Differential Effects of Nebivolol and Metoprolol on Insulin Sensitivity and Plasminogen Activator Inhibitor in the Metabolic Syndrome

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Abstract

Early generation β-blockers lower blood pressure and reduce cardiovascular mortality in coronary artery disease and congestive heart failure, but worsen glucose homeostasis and fibrinolytic balance. Nebivolol is a third-generation β-blocker which increases the bioavailability of nitric oxide. We compared the effect of nebivolol (5mg/d) and the β1-selective antagonist metoprolol (100mg/d) on glucose homeostasis and markers of fibrinolysis in 46 subjects with metabolic syndrome. Subjects underwent a frequently sampled intravenous glucose tolerance test after 3-week washout and placebo treatment, and following randomized treatment with study drug. After 12-week treatment, nebivolol and metoprolol equivalently decreased systolic blood pressure, diastolic blood pressure, and heart rate. Neither drug affected beta cell function, disposition index, or acute insulin response to glucose. Metoprolol significantly decreased the insulin sensitivity index. In contrast, nebivolol did not affect insulin sensitivity, and the decrease in sensitivity was significantly greater following metoprolol than nebivolol (-1.5±2.5 × 10⁻⁴ × min⁻¹ per mU/L versus 0.04±2.19 × 10⁻⁴ × min⁻¹ per mU/L after nebivolol, P=0.03). Circulating plasminogen activator inhibitor also increased following treatment with metoprolol (from 9.8±6.8 to 12.3±7.8 ng/mL), but not nebivolol (from 10.8±7.8 to 10.5±6.2 ng/mL, P=0.05 versus metoprolol). Metoprolol, but not nebivolol, increased F_{2α}-isoprostane concentrations. In summary, treatment with metoprolol decreased insulin sensitivity and increased oxidative stress and the antifibrinolytic plasminogen activator inhibitor-1 in patients with metabolic syndrome, whereas nebivolol lacked detrimental metabolic effects. Large clinical trials are needed to compare effects of nebivolol and the β1 receptor antagonist metoprolol on clinical outcomes in patients with hypertension and the metabolic syndrome.

Keywords

clinical science; insulin resistance; hypertension; cardiovascular pathophysiology; antihypertensive therapy

Introduction

The prevalence of obesity and the metabolic syndrome has reached epidemic proportions in developed countries and conveys an increased risk of cardiovascular mortality.¹,² Elevated
circulating concentrations of plasminogen activator inhibitor-1 (PAI-1), the major physiological inhibitor of fibrinolysis in vivo, are a hallmark of insulin resistance and the metabolic syndrome and, in turn, are associated with an increased risk of thrombotic cardiovascular events.3,4

Insulin resistance and impaired fibrinolysis contribute to increased cardiovascular morbidity and mortality in the metabolic syndrome.4 Importantly, commonly used antihypertensive agents differ in their impact on insulin sensitivity and biomarkers of impaired fibrinolysis. For example, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) improve glucose homeostasis in observational studies and some prospective trials.5-7 ACE inhibitors also decrease PAI-1 antigen and activity under conditions in which the renin-angiotensin-aldosterone system is activated.8 ARBs may have a transient beneficial effect on fibrinolytic balance, but this effect is not sustained.9 In contrast, diuretics impair glucose homeostasis and increase PAI-1 antigen and activity.10

Early generation β-blockers can worsen glucose homeostasis and have little effect or a detrimental effect on fibrinolytic balance.11-17 Nebivolol is a third-generation β-blocker which increases the bioavailability of endogenous nitric oxide.18,19 Nitric oxide decreases the expression of PAI-1,20 and improves insulin sensitivity and muscle glucose uptake.21 Based on the mechanism of action of nebivolol, we hypothesized that nebivolol would have a relatively favorable effect on insulin sensitivity and fibrinolytic balance compared to an earlier generation β-blocker.

Methods

Subjects

Subjects between the ages of 18 to 70 years with the metabolic syndrome were studied. All subjects gave written informed consent, and the study was approved by the institutional review board and implemented according to the Declaration of Helsinki. Metabolic syndrome was defined using the National Cholesterol Education Program (NCEP) criteria of 3 or more of the following: fasting plasma glucose of at least 100 mg/dL (5.5 mmol/L), serum triglycerides of at least 150 mg/dL (1.7 mmol/L), serum HDL cholesterol less than 40 mg/dL (1.04 mmol/L) in men or 50 mg/dL in women, untreated blood pressure of at least 130/85 mm Hg, or waist girth of more than 102 cm in men or 88 cm in women. Subjects with significant cardiovascular (other than hypertension), renal, pulmonary, endocrine (other than insulin resistance or hyperlipidemia), or hematological disease were excluded, as were pregnant women. Patients with diabetes, defined by a fasting glucose of 126 mg/dl (7.0 mmol/L) or medication use, were also excluded.

Study Protocol

Following screening history and physical examination, all anti-hypertensive medications were discontinued for three weeks prior (NCT00775671, Figure 1, upper panel). Spironolactone was discontinued 4 weeks prior to study initiation. Following washout, subjects were treated with placebo in a single-blind fashion for 21 days. For the last three days they were provided a nitrate-controlled diet. On the 20th day, subjects provided a 24-hour urine collection for measurement of electrolytes, and nitric oxide metabolites. The subjects reported to the Clinical Research Center the following day for measurement of fibrinolytic biomarkers and for a frequently sampled IV glucose tolerance test (IVGTT).

Following the first study day, patients were randomized to double-blind treatment with 5 mg nebivolol once daily or 100 mg metoprolol succinate ER once daily for twelve weeks. These doses were chosen based on published comparative studies indicating similar effects on blood pressure.17,22 Randomization was stratified by the presence or absence of

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hypertension and by race. Subjects returned for blood pressure checks and pill counts one, two, four, six, eight, and ten weeks after randomization to active study medication. After twelve weeks of study drug, subjects then repeated the nitrate-controlled diet, urine collection and study day with IVGTT.

**Hemodynamic measurements**

Blood pressure was measured with an aneroid sphygmomanometer (Tycos 767, Welch Allyn, Skaneateles Falls, NY) during office visits, using the appearance and complete disappearance of the Korotkoff sounds (K1 and K5) as systolic and diastolic blood pressures. The mean of 3 supine measurements was used. During the IVGTT, blood pressures were collected with an automated oscillometric recording device (Dinamap, Critikon, Carlsbad, CA).

**Insulin-modified frequently sampled intravenous glucose tolerance test**

Subjects reported to the CRC between 0700 and 0800 after a 12-hour fast and were studied in the supine position. One-half to one hour after taking their last dose of study medication, subjects rested in the supine position for fifteen minutes before their blood pressure was measured as described above. Intravenous catheters were then placed and, thirty minutes later, blood was obtained through a catheter for the measurement of fibrinolytic, endocrine, and inflammatory biomarkers. Two baseline samples were collected ten minutes apart for measurement of glucose and insulin (Figure 1, lower panel). At t=0 min, a bolus of 300 mg glucose/kg body weight was administered in a 25% glucose-saline solution over 1 minute. At t=20 min, a bolus of 0.02 units/kg body weight of regular insulin (Actrapid, Novo Nordisk, Princeton, JNJ) was given intravenously. Blood samples were collected for measurement of glucose and insulin at time t=2, 3, 4, 5, 6, 8, 10, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 90, 110, 130, 150, 170, 180 min. Plasma glucose was measured by glucose oxidase method with a Beckman glucose analyzer at every time point. Plasma insulin concentrations were determined by radioimmunoassay.

The acute insulin response to glucose (AIRg), the area under the insulin curve between 0 and 10 minutes, as well as sensitivity index (SI), the capacity for insulin to promote the disposal of glucose and to inhibit the endogenous production of glucose, were calculated using a modified version of the program MINMOD based on Bergman’s Minimum Model.\(^{23}\) Disposition index (DI), representing the overall ability of islet cells to secrete insulin normalized to the degree of insulin resistance, was also calculated using this model. Beta cell function was assessed by the computer model from the residual insulin secretion following the initial IV dextrose infusion.

**Laboratory Analysis**

Blood samples were collected on ice and centrifuged immediately at 0°C for 20 minutes. All plasma or serum were separated and stored at -80°C until the time of assay. Blood for measurement of PAI-1 and t-PA was collected in vacutainer tubes containing acidified 0.105M sodium citrate (Becton Dickinson, Rutherford, NJ), as use of anti-coagulant minimizes the contribution of platelet activation to PAI-1 antigen concentrations. PAI-1 antigen and t-PA antigen levels were both determined using 2-site enzyme-linked immunosorbent assays (Imulyse, Biopol AB).

Plasma renin activity (PRA) was determined by radioimmunoassay (DiaSorin, Stillwater, MN). Aldosterone was determined using a radioimmunoassay utilizing 125I-aldosterone (MP Biomedicals, Irvine, CA), a primary antibody to aldosterone (NIDDK National Hormone & Peptide Program, Torrance, CA), and a secondary anti-rabbit gamma globulin antibody (Linco Research, St. Charles, MO).
NO metabolites were measured in plasma and urine using a modified Griess reaction (Oxford Biomedical Research, Oxford, MI). Commercially available radioimmunoassay kits were used to measure plasma levels of cGMP (Amersham Pharmacia Biotech AB, Uppsala, Sweden.) Urine NO metabolites were normalized per mg of creatinine. Asymmetric dimethyl L-arginine was measured by mass spectroscopy. F2-isoprostanes were measured in plasma separated from EDTA-anticoagulated blood using negative ion gas-chromatography mass spectroscopy as previously described.24

**Statistical Analysis**

Data are presented as means ± standard deviation unless otherwise stated. Baseline characteristics of the two treatment groups were compared using a Student’s t-test or chi square testing as appropriate. The effects of nebivolol and metoprolol on hemodynamic, metabolic and fibrinolytic variables were compared using General Linear Models in which the between-subject variable was beta blocker. Race, age, BMI and pretreatment PAI-1 antigen were included as a between-subject variable or covariates as indicated. A P value ≤0.05 was considered significant. Analyses were performed using IBM SPSS Statistics v. 19.0.0.

**Results**

**Baseline Characteristics**

Forty-six subjects completed the study protocol. Table 1 provides their characteristics at screening. Subjects randomized to metoprolol were significantly older than those randomized to nebivolol. There were no other differences between the study groups at baseline.

**Hemodynamic Effects of Metoprolol and Nebivolol**

Twelve-week treatment with either metoprolol or nebivolol significantly decreased SBP, DBP and heart rate (P<0.05) and the hemodynamic effects of the two drugs were similar (Figure 1). Metoprolol (from 84±0.76 to 50±0.52 ng Ang l/mL/min, P=0.007) and nebivolol (from 67±0.72 to 23±0.31 ng Ang l/mL/min, P=0.009) similarly reduced PRA (P=0.61 for metoprolol versus nebivolol.) Metoprolol significantly reduced serum aldosterone (from 9.6±2.9 to 8.3±2.8 ng/dL, P=0.006). The effect of nebivolol on aldosterone was not statistically significant (from 9.5±3.0 to 8.5±2.3 ng/dL, P=0.057) but similar to that of metoprolol (P=0.82 for metoprolol versus nebivolol). Twenty-four hour urine sodium excretion was also similar in the two groups at baseline (123.3±59.1 mmol in the metoprolol group and 117.2±47.3 mmol in the nebivolol group), and after 12-weeks of treatment (108.0±49.7mmol in the metoprolol group and 123.9±40.8 mmol in the nebivolol group).

**Metabolic Effects of Metoprolol and Nebivolol**

Table 2 shows the effect of treatment with metoprolol or nebivolol on measures of insulin sensitivity and beta cell function calculated from the IVGTT. Twelve-week treatment with metoprolol significantly decreased the insulin sensitivity index. Nebivolol did not affect insulin sensitivity. Thus, the change in insulin sensitivity index differed significantly in the metoprolol and nebivolol treatment groups (-1.5±2.5 × 10^{-4} × min^{-1} per mU/L after 12 weeks of metoprolol versus 0.2 ±2.19 × 10^{-4} × min^{-1} per mU/L after nebivolol, P=0.03).

**Effects of metoprolol and nebivolol on fibrinolytic balance**

Pretreatment PAI-1 antigen concentrations were similar in the metoprol (9.8±6.8 ng/mL) and nebivolol (10.8±7.8 ng/mL) groups, but PAI-1 antigen concentrations were significantly
higher in the metoprolol-treated subjects after 12 weeks of therapy (12.3±7.8 ng/mL versus 10.5±6.2 ng/mL in nebivolol-treated subjects, P=0.05 after controlling for race and pretreatment PAI-1). There was a significant relationship between pretreatment PAI-1 antigen and post-treatment PAI-1 antigen (P=0.001). There was a significant effect of race on PAI-1 antigen in the nebivolol treatment group (P=0.017). The change in PAI-1 concentrations following 12-weeks of treatment also differed significantly in the two treatment groups (Figure 3).

During beta blockade, PAI-1 antigen correlated with fasting insulin concentration (r=0.45, P=0.002), the change in fasting insulin from pretreatment (r=0.44, P=0.003), and the change in fasting glucose from pretreatment (r=0.38, P=0.01).

T-PA antigen paralleled PAI-1 antigen concentrations. Hence, metoprolol treatment increased t-PA antigen concentrations from 11.2±2.3 ng/mL to 12.8±3.8 ng/mL (P=0.04), although post-treatment t-PA antigen concentrations did not differ significantly between the two groups.

**Effects of metoprolol and nebivolol on nitric oxide metabolites and oxidative stress**

Neither metoprolol nor nebivolol treatment altered plasma concentrations of nitric oxide metabolites (Table 3). Metoprolol increased urine nitric oxide metabolites, whereas nebivolol significantly increased plasma cGMP; however, the change in urine nitric oxide metabolites and plasma cGMP did not differ between treatment groups. Plasma cGMP correlated inversely with PAI-1 antigen concentrations (r=-0.36, P=0.02).

Metoprolol increased plasma F₂-isoprostanes from 1.78±1.04 to 2.22±1.42 ng/mL (P=0.008 after controlling for age). There was a significant interactive effect of age and metoprolol on circulating F₂-isoprostanes (P=0.02). Nebivolol did not significantly affect F₂-isoprostanes (1.78±0.83 ng/mL pretreatment and 1.95±1.63 ng/mL post-treatment). Neither metoprolol nor nebivolol altered plasma concentrations of ADMA (Table 3) or inflammatory cytokines (not shown).

**Discussion**

This study tested the hypothesis that the beta blockers nebivolol and metoprolol differ in their effects on insulin sensitivity and fibrinolytic balance. At doses that were equipotent with respect to reductions in blood pressure, heart rate, and renin activity, metoprolol treatment decreased insulin sensitivity, increased PAI-1 antigen concentrations and increased oxidative stress, whereas nebivolol treatment did not.

Metoprolol is a β₁ receptor-selective antagonist widely used to prevent cardiovascular disease. Like non-selective beta blockers, metoprolol has been reported to increase fasting glucose concentrations and/or insulin concentrations and to decrease insulin sensitivity as measured by HOMA-IR. The mechanism through which metoprolol decreases insulin sensitivity is not known but may involve decreased blood flow due to unopposed α receptor mediated vasoconstriction. It follows that nebivolol, a vasodilator, did not reduce insulin sensitivity; prior studies have reported that nebivolol reduces HOMA-IR. Poirier and colleagues compared the effects of atenolol and nebivolol, and found that, like metoprolol, atenolol significantly reduced insulin sensitivity (insulin-induced glucose disposal rate/mean insulin concentration ratio), but nebivolol did not.

This study is the first to compare the effects of nebivolol and an early generation beta blocker on fibrinolytic balance. Earlier studies reported that β₁ receptor-selective antagonists have no impact or a negative impact on PAI-1. For example, Boman et al
reported that 36-week treatment with atenolol increases PAI-1 activity in patients with hypertension and left ventricular hypertrophy, as we observed with metoprolol in individuals with the metabolic syndrome. Only two prior studies have examined the effect of nebivolol on fibrinolytic balance in humans. In an uncontrolled study in hypertensive patients, nebivolol decreased the PAI-1/α-PA ratio but did not affect PAI-1 antigen or activity concentrations. Vyssoulis et al reported that nebivolol and celioprolol reduced PAI-1 whereas carvedilol did not in patients with uncomplicated hypertension; however, twenty percent of patients were also taking hydrochlorothiazide, which increases PAI-1.

Circulating PAI-1 concentrations are increased during insulin resistance and both glucose and insulin stimulate response elements in the PAI-1 promoter. In the current study, PAI-1 antigen concentrations correlated with the effect of beta-blockade on both insulin and glucose concentrations, suggesting that increased insulin resistance contributed to the increase in PAI-1 concentrations during metoprolol. We hypothesize that the preservation of fibrinolytic balance during nebivolol treatment reflected preserved insulin sensitivity. Stimulation of nitric oxide synthase during nebivolol treatment would also be expected to moderate PAI-1 concentrations; nitric oxide decreases PAI-1 expression through a cGMP-dependent mechanism. Circulating cGMP and nitric oxide metabolite concentrations are imperfect measures of nitric oxide production in humans, however, and we did not find evidence of an effect of nebivolol on vascular nitric oxide production.

Increased oxidative stress contributes to cardiovascular risk in the metabolic syndrome. Nebivolol has been reported to reduce oxidative stress in rodent models. In vivo, LC-MS measurement of F₂-isoprostanes has become the gold standard for assessing oxidative stress. For the most part, studies using less accurate ELISA assays for F₂-isoprostanes report no effect of atenolol, carvedilol, or metoprolol on F₂-isoprostanes in hypertensive or diabetic patients. Fahlbusch also reported no effect of 6-day treatment with either carvedilol or metoprolol on urinary F₂-isoprostane excretion, measured by LC-MS, in healthy volunteers. Fratta et al reported that nebivolol reduced plasma F₂-isoprostanes, measured using a commercially available ELISA, in patients with essential hypertension. Troost et al reported that 7-day treatment with nebivolol decreased urinary F₂-isoprostanes, measured by LC-MS, in healthy volunteers. In the present study in subjects with the metabolic syndrome, the finding that metoprolol increased F₂-isoprostanes whereas nebivolol had no effect may reflect the high baseline levels of F₂-isoprostanes in this obese study population.

**Perspective**

The prevalence of obesity and the metabolic syndrome has reached epidemic proportions in developed countries. While metoprolol and other early generation β-blockers have been shown to reduce cardiovascular mortality in patients with coronary artery disease and congestive heart failure, this is not true in hypertension without these conditions and negative effects of these drugs on insulin resistance, plasminogen activator inhibitor, and oxidative stress, may diminish their beneficial effects in the obese. The present randomized study in individuals with the metabolic syndrome suggests that nebivolol has a favorable effect on fibrinolytic balance compared to metoprolol and lacks negative effects on insulin sensitivity and oxidative stress. Large clinical trials are needed to compare the effects of these two drugs on cardiovascular outcomes in obese patients with the metabolic syndrome.

**Acknowledgments**

Sources of Funding
References


Novelty and Significance

1. What Is New?
   - The β1 selective antagonist metoprolol has detrimental effects on oxidative stress and plasminogen activator inhibitor-1 concentrations, as well as insulin sensitivity, and a third generation β antagonist nebivolol lacks these effects.

2. What Is Relevant?
   - Metabolic syndrome is increasingly prevalent among hypertensive patients.
   - Different classes of β blockers differ in their effects on predictors of cardiovascular disease in this population.

3. Summary
   The newer generation nebivolol avoids the unfavorable metabolic effects of an earlier generation beta blocker. Outcomes trials are needed to determine if this translates into reduced cardiovascular events.
Figure 1.
Study Protocol. Upper figure shows overall study protocol. Lower protocol shows protocol for frequently sampled intravenous glucose tolerance test performed on each study day.
Figure 2.
Effect of metoprolol and nebivolol on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR). Changes are shown as both absolute change ($\Delta$) and percent change ($\%\Delta$) compared to baseline.
Figure 3.
Effect of metoprolol and nebivolol on plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA). *$P<0.05$ versus pretreatment, †$P=0.05$ versus the metoprolol treatment group, after controlling for race and baseline PAI-1 antigen.
Table 1

Subjects characteristics prior to randomization

<table>
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<tr>
<th>Characteristic</th>
<th>Nebivolol Group (N=23)</th>
<th>Metoprolol Group (N=23)</th>
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<tr>
<td>Age (years)</td>
<td>41.3±11.5</td>
<td>47.4±8.5 *</td>
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<td>Gender (M:F)</td>
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<td>SBP (mmHg)</td>
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<td>DBP (mmHg)</td>
<td>83.5±9.2</td>
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<td>HR (beats per minute)</td>
<td>75.8±9.8</td>
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<td>BMI (kg/M^2)</td>
<td>37.0±7.4</td>
<td>36.6±7.0</td>
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<td>Waist Circumference (cm)</td>
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<td>Triglycerides</td>
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<td>HDL-Cholesterol</td>
<td>39.0±7.4</td>
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<td>Fasting Blood Glucose</td>
<td>95.7±9.3</td>
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* P=0.045 versus nebivolol group
Table 2

Effect of treatment on metabolic parameters

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<td><strong>Fasting plasma glucose (mg/dL)</strong></td>
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<tr>
<td>Nebivolol</td>
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<td>99.7±9.9</td>
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<tr>
<td>Metoprolol</td>
<td>99.5±10.7</td>
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<tr>
<td><strong>Fasting insulin (mU/L)</strong></td>
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<td>Nebivolol</td>
<td>5.55±3.12</td>
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<td>Metoprolol</td>
<td>4.91±2.73</td>
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<td><strong>AIRg (mU/L-min)</strong></td>
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<tr>
<td>Nebivolol</td>
<td>241.1±213.7</td>
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<td>Metoprolol</td>
<td>278.1±212.0</td>
<td>279.5±177.9</td>
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<td><strong>ISI (10^{-4} x min^{-1} per mU/L)</strong></td>
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<tr>
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<td>Metoprolol</td>
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<td><strong>Disposition Index (U)</strong></td>
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<td>Metoprolol</td>
<td>1335.6±725.1</td>
<td>1285.6±1049.2</td>
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Table 3

Effect of treatment on plasma and urine nitric oxide metabolites

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<tr>
<td><strong>Plasma Nitric Oxide Metabolites (µM)</strong></td>
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<tr>
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<td>32.3±9.3</td>
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<td>Metoprolol</td>
<td>31.2±11.8</td>
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<td><strong>Plasma cGMP (nM)</strong></td>
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<tr>
<td>Nebivolol</td>
<td>44.4±28.9</td>
<td>53.4±32.1</td>
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<td>Metoprolol</td>
<td>48.9±35.1</td>
<td>53.4±46.2</td>
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<td><strong>Urine Nitric Oxide Metabolites (µmol/mg Cr)</strong></td>
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<tr>
<td>Nebivolol</td>
<td>0.181±0.143</td>
<td>0.221±0.300</td>
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<td>Metoprolol</td>
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<td>0.225±0.148</td>
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<td><strong>Asymmetric Dimethyl Arginine (nM)</strong></td>
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<tr>
<td>Nebivolol</td>
<td>572.5±97.8</td>
<td>571.5±82.9</td>
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<td>Metoprolol</td>
<td>536.2±55.2</td>
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