Vasodilatory Effects of Troglitazone Improve Blood Pressure at Rest and During Mental Stress in Type 2 Diabetes Mellitus

Bong Hee Sung, Joseph L. Izzo, Jr, Paresh Dandona, Michael F. Wilson

Abstract—The present study examined the hemodynamic mechanisms of blood pressure (BP) lowering by troglitazone in patients with type 2 diabetes mellitus (DM) at rest and during a mental arithmetic test (MAT). Twenty-two patients with DM with normal to high-normal BP and 12 controls matched for age, gender, glucose tolerance, and BP were studied. DM subjects showed significantly higher systolic BP response during MAT than controls (157 versus 139 mm Hg; P<0.01). All 22 DM patients and 5 of 12 controls had systolic BP >140 mm Hg during MAT. Heart rate and diastolic BP were not significantly different between the 2 groups. The DM group was then randomized to receive troglitazone (n=10; 400 mg/d) or glyburide (n=12; 20 mg/d). MAT was repeated after 6 months of treatment. Both treatments reduced glucose equally (−1.7 mmol/L for troglitazone and −1.5 mmol/L for glyburide), but only troglitazone reduced insulin (−15 μU/mL; P<0.001) and C-peptide (−0.9 ng/mL; P<0.02) levels. Troglitazone significantly reduced BP at baseline (P<0.05) and systolic BP response to MAT (P<0.01), whereas glyburide did not affect BP at baseline or during MAT. Stroke volume and cardiac output did not change with either drug, but troglitazone decreased peripheral vascular resistance (−112 dyne·s·cm⁻²; P<0.05). Improved insulin resistance rather than an improved glycemic control is associated with lower resting and stress BP values in patients with DM. A reduction in vascular resistance may be a primary hemodynamic mechanism of the manner in which troglitazone lowers BP. Insulin sensitizers may offer potential therapeutic advantage in subjects with DM with elevated BP. (*Hypertension. 1999;34:83-88.*)

Key Words: troglitazone ■ blood pressure ■ vasodilation ■ insulin ■ stress, mental

Epidemiological studies have reported that diabetic persons have increased prevalence of hypertension, and the San Antonio Heart Study suggests that 85% of diabetics are hypertensive and obese by the fifth decade of their life.1–3 It is also well documented that diabetic patients are prone to develop microvascular and macrovascular disease and have increased mortality.4–7 Although it is not clear how years of poor diabetic control lead to elevated blood pressure (BP), normalizing BP in the diabetic population is particularly important to prevent progression of diabetes mellitus (DM)–related complications.

Insulin resistance is frequently associated with hypertension,8–11 and recent studies have shown that thiazolidinedione derivatives, which are insulin sensitizers, lower BP in diabetic hypertensives12 and obese subjects.13 Because this class of drugs improves insulin sensitivity and glycemic control, it is not clear whether the BP-lowering effect is due to glycemic control or to improvement in insulin sensitivity. In addition, recent studies suggest that troglitazone may improve BP by direct actions on the vasculature. Song and colleagues14 reported that troglitazone inhibits L-type Ca²⁺ current in rat tail artery and aortic vascular smooth muscle cells, and Fujishima et al15 reported that a single oral dose of troglitazone increased forearm vasodilation in healthy volunteers without change in glucose, insulin, and BP. Thus, it is not clear whether the BP-lowering action of troglitazone is associated with insulin sensitivity.

Previously we have demonstrated that normotensive, insulin-resistant women showed exaggerated BP response to stress.16 Enhanced BP response to a stressor has been reported to be a predictor for future development of hypertension and increased risk for cardiovascular disease.17–19 In this study we first examined whether patients with type 2 DM show exaggerated BP response to stress. Type 2 diabetics were then randomized into the troglitazone (insulin sensitizer) or glyburide (oral glycemic agent sulfonylurea) group to investigate whether lowering insulin resistance and/or glucose metabolism improves BP at rest and during stress. Levels of glucose, insulin, C-peptide, and HbA₁c were measured after 6 months of the treatments, and resting and stress BP were compared between the 2 treatments. To elucidate the hemodynamic mechanism of BP lowering by troglitazone, stroke volume and cardiac output were measured by echocardiogram.

Methods

Study Population

Volunteers were recruited through advertisements in the local community. Respondents were initially interviewed by telephone,
and those who met the inclusion criteria underwent screening and physical examination. Smokers, hypertensives, and subjects with known cardiovascular disease were excluded. The enrollment criteria of type 2 DM was fasting glucose ≥7.8 mmol/L and <16.7 mmol/L on >2 separate occasions. The control group was selected from volunteers who had a normal glucose tolerance test. The final study population consisted of 22 patients with type 2 DM and 12 age- and gender-matched controls. All subjects had normal BP (<140/90 mm Hg). The study protocol was approved by the Human Ethics Committee of the Millard Fillmore Hospital. Informed consent was obtained from each volunteer after the procedures were explained.

**Study Protocol**

This study was performed as a 2-part protocol. The first part was to compare BP response to a mental arithmetic test (MAT) in persons with and without DM. Twenty-two DM patients and 12 age- and gender-matched controls participated in this protocol. The second part was designed to compare metabolic and hemodynamic effects of troglitazone and glyburide in subjects with DM. The same 22 DM patients were randomized to either the troglitazone or glyburide group and treated for 6 months. Levels of glucose, insulin, C-peptide, and HbA₁c were measured at baseline and after 6 months of treatment. Resting and stress BP were compared between the 2 treatments. Stroke volume and cardiac output were measured by echocardiogram with the use of the single-plane area-length method at baseline and after treatment, and peripheral vascular resistance was calculated. MAT was repeated after 6 months of treatment.

**Mental Arithmetic Test**

The subjects reported to the laboratory at 8 AM after 12 hours of fasting. All study subjects were requested to refrain from alcohol and caffeine at least 12 hours before the experiment. After subjects rested in a comfortable chair for 20 minutes, baseline hemodynamic measurements were made. Participants were instructed to serially subtract the numbers 3 and 7 from a 3-digit number during 5-minute periods. They were asked to provide the subtraction aloud and to provide answers as quickly and accurately as possible. When an incorrect answer was given, they were asked to repeat the subtraction. Heart rate and BP were measured at 1-minute intervals during the MAT.

**Treatment**

The same 22 DM subjects were studied before and after randomization to either troglitazone or glyburide treatment. Ten patients were treated with 400 mg/d of troglitazone for 6 months, and 12 patients were treated with 20 mg/d of glyburide for 6 months. Because the purpose of the study was to examine the cardiovascular effects of troglitazone and not glycemic control, exercise and dietary prescriptions were not changed during the study. All study subjects were followed monthly for adverse experiences and laboratory evaluation.

**Statistical Analysis**

Baseline group difference was examined by unpaired Student’s t test and 1-way ANOVA as appropriate. Hemodynamic responses to MAT between groups were examined by 2-way ANOVA with repeated measures. The differences in treatment on metabolic and hemodynamic variables were analyzed by 2-way ANOVA. The Systat (Systat Inc) software package was used for statistical analysis. A value of P<0.05 was considered significant. All group data are reported as mean±SD unless otherwise indicated.

**Results**

**Comparison of Baseline Characteristics of DM and Control Groups**

As summarized in Table 1, both groups were comparable in age and gender distribution, although the diabetic group had significantly higher body mass index than the control group (P<0.001). As expected, the DM group had significantly higher fasting glucose and insulin levels than the control group. All control subjects had normal fasting glucose (mean, 4.9±0.6 mmol/L) and insulin levels (mean, 6.8±2.0 µU/mL). Their mean glucose levels for 30, 60, 90, and 120 minutes after glucose challenge were 6.7±1.4, 7.3±1.8, 5.7±1.2, and 5.2±1.7 mmol/L, and mean insulin levels were 46±12, 65±14, 50±11, and 28±7 µU/mL. These results confirm that our control subjects did not have glucose intolerance. All study subjects were normotensive, and baseline heart rate and BP were similar between the DM and control groups.

**Comparison of Hemodynamic Response to MAT of DM and Control Groups**

Serial subtraction is considered a moderately challenging cognitive stressor and has been used as a standard mental stress test. MAT significantly increased BP and heart rate in both groups. However, the mean increment in systolic BP during MAT was significantly higher in the DM group than in the control group (24 versus 12 mm Hg; P<0.001). Baseline systolic BP ranged from 122 to 139 mm Hg in the DM group, and MAT increased systolic BP into the hypertensive range (147 to 170 mm Hg) in all 22 diabetic patients. In contrast, 5 of 12 control subjects became hypertensive during MAT. The DM group also had higher diastolic BP response than the control group, but it was not statistically significant (14 versus 8 mm Hg; P=NS; heart rate response was similar between the groups. Figure 1 illustrates mean hemodynamic response to MAT between DM and control groups.

**Comparison of Metabolic and Hemodynamic Effects of Troglitazone and Glyburide**

Both drugs were well tolerated, and no significant adverse reaction or abnormal laboratory test result was reported. Table 2 compares metabolic and hemodynamic effects of troglitazone and glyburide in the DM group. Pretreatment baseline demographic, metabolic, and hemodynamic variables were similar between troglitazone- and glyburide-treated groups. Both treatments lowered fasting glucose levels significantly and equally (−1.7 versus −1.5 mmol/L; P<0.001). However, only troglitazone treatment also reduced insulin and C-peptide levels significantly. Neither treatment significantly changed HbA₁c levels, and body weight re-
mained similar with either treatment (221 ± 18 to 221 ± 21 lb for troglitazone versus 199 ± 20 to 197 ± 19 lb for glyburide).

Resting and stress BP changes by treatment are illustrated in Figure 2. As shown in Figure 2A, there was a significant reduction in posttreatment baseline BP with troglitazone but not with glyburide. Troglitazone lowered baseline systolic BP (−9 mm Hg; *P < 0.05) and diastolic BP (−6 mm Hg; *P < 0.05). Figure 2B compares hemodynamic changes in response to MAT between predrug and postdrug treatment. Troglitazone significantly lowered the systolic BP response to MAT (−11 mm Hg; *P < 0.01), although glyburide treatment did not change the hemodynamic response to MAT. Four of 10 troglitazone-treated patients raised systolic BP into the hypertensive range during mental stress compared with all of the glyburide-treated diabetics who had a hypertensive systolic BP response. There was no significant change in heart rate or diastolic BP response to MAT with either drug treatment.

As shown in Table 2, there were no significant changes in heart rate, stroke volume, and cardiac output by either treatment. However, there was a significant reduction in peripheral vascular resistance in the troglitazone-treated group but not in the glyburide-treated group (−112 versus −21 dyne · s · cm⁻⁵; *P < 0.05). Figure 3 illustrates the underlying hemodynamic mechanisms of the manner in which troglitazone lowers BP. Reduction in mean BP was accompanied by decreased peripheral vascular resistance.

**Discussion**

The present study reports 3 major findings. First, our type 2 diabetics had significantly higher BP responses to stress compared with age- and gender-matched nondiabetic controls with similar baseline BP. Second, troglitazone but not glyburide lowered resting BP and normalized the exaggerated BP responses to mental stress in type 2 diabetics. Both drugs achieved equal glycemic control, which suggests that the hemodynamic improvement may be directly related to improved insulin sensitivity. Third, troglitazone reduced vascular resistance, which may be the primary underlying hemodynamic mechanism. Most of the diabetic study subjects had pretreatment systolic BP > 130 mm Hg, which is now considered the treatment threshold by the Joint National Commission VI. Thus, insulin sensitizers may offer a therapeutic advantage in management of hypertension in the diabetic population.

Most of the previous studies have focused on the effects of troglitazone on resting BP. To our knowledge, this is the first study to document that troglitazone treatment improves the BP response to mental stress. BP response to a structured stress test performed in the laboratory may represent BP increases during naturally occurring stresses in daily life. Increased BP reactivity has been reported to predict the subsequent development of hypertension in normotensive individuals with other risk factors. During serial subtraction, all of our diabetic patients with normal to high-normal BP raised systolic BP into the hypertensive range. Systolic BP is related to the rate of progression of albuminuria in type 2 DM, and an intermittent increase in systolic BP during stress may have clinical consequences in diabetics. These
findings may be important in risk assessment and prevention of hypertension in the diabetic population.

There are several possible mechanisms by which our diabetic patients showed exaggerated BP response to mental stress. A positive association between insulin resistance and enhanced BP response to mental stress has been reported in normotensive insulin-resistant women and normotensive young men. The vasodilatory actions of insulin have been demonstrated in human forearm and dorsal hand veins. Our diabetic group may have diminished insulin-mediated vasodilation. Cardillo et al reported that mental stress caused nitric oxide–mediated vasodilation in normal subjects. Reduced endothelial nitric oxide production in DM is another possible mechanism for the greater BP response shown in our diabetic patients during mental stress. Recently, Kotchen et al reported that an insulin sensitizer enhanced acetylcholine-induced vasodilation in fructose-fed rats. Troglitazone may normalize exaggerated BP response to mental stress in diabetics by improving abnormal vascular responsiveness associated with insulin resistance.

Previously, Ogihara et al reported that troglitazone improves glucose control and insulin resistance and lowers BP in diabetic hypertensives. Similar findings have been reported in obese subjects with and without insulin resistance. Because troglitazone lowers both insulin and glucose levels, it was not clear from these studies whether the beneficial BP effects of troglitazone were due to improved insulin sensitivity or improved glycemic control. The present study compared the metabolic and hemodynamic effects of troglitazone with those of glyburide. Body weight did not change with either treatment, and both drugs reduced glucose levels equally well. However, both drugs failed to improve HbA1c levels. Because the purpose of this study was to examine the cardiovascular effects of troglitazone and not glycemic control, we did not request strict aggressive control of dietary conditions. Blood glucose levels of our diabetic patients were still elevated with both treatments, and optimal glycemic control was not obtained. This may explain why troglitazone or glyburide treatment failed to lower HbA1c levels in our diabetic patients.

However, troglitazone but not glyburide lowered insulin, C-peptide levels, and BP at rest and during stress. These results suggest that improving insulin sensitivity is associated with a fall in BP. More importantly, the present study demonstrates that troglitazone lowers BP by decreasing peripheral vascular resistance without significant change in

**TABLE 2. Comparison of Metabolic and Hemodynamic Changes of Troglitazone and Glyburide**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Troglitazone</th>
<th>After Troglitazone</th>
<th>Before Glyburide</th>
<th>After Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L</td>
<td>10.1±1.5</td>
<td>8.4±1.5*</td>
<td>10.7±2.0</td>
<td>9.2±1.3*</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>27.3±10</td>
<td>11.7±5†</td>
<td>20.4±11</td>
<td>19.4±12</td>
</tr>
<tr>
<td>C-peptide, ng/mL</td>
<td>3.3±0.8</td>
<td>2.4±0.7†</td>
<td>3.0±0.8</td>
<td>3.1±1.0</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.3±0.8</td>
<td>8.2±1.2</td>
<td>8.7±1.2</td>
<td>8.3±1.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75±8</td>
<td>74±10</td>
<td>75±8</td>
<td>76±7</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133±10</td>
<td>124±8†</td>
<td>133±10</td>
<td>130±9</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75±8</td>
<td>69±6†</td>
<td>74±9</td>
<td>72±8</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>83±11</td>
<td>85±9</td>
<td>81±10</td>
<td>79±11</td>
</tr>
</tbody>
</table>

Values are mean±SD. P<0.05.

*Drug effect.
†Treatment difference.

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Changes in mean BP, cardiac output, and peripheral vascular resistance after treatment with troglitazone and glyburide were compared to examine the hemodynamic mechanism of the manner in which troglitazone lowers BP. Neither drug changed cardiac output. Troglitazone lowered mean BP by significant reduction in peripheral vascular resistance.
cardiac output. Although the BP-lowering effect of troglitazone has been reported in several animal\textsuperscript{29,30} and human studies,\textsuperscript{12,13} the underlying hemodynamic mechanisms have not been well delineated. Our results indicate that reduced vascular resistance may be a primary hemodynamic effect of troglitazone. However, whether these vasodilatory effects of troglitazone are direct or indirect is not yet known. Ogihara et al\textsuperscript{12} reported that reduction in mean BP in troglitazone-treated diabetic hypertensives was significantly related to a decreased plasma insulin level.\textsuperscript{1} Hyperinsulinemia has been associated with increased sympathetic nervous activity,\textsuperscript{31,32} and troglitazone may decrease sympathetic nervous activity, perhaps by reducing plasma insulin levels.

Alternatively, several animal studies showed that thiazolidinedione compounds have direct effect on vascular smooth muscle cells,\textsuperscript{14,33} and pioglitazone attenuates the development of hypertension in rat models.\textsuperscript{34} Troglitazone directly reduces arterial contraction in vitro by inhibiting vascular smooth muscle cell calcium currents.\textsuperscript{14} Recently, Fujishima and colleagues\textsuperscript{15} reported that a single oral dose of troglitazone increased forearm vasodilation in healthy volunteers. Because forearm vasodilation was not accompanied by a change in serum glucose, insulin, or nitrate ion levels, they speculated that vasodilatory effects of troglitazone seemed to be not associated with improving insulin sensitivity or nitric oxide production. However, there was also no fall in BP in their healthy volunteers, and the finding does not provide an explanation of the BP-lowering effect of troglitazone after chronic administration in association with improved insulin sensitivity.

In contrast to the healthy volunteers of Fujishima et al,\textsuperscript{15} our troglitazone-treated diabetic patients had significant decreases in glucose, insulin, and C-peptide levels accompanied by fall in BP and vascular resistance. Although our study supports the concept that troglitazone lowers BP by decreasing vascular resistance, whether lowering vascular resistance is a direct effect or an indirect effect by improving insulin sensitivity is still an open question. Another important issue is the study group. High-normal BP is no longer considered acceptable in persons with DM, although there are no trial data yet in this group. This study clearly demonstrates that high-normal values can be fully normalized by troglitazone. Thus, it is possible that other antihypertensive drugs may not be necessary in some troglitazone-treated patients. Present data may help to generate interest in a controlled clinical trial to investigate the role of insulin sensitizers in early hypertension.

The Joint National Commission VI recommends treating high-normal BP in the diabetic population.\textsuperscript{21} Lowering BP in the diabetic population is particularly important for preventing progression of DM-related complications. Troglitazone clearly has favorable effects on BP at rest and in response to stress in type 2 DM. Hypertension is prevalent in DM, and diabetic patients are prone to develop microvascular and macrovascular disease. Our findings may have significant clinical implications for the selection of treatment for prevention and treatment of hypertension in type 2 DM.

Acknowledgments

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