	122 ± 2	90 ± 2	32 ± 1	101 ± 2
p	0.0001	0.0001	0.013	0.0001

Key: SBP= systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MABP= mean arterial blood pressure; 4WF = 4th week of fasting; CPT = cold pressor test

Table 7: Comparison of the magnitude of the pressor response to the cold pressor test before and after dietary restriction

% Change	1BF	4WF	p
SBP	20 ± 2	15 ± 2	0.006
DBP	22 ± 2	17 ± 2	0.032

Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; 1BF = one week before fasting; 4WF = 4th week of fasting; CPT = cold pressor test

DISCUSSION

The role of the autonomic nervous system in blood pressure regulation cannot be overemphasized. The effect of the Ramadan model of intermittent dietary restriction (IDR) on health has not been well explored in this environment. This study evaluated the effect of IDR on blood pressure changes induced by acute sympathetic activation using the Ramadan model.

In the present study, IDR led to significant decreases ($p < 0.0001$) in body weight and body mass index (BMI) and slight resting blood pressures. However, although the reduction in body weight and BMI was similar to earlier reports,[7,9,32] the effect on resting blood pressures seems to add to existing contradiction. For instance, reduced resting

systolic blood pressure (SBP) alone was reported by some researchers[9,32] while some others had documented a fall in diastolic blood pressure only with increased SBP,[33-34] and still others, a reduction in both systolic and diastolic blood pressures[7] following the Ramadan fast. It is unclear why this is so but it may be due to genetic or environmental differences (including dietary) among the populations studied; certainly, more work is required in this area. The reduced body weight and BMI seen after 4 weeks of fasting in this study may be associated with reduced meal frequency during this period and increase in growth hormone (GH) secretion. There is usually an increase in GH secretion during fasting and its metabolic effects include increase in lipolysis and reduction in the peripheral utilization of glucose.[35]

However, GH and lipid levels were not determined in the present study.

The cold pressor test (CPT), apart from being a reliable tool for assessment of autonomic nervous system, is also useful in predicting future cardiovascular disease like hypertension and strokes.[20-23] The increased sympathetic outflow to the CPT leading to increased SBP and DBP in both sexes observed in this study is similar to that reported earlier.[16,19-20,22-23] Vascular hyperreactivity which is a definite index of predisposition to future hypertension[22] was observed among this study group with some even displaying both systolic and diastolic hyperreactivity. This is similar to our earlier reports in normotensive young adults.[19]

The magnitude of the pressor response to the CPT was reduced after the intermittent dietary restriction in our subjects. A similar response was obtained in rats subjected to long-term caloric restriction.[4] This is an important indicator that such intermittent fasting may help in reducing the sympathetic outflow to stressors in the environment and therefore contribute to a reduction in the development of hypertension since cardiovascular reactivity has been shown to be a predictor of future hypertension.[20] For instance, an increased incidence of about 23% has been reported in those subjects with increased stress reactivity compared to their normoreactive counterparts.[36-37] The reduction in the magnitude of response (% Δ BP) to the CPT following IDR in the current study and similar reports implies a reduction in vascular response and a suppression of sympathetic nervous system contribution to blood pressure elevation. Systolic hyperreactivity was consistently higher than diastolic hyperreactivity both before and after IDR. This finding is important in that systolic hyperreactivity has been documented to confer greater risk for developing cardiovascular accidents compared with diastolic hyperreactivity.[21] There are however suggestions that the absolute values of systolic blood pressure during the cold pressor test are better predictors of future hypertension compared with the changes in systolic blood pressure caused by the test.[23,38]

It has been reported that vascular reactivity correlates positively with BMI.[39] The observation among our subjects is not different since BMI reduced following the intermittent dietary restriction (IDR) and there was an associated reduction in the vascular reactivity recorded in the subjects compared to that before fasting. This reduction in BMI may be contributory to the reduction in vascular response observed among the subjects since weight loss in the obese has a normalizing effect on SNS dominance over PNS.[12]

There was also a reduction in the magnitude of the pulse pressure and mean arterial blood pressure response to the CPT in the 4th week of fasting. Pulse pressure is reported to be an even more important predictor of morbidity and mortality than the other blood pressure parameters.[40] Its reduction in the 4th week of fasting suggests that IDR may be important in reducing morbidity and mortality in individuals susceptible to hypertension and other cardiovascular events. Intermittent fasting had been associated with catecholamine inhibition and decrease in sympathetic tone leading to reduced venous return. This leads to a fall in blood pressure, heart rate and cardiac output.[41] Dietary restriction also

reduces oxidative stress and increase endothelial bioavailability of nitric oxide.[42] Nitric oxide decreases sympathetic nervous system contribution to blood pressure elevation.[43]

CONCLUSION

The results of this study confirms our earlier report that normotensive Nigerians have both systolic and diastolic hyperreactivity and this may be explored further for targeted interventions. Intermittent dietary restriction led to a reduction in the pressor response to the cold pressor test and hyperreactivity in susceptible individuals. We therefore conclude that four weeks' intermittent dietary restriction modulated blood pressure responses to acute sympathetic activation and intermittent dietary restriction using the Ramadan model may be beneficial in hypertensive patients and normotensive subjects predisposed to developing hypertension in the future.

Acknowledgement

This study was funded in part by a Research Grant of the Lagos State University College of Medicine, 2015. We thank G.A. Umoren for technological support.

Conflict of Interest

None

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