Angiotensin Receptor Blockade Improves Arterial Distensibility and Reduces Exercise-Induced Pressor Responses in Obese Hypertensive Patients With the Metabolic Syndrome

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Patients with the metabolic syndrome have three or more of five cardiovascular risk factors and increased oxidative stress, arterial stiffness and pressor responses to exercise, which may contribute to their threefold greater risk for coronary heart disease. In addition to lowering basal blood pressure (BP), angiotensin receptor blockers (ARBs) may benefit metabolic syndrome patients by reducing oxidative stress, arterial stiffness, and pressor responses to exercise.

Twelve patients, 7 women and 5 men, with the metabolic syndrome (aged 45 ± 2 years, BP 145 ± 5/85 ± 2 mm Hg, waist girth 110 ± 3 cm, triglycerides 186 ± 23 mg/dL, HDL cholesterol 44 ± 2 mg/dL, glucose 99 ± 3 mg/dL) were studied off medications, while on modest sodium restriction (\( \leq 100 \) mmol/d). Patients were randomized to the ARB losartan or placebo for 3 weeks then crossed over to the complement for 3 weeks. Studies were performed at the end of each phase following an overnight fast. Serum lipids and biomarkers of oxidative stress (F2-isoprostanes, thiobarbituric acid reacting substances) were unchanged by losartan, whereas large artery elasticity at rest, measured with the HDI PulseWave, increased from 13.6 ± 0.7 on placebo to 16.2 ± 1.1 mL/mm Hg on losartan, \( P < .05 \). Losartan lowered systolic BP pre-exercise from 142 ± 3 to 131 ± 5 mm Hg (\( P < .001 \)) and systolic BP after 6 min of treadmill exercise from 192 ± 6 to 169 ± 5 mm Hg (\( P < .001 \)). Losartan lowered systolic BP (\(-23 \pm 3 \) v \(-11 \pm 2 \) mm Hg, \( P < .05 \)) and pulse pressure (\(-4 \pm 1 \) v \(-15 \pm 2 \) mm Hg, \( P < .05 \)) more during exercise than rest. Losartan reduces the pressor response to exercise, perhaps by enhancing arterial compliance. In addition to lowering basal BP, angiotensin receptor blockade in patients with metabolic syndrome improves arterial compliance and reduces pressor reactivity to exercise. Am J Hypertens 2004;17:477–482 © 2004 American Journal of Hypertension, Ltd.

Key Words: Angiotensin receptor blockade, metabolic syndrome, arterial compliance, hypertension, exercise blood pressure.

The metabolic syndrome is defined by the National Cholesterol Education Program (NCEP-3) as three or more of five risk factors: abdominal obesity (waist circumference), resting blood pressure (BP), fasting glucose, triglycerides, and HDL cholesterol. The metabolic syndrome affects an estimated 23.7% or \( \approx 47,000,000 \) adults in the United States and is associated with about threefold greater risk for coronary heart disease. The metabolic syndrome is strongly related to both age and body mass index.

Because the median age and weight of people in the United States and much of the world are rising, the metabolic syndrome and its complications are likely to increase as well. Interventions that favorably affect multiple risk factors may be particularly useful in addressing current and future health and economic challenges presented by the metabolic syndrome.

The metabolic syndrome and its components are associated with several cardiovascular risk factors including...
reduced arterial distensibility and greater pressor responses to exercise, which are independently associated with coronary heart disease. The greater vascular stiffness could lead to larger increases of systolic pressure with exercise which raises stroke volume.

Oxidative stress is a key signaling event in vascular remodeling. Angiotensin induces the production of reactive oxygen species and magnifies oxidative stress in response to other signaling agents in vitro. Obesity and markers of insulin resistance are associated with a more active renin-angiotensin-aldosterone system, which may contribute to enhanced oxidative stress, vascular remodeling, and pressor responses to exercise. Angiotensin receptor blockers (ARBs) reduce oxidative stress, vascular stiffness, and pressor-induced exercise responses, which suggests these agents may be particularly beneficial in patients with the metabolic syndrome. Therefore, we studied effects of the ARB losartan on indices of oxidative stress, arterial compliance, and pressor responses to exercise in patients with the metabolic syndrome.

**Methods**

**Human Volunteers**

All subjects read and signed a written consent form approved by the Office of Research Protection and Integrity at the Medical University of South Carolina, and 12 subjects meeting inclusion and exclusion criteria were enrolled. Volunteers included 7 women (5 post-menopausal, 2 pre-menopausal) and 5 men whose body mass indices all exceeded 27 kg/m². The mean of BP in the absence of antihypertensive medications measured on each of three qualifying visits in the sitting position were in the range of 130 to 159 mm Hg systolic or 85 to 99 mm Hg diastolic. All individuals had a waist circumference >102 cm for men or >88 cm for women and at least one metabolic factor including triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL, for men or <50 mg/dL for women, or impaired fasting glucose ≥110 to 125 mg/dL. Subjects with fasting glucose ≥126 mg/dL, renal insufficiency (serum creatinine >1.5 mg/dL), clinical cardiovascular disease or any chronic illnesses requiring treatment were excluded from further participation.

**Physiologic Measurements**

Blood pressure was measured in the laboratory on each study visit by a trained observer using a mercury sphygmomanometer and an appropriately sized cuff. Systolic BP was defined by the first Korotkoff sound and diastolic BP by the disappearance of the last Korotkoff sound (phase 5). Blood pressure was measured in the seated position after 5 min of rest in triplicate at 2-min intervals and the mean of the last two readings at each visit used for qualifying purposes.

Heart rate (in beats per minute) was measured at each visit by counting the volunteer’s radial pulse for 60 sec between the second and third measurement of casual (seated) BP.

During the exercise treadmill test, BP and heart rate were measured in triplicate using a mercury sphygmomanometer and appropriately sized arm cuff after 5-min rest in the seated position with single measurements at 3 (stage 1, 1.7 miles/h at 10% elevation) and 6 min (stage 2, 2.5 miles/h at 12% elevation) on a treadmill (modified Bruce protocol). Arterial compliance in the laboratory was measured by analysis of the radial artery pulse waveform as recorded with a sensory array taniometer (HDI/PulseWaveTM CR-2000; Hypertension Diagnostics, Inc., Eagan, MN). The analysis provides an estimate of both large (C1) and small (C2) artery compliance which have been instructive in several studies. However, questions about the accuracy and interpretation of these data have been raised.

**Biochemical Measurements**

A comprehensive metabolic panel including electrolytes, blood urea nitrogen, creatinine, liver enzymes, total protein, albumin, and calcium was obtained by auto-analyzer at the Medical University Hospital Laboratory (Charleston, SC).

Triglycerides were measured by the fluorometric method. Total cholesterol was measured by the colorimetric method, and HDL cholesterol was prepared from whole plasma by precipitation with phosphotungstic acid. Very low-density lipoprotein cholesterol and LDL cholesterol were calculated.

For the indices of oxidative stress, F2-isoprostanes were assayed in plasma subjected to thin layer chromatography and subsequently to the highly sensitive and specific gas chromatography/mass spectroscopy assay method. Thiobarbituric acid reacting substances (TBARS) were measured as described.

**Protocol**

Subjects were seen on qualifying visits at weeks −3, −2, and −1. All volunteers were given an Omron (Schaumburg, IL) automated BP monitor. They were instructed to measure their BP twice daily throughout the entire study as an additional safety measure and to report readings ≥160/100 or <100/60 mm Hg. Twelve subjects met the inclusion/exclusion criteria and entered the active study period. Volunteers continued their regular diets for 1 additional week (week 0) and came to the General Clinical Research Center (GCRC) in the morning after an overnight fast. While in the GCRC, subjects underwent measurements of BP, heart rate, arterial compliance using the HDI Pulsewave, and indices of oxidative stress under resting (supine) baseline conditions. In the early afternoon after lunch, subjects underwent the limited exercise tolerance test (modified Bruce protocol).

After the measurements were completed, subjects were
instructed to begin a moderate sodium restriction (2400 mg/d) and were randomized to receive either placebo tablets or 50 mg of losartan once daily. Volunteers were seen 1 week later, and the losartan or placebo dose was increased to 100 mg once daily for the next 2 weeks in all subjects in an attempt to ensure 24-h antagonism of the AT1 receptor for those receiving active compound. The 100-mg losartan dose was tolerated by all subjects without symptoms of hypotension or BP readings <100/60 mm Hg in the office or at home.

After 3 weeks on placebo or losartan, subjects returned after an overnight fast to the GCRC with a 24-h urine collection to assess adherence with the moderate dietary sodium restriction. They underwent a repeat of the initial protocol while on the either the placebo or losartan. After completing the second laboratory assessment, subjects continued the moderate sodium restriction and were switched to the complement of the placebo or losartan for 3 weeks with dose titration after 1 week as described. Three weeks later, or 6 weeks after their initial laboratory assessment, subjects returned to the GCRC in the morning after an overnight fast with a 24-h urine collection for their third laboratory testing per protocol.

Results

Twelve subjects with the metabolic syndrome were enrolled and completed the study protocol. Results of this study have been reported in abstract form.27 Descriptive baseline characteristics of these subjects are provided in Table 1. Every volunteer had a high normal BP, waist circumference >40 inches in men and >35 inches in women, and at least one other risk factor. The HDL-cholesterol was <50 mg/dL in 5 women and <40 mg/dL in 2 men, triglycerides were ≥150 mg/dL in 5 subjects, and fasting glucose was ≥110 mg/dL in 2 patients.

The effects of the 3-week randomized assignment to losartan as compared to placebo on selected hemodynamic and metabolic variables are shown in Table 2. As expected, losartan significantly reduced systolic and diastolic BP under baseline supine resting conditions. The decrease in baseline resting pulse pressure was marginally significant at P < .1 using a two-tailed t test. Heart rate and body weight did not change (not shown). Large artery compliance (elasticity index) increased significantly on losartan as compared to placebo, whereas small artery elasticity did not change significantly with short-term angiotensin receptor blockade. Losartan did not change plasma F2-isoprostanes or TBARS, the indices of oxidative stress.

In addition to lowering resting BP, losartan significantly reduced the systolic BP (Fig. 1) and pulse pressure responses (Table 2) to a standardized exercise treadmill test. The reduction of systolic BP after 6 min of exercise (Bruce protocol stage 2) was larger than the reduction in resting systolic BP (−23 ± 3 vs. −11 ± 2 mm Hg, P < .05). The reduction of systolic BP immediately after completing the treadmill test was also greater than the decline in resting BP. The differences in systolic BP at all other points were not significantly greater than the decline in resting systolic BP. Heart rate during and after the treadmill test were not significantly different between the placebo and losartan phases (not shown).

Discussion

The principal findings of this study are that short-term therapy with the angiotensin receptor blocker losartan in obese subjects with the metabolic syndrome improves large artery distensibility (compliance) and reduces the

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<th>Table 1. Descriptive baseline characteristic of the metabolic syndrome subjects on usual diet</th>
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BMI = body mass index; BP = blood pressure; S/D/PP = systolic/diastolic/pulse pressure; LAEI = large artery elasticity index; SAEI = small artery elasticity index; TBARS = thiobarbituric acid reacting substance.
systolic BP response to exercise. In addition to the five variables used to define the metabolic syndrome by the National Cholesterol Education Program,1 subjects with the cluster of risk factors related to abdominal obesity and insulin resistance have several other risk factors for cardiovascular disease,5 including reduced arterial compliance6 and enhanced pressor responses to a standardized exercise test.7,8 Therapeutic interventions that simultaneously address multiple risk factors in patients with the metabolic syndrome may be particularly beneficial in reducing the heightened coronary heart disease risk. In addition to decreasing basal BPs, in separate studies angiotensin receptor blockers were shown to improve insulin action,28 arterial remodeling14 and stiffness17 and to reduce pressor responses to exercise,18 which may be particularly beneficial for high-risk metabolic syndrome patients.

Oxidative stress has emerged as a fundamental signaling event in the pathogenesis of hypertension, vascular remodeling, and target organ complications.10,11 Angiotensin appears to mediate adverse cardiovascular effects through reactive oxygen signaling pathways directly and by amplifying oxidative stress induced by other agents. Patients with the metabolic syndrome have multiple hemodynamic and vascular abnormalities, including increased BP, vascular stiffness, and pressor responses to exercise, which could be explained by an amplifying effect of angiotensin on oxidative stress signaling pathways. Although previous studies collectively support this notion, this is the first study to simultaneously assess measures of oxidative stress, vascular stiffness, and exercise pressor responses during angiotensin receptor blocker therapy.

A 3-week treatment period with the angiotensin receptor blocker losartan lowered basal and exercise BP and improved an index of large artery distensibility. However, these improvements were not associated with a reduction in two markers of oxidative stress (Table 2). These findings suggest either that the improvements in BP and arterial distensibility seen during short-term losartan therapy are mediated by effects unrelated to reduction of oxidative stress or that the markers selected were relatively insensitive for detecting an angiotensin receptor blocker-mediated reduction in oxidative stress.

Previous studies strongly suggest that angiotensin increases BP through oxidative stress-dependent pathways.29 Changes in oxidative stress can also modulate vascular tone and properties of the arterial wall.10,13,29 Angiotensin receptor blockers can reduce oxidation of LDL cholesterol in diabetics and improve arterial remodeling and distensibility in hypertensive patients.14,16,17
Exercise and prolonged exercise tolerance in patients with angina pectoris, whereas resting BPs were unchanged. However, in another study, losartan therapy for up to 6 months did not lower exercise BP. Differences between the studies include higher BPs (stages 1 and 2) of subjects in the previous report compared to high normal to stage 1 in this study. Our subjects followed a moderate salt restriction of ~2400 mg/d, which may be different from the diet of volunteers in the previous report. Another potentially important difference is that the losartan dose was 50 mg throughout the entire 6 months of treatment in the previous study and 100 mg during the last 2 weeks of the present investigation. Moreover, subjects in our study had the metabolic syndrome, whereas this was not specified in the previous report. Systolic BP responses to exercise are greater in older, obese, and hypertensive patients who are known to have lower arterial compliance and reduced baroreflex sensitivity. The characteristics of volunteers in various studies may impact key variables, for example, arterial compliance and baroreflex sensitivity, which could, in turn, modulate exercise pressor responses.

In summary, subjects with the metabolic syndrome have multiple risk factors that are independently predictive of greater cardiovascular risk beyond the five variables used to define the syndrome. Therapeutic interventions that improve multiple risk factors may be especially beneficial in ameliorating the substantial excess cardiovascular disease risk of the large and growing population of individuals with the metabolic syndrome. In this study, a 3-week treatment period with the angiotensin receptor blocker losartan, at 100 mg daily for the last 2 weeks, in 12 adults with the metabolic syndrome improved arterial compliance and lowered exercise BP significantly more than resting BP. Given the 3-week duration of the treatment intervention, the improvement of arterial compliance probably had a functional basis and did not appear to cause changes in oxidative stress. The improvement of arterial compliance may have contributed to the reduction in the exercise-induced pressor response in this short-term study. In other studies with calcium channel blockers and angiotensin-converting enzyme inhibitors, the magnitude of the reduction in resting and exercise BPs are comparable, at least in the short term. Thus, angiotensin receptor blockers may be especially useful for reducing multiple cardiovascular risk factors in subjects with the metabolic syndrome.

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References