Effect of Diet and Exercise Intervention on Blood Pressure, Insulin, Oxidative Stress, and Nitric Oxide Availability

Christian K. Roberts, PhD; Nosratola D. Vaziri, MD; R. James Barnard, PhD

Background—Diet and exercise can affect blood pressure and atherosclerotic risk.

Methods and Results—The present study was designed to examine the effects of a short-term, rigorous diet and exercise intervention on blood pressure, hyperinsulinemia, and nitric oxide (NO) availability. Men (n=11) were placed on a low-fat, high-fiber diet combined with daily exercise for 45 to 60 minutes for 3 weeks. Pre- and post fasting blood was drawn for serum lipid, insulin, 8-isoprostaglandin F$_{2\alpha}$ (8-iso-PGF$_{2\alpha}$), and glucose measurements. Anthropometric parameters, blood pressure (BP), and 24-hour urinary NO metabolite excretion (NOX), a marker of NO bioavailability, were measured. Systolic (P<0.01) and diastolic BP (P<0.01) and 8-iso-PGF$_{2\alpha}$ decreased (P<0.05), whereas urinary NOX increased (P<0.05). There was a significant reduction in fasting insulin (P<0.01) and a significant correlation between the decrease in serum insulin and the increase in urinary NOX (r$^2=0.68$, $P<0.05$). All fasting lipids decreased significantly, and the total cholesterol to high-density lipoprotein cholesterol ratio improved. Although body weight and body mass index (P<0.01) decreased, obesity was still present and there were no correlations between the change in body mass index and the change in insulin, BP, or urinary NOX.

Conclusions—This intervention resulted in dramatic improvements in BP, oxidative stress, NO availability, and the metabolic profile within 3 weeks, mitigating the risk for atherosclerosis progression and its clinical sequelae.

Key Words: hypertension ■ free radicals ■ oxygen ■ insulin

Hypertension affects more than 50 million people in the United States and is a hallmark risk factor for stroke, congestive heart failure, renal insufficiency, and coronary artery disease. It has been estimated that one quarter of all adults have hypertension and only 47% have optimal blood pressure (BP, <120/80) in the United States. Hypertension is a major component of the metabolic syndrome which affects 23% of the population in Westernized societies.

Recently, attention has focused on oxidative stress as a causative factor in hypertension. We have shown that a high-fat, refined carbohydrate diet results in oxidative stress, decreased NO availability, and endothelial dysfunction in animals. One study in humans has demonstrated that a low-fat diet with fruits, vegetables, and low-fat dairy can reduce BP in both hypertensive and normotensive individuals. Furthermore, exercise has been shown to lower BP in hypertensive individuals. Accordingly, this study was designed to investigate the effects of a combined, short-term diet and exercise intervention on hypertension, oxidative stress, and NO availability in men.

Methods

Diet and Exercise Intervention
The study protocol was approved by the Human Subjects Protection Committee and informed consent of all subjects was obtained before enrollment. Serum was obtained from 11 men (age range=38 to 72 years) who voluntarily participated in the Pritikin Longevity Center 21-day residential diet and exercise intervention. Diseases under drug therapy included hypercholesterolemia and hypertension in 3 individuals each. Hypertension was present in 7 patients and type 2 diabetes in 2 patients.

Once enrolled, a complete history was taken and participants received a physical examination and underwent a 21-day diet and exercise intervention. Meals were served buffet style, and all participants were allowed to eat ad libitum. This was intended to explore the effect of altered food composition as opposed to its quantity. Prepared meals contained ~10% of calories from fat (polyunsaturated/saturated fatty acid ratio=1.24), 15% to 20% from protein, and 70% to 75% from primarily unrefined carbohydrate. Carbohydrates were from high-fiber whole grains (≥5 servings/d), vegetables (≥4 servings/d), and fruits (≥3 servings/d). Protein was primarily derived from plant sources, with nonfat dairy (up to 2 servings/d) and fish or fowl served (in 3 1/2 oz. portions) 1 d/wk and soups or casseroles (2 d/wk). Alcohol, tobacco, and caffeine were not allowed.

BP at rest was measured using standard auscultation techniques after several minutes of quiet rest in the supine position. The exercise regimen consisted of daily walking at the training heart rate for 45 to 60 minutes, determined by a graded treadmill stress test. The training heart rate was defined as 70% to 85% of the maximal heart rate obtained during the treadmill exercise tolerance test.

Fasting blood samples were drawn on days 1 and 21, and serum was separated by centrifugation and stored at −80°C until analyzed.

Received July 30, 2002; revision received September 16, 2002; accepted September 16, 2002.

From the Department of Physiological Science, University of California, Los Angeles (C.K.R., R.J.B.), and the Division of Nephrology and Hypertension, Department of Medicine, University of California, Irvine (C.K.R., N.D.V.).

Correspondence to R. James Barnard, Department of Physiological Science, UCLA, P.O. 951527, Los Angeles, CA 90095-1527. E-mail jnbarnard@physci.ucla.edu

© 2002 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000040584.91836.0D
Roberts et al  
Lifestyle Modification and Hypertension  
2531

### Metabolic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>107.1±5.8</td>
<td>103.1±5.7†</td>
<td>3.7</td>
</tr>
<tr>
<td>BMI</td>
<td>37.6±2.8</td>
<td>36.1±2.6†</td>
<td>3.9</td>
</tr>
<tr>
<td>Total-C, mg/dL</td>
<td>191.5±9.2</td>
<td>154.5±6.9†</td>
<td>19.3</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>113.2±6.1</td>
<td>87.5±6.0†</td>
<td>22.7</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>41.6±3.1</td>
<td>35.5±1.8†</td>
<td>14.8</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>223±52</td>
<td>131±20*</td>
<td>41.3</td>
</tr>
<tr>
<td>Total-C/HDL-C</td>
<td>4.95±0.42</td>
<td>4.39±0.35*</td>
<td>11.3</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137.8±4.3</td>
<td>119.0±2.9†</td>
<td>13.6</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>81.4±2.2</td>
<td>73.4±2.4†</td>
<td>9.8</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>22.9±3.9</td>
<td>12.3±1.8†</td>
<td>46.2</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>105.8±5.6</td>
<td>98.5±3.9</td>
<td>7.0</td>
</tr>
</tbody>
</table>

All data are expressed as mean±SEM. 
*P<0.05, †P<0.01 postintervention vs preintervention.

### Determination of Metabolic Parameters, 8-Isoprostaglandin F$_{2\alpha}$, and Urinary NO Metabolite Excretion

#### Effect of diet and exercise intervention on 8-iso-PGF$_{2\alpha}$ (A). Effect of diet and exercise intervention on urinary NOX (B). Relationship between urinary NOX and insulin (C). Values are means±SE. 
*P<0.05 versus Post versus Pre.

with significant improvement in insulin sensitivity and increase urinary NOX.

The Dietary Approaches to Stop Hypertension (DASH) clinical trial,\(^*$ which tested a diet high in fruits and vegetables and low-fat dairy and reduced red meat, sugar, and refined carbohydrates, demonstrated significant BP reduction after 8 weeks. In the present intervention, more pronounced reductions in systolic (19 mm Hg) and diastolic (8 mm Hg) BP occurred within 3 weeks. At the beginning of the study, 7 of the 11 subjects were hypertensive, but at the end none had hypertension (>140 mm Hg systolic or >90 diastolic). The more robust reductions in BP and other changes noted in the present study compared with previous studies were most likely due to the more rigorous dietary changes, the added exercise, or a combination of the two. Weight loss per se was probably not a significant contributor in the present study, as there was no association between changes in BP and BMI. The average BMI decreased from 37.5 to 36.1, indicating the presence of obesity post-intervention despite blood pressure normalization. In a recent study,\(^*$ intentional weight loss achieved by gastric surgery, yielding a sustained weight loss of ~20 kg, had no effect on the incidence of hypertension during an 8-year observation period.

Increased intake of fiber, antioxidants, and other phytochemicals, as well as the reduced fat and refined sugar...
consumption, most likely contributed to the reductions in insulin and oxidative stress and the improvements in urinary NOx and BP in the present study. Vogel et al\textsuperscript{10} demonstrated that a single high-fat meal could impair endothelial function in healthy individuals, and this response was blocked by pretreatment with antioxidant vitamins C and E, suggesting an oxidative mechanism.\textsuperscript{11} Title et al\textsuperscript{12} reported an impairment in endothelium-dependent flow-mediated vasodilation in healthy subjects after an oral glucose load, which was also prevented with antioxidant pretreatment. More recent data suggests that fruits and vegetables may reduce BP,\textsuperscript{13} protect against lipid peroxidation, and augment antioxidant capacity as evidenced by increased plasma carotenoids (ie, cryptoxanthin, lutein, β-carotene)\textsuperscript{14,15} and serum oxygen radical-absorbing capacity.\textsuperscript{14}

Isoprostanes are a family of eicosanoids produced mainly by non-enzymatic oxidation of arachidonic acid by reactive oxygen species. Consequently, their production is increased in the presence of oxidative stress. The reduction of 8-iso-PGF\textsubscript{2α} in the present study suggests amelioration of oxidative stress by the diet and exercise intervention. Thompson et al\textsuperscript{16} documented a 35% reduction in urinary 8-iso-PGF\textsubscript{2α} after 14 days of consuming an array of fruits and vegetables and suggested that this was important for maximizing exposure to a variety of beneficial phytochemicals, many of which remain undefined. This may contribute to an increase in NO availability, as observed in this study, as well as a decrease in other oxidative processes that contribute to hypertension and other chronic diseases.

There was a significant improvement in NO availability after the diet and exercise intervention. This could be due to either an increase in NO production or a decrease in NO sequestration by reactive oxygen species. The reduction in 8-iso-PGF\textsubscript{2α} suggests a reduction in reactive oxygen species and hence reduced scavenging of NO. The latter conclusion is based on our previous animal studies, which documented that consumption of a Western-type diet can limit NO availability via enhanced reactive oxygen species-mediated inactivation and sequestration of NO.\textsuperscript{5}

The exercise component may have contributed to the improved NO availability and reduction in BP. Exercise training has been shown to increase NO production and NOS expression, enhance antioxidant enzyme levels, and ameliorate endothelial dysfunction.\textsuperscript{16} Thus, the added exercise may have contributed to the increased urinary NO\textsubscript{x} and decreased 8-iso-PGF\textsubscript{2α}, as well as the more significant drop in BP noted in the present study compared with previous studies.\textsuperscript{6} In addition, both the diet and exercise could contribute to the improvement in insulin sensitivity in the present study. Petrie et al\textsuperscript{17} have shown that insulin sensitivity is related to endothelial function, a process that may account for the significant correlation between the reduction in insulin and the increase in urinary NO\textsubscript{x} found in the present study.

One limitation is that the assay used to detect lipid peroxidation is dependent on both the extent of oxidative stress and on lipid substrate abundance. Additionally, 8-iso-PGF\textsubscript{2α} may be produced by cyclooxygenase-dependent mechanisms, although this is thought to be negligible under physiological conditions.\textsuperscript{18}

The present study demonstrates that an unrestricted low-fat, high-fiber diet combined with daily exercise can significantly lower BP and ameliorate hypertension, as well as improve risk factors for other chronic diseases in a very short time. It is of note that merely a change in the food composition without restriction in food consumption resulted in improvements in all parameters. The greater changes observed in the present study compared with previous studies suggests that more intensive changes in lifestyle lead to greater improvements. Additionally, the improvements achieved in the lipids, insulin/glucose, oxidative stress, NO availability, and blood pressure may mitigate the progression of chronic diseases such as coronary artery disease and diabetes.

Acknowledgments
This study was supported by a grant from the L-B Research/Education Foundation. Christian Roberts is supported by a National Research Scholarship Award postdoctoral fellowship, NIH F32 HL68406-01.

References
Effect of Diet and Exercise Intervention on Blood Pressure, Insulin, Oxidative Stress, and Nitric Oxide Availability
Christian K. Roberts, Nosratola D. Vaziri and R. James Barnard

Circulation. 2002;106:2530-2532; originally published online October 21, 2002; doi: 10.1161/01.CIR.0000040584.91836.0D
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/20/2530

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/