Efonidipine Simultaneously Improves Blood Pressure, Endothelial Function, and Metabolic Parameters In Non-Diabetic Patients with Hypertension

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Running Title: Vascular and Metabolic Effects of Efondipine

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Hypertension is characterized by endothelial dysfunction and frequently clusters with metabolic disorders that are characterized by insulin resistance (1,2). These co-morbidities may be explained, in part, by reciprocal relationships between endothelial dysfunction and insulin resistance (1). By contrast with calcium channel blockers (CCB), treatment of hypertension with beta-blockers and diuretics is associated with a higher risk of type 2 diabetes (3). This advantage of CCB may relate to specific mechanisms that target the vicious synergy between endothelial dysfunction and insulin resistance. CCB activate nitric oxide (NO) synthase in vitro and enhance NO production in vivo (4). This may impact on the roles of adiponectin, leptin, and resistin to influence metabolic signals, inflammation, and atherosclerosis (5-7).

Efonidipine hydrochloride is a 1,4-dihydropyridine type CCB with long-lasting vasodilator actions and little reflex tachycardia (8). Efonidipine improves endothelial function in patients with hypertension when compared with doses of nifedipine that result in comparable decreases in mean blood pressure (9). Therefore, we hypothesized that efonidipine therapy may simultaneously improve endothelial dysfunction, adipocytokine profiles, and other metabolic parameters in non-diabetic patients with hypertension.

RESEARCH DESIGN AND METHODS
We evaluated effects of efonidipine in a randomized, double-blind, placebo-controlled, crossover study. Thirty-nine hypertensive patients (systolic blood pressure <180 and diastolic blood pressure <110 mmHg) were considered eligible for this study. We excluded patients with severe hypertension, unstable angina, acute myocardial infarction, or renal insufficiency. None of our subjects were diabetic (based on history or criteria according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (10)) or smokers. To minimize acute side effects, during an initial run-in period, study medication was titrated from 40 to 80 mg of efonidipine upwards over a 2 week period if no hypotension (systolic blood pressure<100 mmHg) and hypertension (systolic blood pressure>140 mmHg) was noted. After the run-in period, all patients underwent a 3-week washout period. At the end of the washout period, participants were randomly assigned to either efonidipine 40 to 80 mg or placebo daily during 8 weeks. Patients were then crossed-over to the second treatment arm upon completion of the first treatment arm (without washout phase). The Green Cross Pharmaceutical company (Yongin, Korea) provided the identical placebo (purchased by investigators). One patient suffered from facial flushing and was withdrawn. Thus, data from 38 patients were analyzed. This study was approved by the Gil Hospital Institute Review Board.

Blood samples were obtained at 8:00 a.m. following overnight fasting before and after each treatment period. Assays for plasma insulin, malondialdehyde, adiponectin, leptin, and resistin were performed in duplicate by immunoradiometric assay or by ELISA as previously described (11-13). Quantitative Insulin-Sensitivity Check Index (QUICKI) was calculated as described (14). Imaging studies of the right brachial artery were performed by ultrasound as described (11-13).

Data are expressed as mean±SEM or
median (range: 25%-75%). We used Student’s paired t test or Wilcoxon Signed Rank test to compare relative changes in response to treatment. Pearson or Spearman correlation coefficient analysis was used to assess associations between parameters. We calculated that 30 subjects would provide 80% power for detecting an absolute increase of 1.5% or greater in flow-mediated dilation of the brachial artery between placebo and efonidipine, with \( \alpha = 0.05 \) (15). A value of \( P < 0.05 \) was considered to represent statistical significance.

RESULTS
The mean age of our subjects was 46±2 years and the male:female proportion was 21:17. Baseline characteristics are reported in Table 1. No carryover effects were found (data are not shown).

When compared with placebo, efonidipine therapy reduced systolic and diastolic blood pressure by 9±1% (\( P < 0.001 \)) and 9±1% (\( P < 0.001 \)), respectively. When compared with placebo, efonidipine improved flow-mediated dilator response to hyperemia by 21±7% (\( P < 0.001 \)) and reduced plasma malondialdehyde levels by 8±3% (\( P = 0.011 \)).

There were positive correlations between baseline adiponectin and HDL-cholesterol levels (\( r = 0.533 \), \( P < 0.001 \)) as well as between baseline body mass index (BMI) and baseline adiponectin (\( r = -0.507 \), \( P = 0.001 \)) or baseline leptin levels (\( r = 0.508 \), \( P = 0.001 \)). When compared with placebo, efonidipine therapy increased plasma adiponectin levels by 15±4% (\( P = 0.013 \)) and decreased plasma leptin and resistin levels by 12±4% (\( P = 0.030 \)) and 1±6% (\( P = 0.001 \)), respectively. Insulin sensitivity assessed by QUICKI did not change significantly (increase of 3±2%, \( P = 0.239 \)). Plasma resistin levels were not correlated with either insulin sensitivity or BMI. There were no significant correlations between percent changes in adiponectin and percent changes in leptin or resistin levels following efonidipine therapy (-0.054 \( \leq r \leq -0.030 \)). However, we did observe correlations between percent changes in adiponectin levels and percent changes in HDL-cholesterol (\( r = 0.434 \), \( P = 0.006 \)) and QUICKI (\( r = 0.379 \), \( P = 0.019 \)) following efonidipine therapy. In a multiple regression model, percent changes in adiponectin levels following efonidipine therapy persisted as an independent predictor of percent changes in HDL-cholesterol (\( = 0.459 \), \( P = 0.006 \)) and QUICKI (\( = 0.467 \), \( P = 0.067 \)).

Following efonidipine therapy, improvement in flow-mediated dilation was correlated with percent changes in plasma levels of malondialdehyde (\( r = -0.479 \) and \( P = 0.002 \)), leptin (\( r = -0.424 \) and \( P = 0.008 \)), insulin (\( r = -0.354 \) and \( P = 0.029 \)), and QUICKI (\( r = 0.471 \) and \( P = 0.003 \)). Improvement in flow-mediated dilation persisted as an independent predictor of percent changes in malondialdehyde (\( = -0.822 \), \( P = 0.017 \)) and QUICKI (\( = 1.032 \), \( P = 0.034 \)). Following efonidipine therapy, there were significant correlations between percent changes in plasma levels of malondialdehyde and percent changes in plasma levels of leptin (\( r = 0.364 \), \( P = 0.025 \)).

CONCLUSIONS
Efonidipine has distinct properties when compared with other CCB. Efonidipine has higher affinity for T-type Ca2+ channels (16) and larger effect to improve endothelial function in patients with hypertension (9) when compared with nifedipine. Finally, urinary excretion of 8-hydroxy-2’-deoxyguanosine and serum
malondialdehyde-modified low-density lipoprotein are both decreased by efonidipine, but not nifedipine, therapy. Although we did not directly compare efonidipine with other CCB in the current study, it will be of interest to do so in future studies.

Potential mechanisms for CCB to influence insulin sensitivity may relate to their ability to target the vicious synergy between endothelial dysfunction and insulin resistance. Therefore, we assessed metabolic parameters including plasma levels of lipids, adiponectin, leptin, and resistin, and QUICKI. Efonidipine had a neutral metabolic effect with respect to the lipid profile and QUICKI. However, improvement in flow-mediated dilation persisted as an independent predictor of changes in QUICKI.

Amlodipine has no significant effect on adiponectin levels in patients with hypertension (17). In our study, efonidipine increased adiponectin levels without a corresponding change in BMI. Increasing adiponectin levels is predicted to improve both insulin sensitivity and endothelial function by multiple mechanisms (18). Regulation of metabolic homeostasis and hemodynamic homeostasis may be coupled by vascular actions of insulin to stimulate production of NO (19). In the current study, changes in adiponectin levels persisted as an independent predictor of changes in HDL-cholesterol and QUICKI. Effects of efonidipine to reduce plasma leptin and malondialdehyde levels and improve endothelium-dependent dilation are significantly correlated. In summary, efonidipine therapy simultaneously improves blood pressure, endothelial function, and metabolic parameters without substantially altering insulin sensitivity in non-diabetic patients with hypertension.

ACKNOWLEDGMENTS
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REFERENCES


Table 1. Effects of Efonidipine in 38 Patients with Hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Efonidipine</th>
<th>% Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>24.7±0.5</td>
<td>24.7±0.5</td>
<td>24.6±0.5</td>
<td>0.4±0.3 (2.0)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>86±2</td>
<td>82±2 (12)</td>
<td>84±2 (13)</td>
<td>4±3 (16)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>155±2</td>
<td>148±2 (15)</td>
<td>134±2 (14)‡</td>
<td>-9±1 (8)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>95±1</td>
<td>91±1 (9)</td>
<td>83±2 (9)‡</td>
<td>-9±1 (8)</td>
</tr>
<tr>
<td>Lipids (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>186±4</td>
<td>183±5 (31)</td>
<td>187±5 (29)</td>
<td>3±2 (12)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>162±19</td>
<td>157±18 (112)</td>
<td>155±16 (101)</td>
<td>15±9 (54)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>105±4</td>
<td>102±4 (22)</td>
<td>106±4 (25)</td>
<td>5±3 (16)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>49±3</td>
<td>53±3 (20)</td>
<td>50±2 (14)</td>
<td>-3±3 (21)</td>
</tr>
<tr>
<td>Vasomotor Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow-mediated Dilation (%)</td>
<td>4.28±0.22</td>
<td>5.42±0.26 (1.58)</td>
<td>6.20±0.25 (1.52)‡</td>
<td>21±7 (41)</td>
</tr>
<tr>
<td>Nitroglycerin Dilation (%)</td>
<td>13.87±0.70</td>
<td>14.62±0.68 (4.21)</td>
<td>14.84±0.80 (4.90)</td>
<td>2±4 (23)</td>
</tr>
<tr>
<td>Malondialdehyde ( M)</td>
<td>1.20±0.04</td>
<td>1.22±0.04 (0.25)</td>
<td>1.12±0.05 (0.31)*</td>
<td>-8±3 (18)</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>0.80 (0.50-1.40)</td>
<td>0.85 (0.40-1.40)</td>
<td>0.65 (0.50-1.30)</td>
<td>25±18 (109)</td>
</tr>
<tr>
<td>Insulin Resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin ( g/ml)</td>
<td>4.3±0.6</td>
<td>4.2±0.6 (3.7)</td>
<td>4.6±0.6 (3.9)*</td>
<td>15±4 (23)</td>
</tr>
<tr>
<td>Insulin ( U/ml)</td>
<td>7.33 (4.89-12.05)</td>
<td>7.63 (4.91-11.25)</td>
<td>6.78 (4.50-9.20)</td>
<td>3±8 (52)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>103±2</td>
<td>102±2 (12)</td>
<td>100±2 (15)</td>
<td>-2±2 (10)</td>
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<tr>
<td>QUICKI</td>
<td>0.360±0.010</td>
<td>0.351±0.006 (0.039)</td>
<td>0.359±0.007 (0.040)</td>
<td>3±2 (13)</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>5.2±0.6</td>
<td>5.2±0.6 (3.6)</td>
<td>4.7±0.5 (3.3)*</td>
<td>-12±4 (26)</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>7.66 (5.81-10.34)</td>
<td>7.76 (5.83-10.41)</td>
<td>8.12 (5.31-9.99)‡</td>
<td>-1±6 (39)</td>
</tr>
</tbody>
</table>

Data are expressed as means ±SEM (SD) or median (25th percentile-75th percentile).
*P<0.05, ‡P<0.001 vs. placebo.
Quantitative Insulin-Sensitivity Check Index (QUICKI)=1/[log (insulin) + log (glucose)]¹⁴