Effect of the Angiotensin II Type 1 Receptor Blocker Candesartan on Endothelial Function in Patients With Essential Hypertension

Lorenzo Ghiadoni, Agostino Virdis, Armando Magagna, Stefano Taddei, Antonio Salvetti

Abstract—Patients with essential hypertension are characterized by impaired basal and agonist-evoked nitric oxide release and increased endogenous endothelin (ET)-1–induced vasoconstriction. To assess whether candesartan, an angiotensin II type 1 receptor blocker, can improve endothelial function, we studied the changes in forearm blood flow (FBF) induced in 15 hypertensive patients and in 15 control subjects by the intrabrachial infusion of L-arginine (L-NMMA), norepinephrine, the ET A/B receptor antagonist TAK 044, sodium nitroprusside, and acetylcholine. In hypertensive patients, the FBF study was repeated 2 and 12 months after the start of treatment with candesartan cilexetil (8 to 16 mg daily). Compared with controls (maximal FBF decrease, −46±11%), hypertensive patients showed a reduced (P<0.001) vasoconstrictor response to L-NMMA (maximal FBF decrease, −28±7%); the response to norepinephrine was only slightly impaired, and the response to sodium nitroprusside was similar to that of controls. Finally, TAK-044 caused greater vasodilation in hypertensive patients (maximal FBF increase, 77±9%) than in controls (maximal FBF increase, 17±10%). In hypertensive patients, candesartan cilexetil significantly enhanced vasodilatation to L-NMMA after 2 and 12 months (maximal FBF decrease, 37±2% [P<0.05] and 42±2% [P<0.001], respectively). The responses to norepinephrine, acetylcholine, and sodium nitroprusside were not modified after 2 months. After 12 months, the responses to acetylcholine and sodium nitroprusside were significantly (P<0.05) enhanced at the highest rates. Vasodilation to TAK-044 was abolished after treatment with candesartan cilexetil; this effect is associated with a reduced plasma ET-1 concentration. This study demonstrated that the angiotensin II receptor blocker candesartan improves tonic nitric oxide release and reduces vasoconstriction to endogenous ET-1 in the forearm of hypertensive patients. (Hypertension. 2000;35[part 2]:501-506.)

Key Words: endothelium ■ nitric oxide ■ endothelin ■ angiotensin antagonist ■ hypertension, essential

Endothelial cells play a key role in the local modulation of vascular tone and structure by producing and releasing vasodilating substances (mainly nitric oxide [NO]). In pathological conditions such as hypertension or atherosclerosis, they produce endothelium-derived contracting factors and endothelin-1 (ET-1).1 NO causes vasodilation and also inhibits platelet aggregation, smooth muscle cell proliferation and migration, monocyte adhesion, and ET synthesis, thus protecting the vessel wall from the development of atherosclerosis and thrombosis.2 Endothelial dysfunction is a condition characterized by reduced NO availability due to oxidative stress and a parallel increase of production and/or the activity of vasoconstricting substances such as angiotensin II and ET; this reduced availability thereby promotes pathological processes that lead to atherosclerosis and thrombosis.3 Moreover, ET-1 can contribute to vascular dysfunction, causing structural changes in the vessels.3

In patients with essential hypertension, endothelial dysfunction is characterized by the impaired basal and agonist-dependent release of NO.4–9 The latter alteration is associated with the reduced NO availability8,9 caused both by decreased NO synthase activity10 and oxidative stress.9 Moreover, in essential hypertension, vasoconstriction to endogenous ET-1 is increased11,12 despite normal plasma levels of the peptide.13,14 Treatment with an ET-receptor antagonist lowers blood pressure,13 which suggests that ET-1 plays a role in the increased vascular tone found in patients with essential hypertension.

Angiotensin II can impair endothelial function by at least 2 mechanisms. First, angiotensin II can curtail endothelium-dependent relaxation by increasing the production of oxygen free radicals.16,17 This could be crucial because in patients with essential hypertension, oxidative stress causes a reduction in NO availability and, consequently, reduces vasodilatation to acetylcholine.9 Second, angiotensin II activates ET-1 synthesis and release from cultured endothelial cells.18,19 In both mechanisms, these negative angiotensin II–induced effects on endothelial function are mediated by the angiotensin II type 1 (AT-1) receptor subtype.

The aim of the present, unblinded, open-label study was to evaluate whether endothelial dysfunction in patients with essential hypertension is improved after treatment with the angiotensin II type 1 receptor blocker candesartan cilexetil, a drug that has been shown to have anti-hypertensive1 and antithrombotic2 effects.
essential hypertension can be improved by treatment with candesartan, a nonpeptide AT-1 receptor antagonist. The effects of candesartan on impaired basal and agonist-evoked NO release and on the vasoconstrictor effect of endogenously generated ET-1 were evaluated.

**Methods**

**Patients**

The study population included 15 patients with essential hypertension and 15 matched, healthy control subjects. Patients with hypercholesterolemia, diabetes mellitus, ischemic heart and/or cerebrovascular disease, impaired renal function, and other major diseases were excluded from the study. Smokers and/or patients consuming more than 30 g of ethanol per day were likewise excluded from the study. Patients with essential hypertension were recruited from among newly diagnosed persons in our outpatient clinic who reported a family history of essential hypertension and whose supine arterial blood pressure (after 10 minutes of rest), as measured by mercury sphygmomanometer, was consistently found to be $\geq140/90$ mm Hg. Secondary forms of hypertension were excluded during hospitalization by routine diagnostic procedures. Patients were enrolled if they were previously untreated (n=10) or if they reported a history of discontinued pharmacological antihypertensive treatment (n=5). Among the latter subgroup, no patient had previously received an AT-1 receptor blocker, and any pharmacological treatment was discontinued for $\geq4$ weeks before performing the study. Moreover, to avoid possible drop-outs because of a lack of blood pressure normalization by candesartan cilexetil treatment, hypertensive patients were tested for a response to the compound 4 weeks before enrollment in the study. Blood pressure response to a single dose of candesartan cilexetil was evaluated, and only those patients who showed a $>10\%$ decrease in blood pressure induced by drug administration were enrolled. After this procedure, we screened 28 patients with essential hypertension and selected 15 patients (12 men and 3 postmenopausal women) who responded to candesartan cilexetil treatment. The mean age of these patients was 53.8±4.7 years, and blood pressure values were 153.9±7.5/103.1±2.4 mm Hg. The 15 control subjects (12 men and 3 postmenopausal women) were defined as healthy according to the absence of a familial history of essential hypertension and blood pressure values $<140/90$ mm Hg. They had a mean age of 52.4±5.6 years and blood pressure values of 119.8±3.9/78.1±3.1 mm Hg.

The study protocol was approved by the local Institutional Ethics Committee, and written, informed consent was obtained from all subjects before their participation in the study. The baseline results of 10 hypertensive patients and 10 controls were previously published.12

**Experimental Procedure**

In brief, a polyethylene cannula (21 gauge; Abbot) was inserted into the brachial artery under local anesthesia (2% lidocaine). The cannula was connected through stopcocks to a pressure transducer (model MS20, Electromedics) to determine systemic mean arterial blood pressure ($\frac{1}{3}$ pulse pressure + diastolic pressure), heart rate (model VSM1, Physiocontrol), and intra-arterial infusions. Forearm blood flow (FBF) was measured by strain-gauge venous plethysmography (LOOSCO).20 Details regarding the sensitivity and reproducibility of this method were published previously.21

**Experimental Design**

Basal release of NO was evaluated by determining the dose-response curve to intra-arterial N$\textsuperscript{6}$-monomethyl-L-arginine (L-NMMA),22,23 a competitive antagonist for NO-synthase (at dose-rates of 0.15, 0.45, 1.5, 4.5, and 15 μg/min per 100 mL of forearm tissue; 5 minutes for each dose), an endothelium dependent vasodilator.1 Moreover, to assess NO production during acetylcholine infusion, the muscarinic agonist was repeated in the presence of L-NMMA by prolonging the infusion of the highest rate of the NO-synthase inhibitor. Endothelium-independent vasodilatation was evaluated by a dose-response curve to intra-arterial sodium nitroprusside (at infusion rates of 0.5, 1, and 2 μg/min per 100 mL of forearm tissue; 5 minutes for each dose).24

Finally, the contribution of endogenously-generated ET-1 to basal vascular tone was evaluated by determining the dose-response curve for the intra-arterial infusion of the nonselective ET A/B receptor and ET-1 receptor antagonist TAK 044 (10, 30, and 100 μg/min per 100 mL of forearm tissue; 5 minutes for each dose).25

All infusions were performed consecutively in each patient. The sequence of basal acetylcholine and sodium nitroprusside was randomized. A 30-minute wash-out was allowed between each dose-response curve to recover basal FBF, and a 60-minute period was allowed when L-NMMA was infused. However, because no large-scale experience is available with TAK-044, this compound was always administered as the last infusion. Previous experience supported the feasibility of prolonged studies with multiple infusion rates.9,26

After the first FBF study, patients with essential hypertension were given 8 mg of candesartan cilexetil once daily. After 1 month, if blood pressure values were $\geq140/90$ mm Hg, the dose was increased to 16 mg once daily for the remainder of the 11 months of active treatment. Five patients required an increase in the dose to 16 mg after 1 month of treatment. Additional clinic visits were scheduled every 4 weeks for the duration of the study. The FBF study was repeated after 2 (prolonged treatment) and 12 (long-term treatment) months of candesartan cilexetil administration.

Blood pressure measurements were performed in our outpatient unit by a standard mercury sphygmomanometer. Blood pressure values were determined as the mean of 3 measurements made at 2-minute intervals after the patients had been seated for 10 minutes. Circulating levels of plasma ET-1, active renin, and angiotensin II were assessed at baseline in normotensive subjects and in patients with essential hypertension; they were repeated in hypertensive patients after 2 and 12 months of treatment with candesartan cilexetil. Plasma ET-1,27 plasma renin activity,28 and plasma angiotensin II29 were measured by radioimmunoassay.

**Data Analysis**

Data were analyzed in terms of changes in FBF. Because arterial blood pressure did not change significantly within the FBF studies, increments in FBF were taken as evidence of local vasodilatation. Results are expressed as mean±SEM; in figures, data are presented as percent increase of FBF above baseline. Differences between 2 means were compared by paired or unpaired Student’s t tests, as appropriate. Responses to acetylcholine and sodium nitroprusside were analyzed by ANOVA for repeated measures, and Scheffe’s test was applied for multiple comparison testing. Differences were considered significant at P<0.05.

**Drugs**

Acetylcholine HCl (Farmigea), sodium nitroprusside (Malesci), nor-epinephrine (Jacopo Monaco), and L-NMMA (Clinalfa AG) were obtained from commercially available sources, and they were freshly diluted to the desired concentration by adding normal saline. Sodium nitroprusside was dissolved in glucosate solution and protected from light by aluminum foil.

**Results**

At baseline, L-NMMA infusion caused a significantly (P<0.01) higher reduction in FBF in normotensive subjects (from 3.4±0.6 to 1.8±0.4 mL/100 mL of forearm tissue per
min; maximum, −46±11%) than in hypertensive patients (from 3.2±0.4 to 2.3±0.3 mL/100 mL of forearm tissue per min; maximum, −28±7%). The response to norepinephrine increased only slightly (Figure 1; normotensives: FBF from 3.1±0.3 to 1.7±0.2 mL/100 mL of forearm tissue per min; maximum, −45±4%; hypertensives: FBF from 3.3±0.4 to 2.2±0.3 mL/100 mL of forearm tissue per min; maximum −35±9%).

Acetylcholine caused a dose-dependent increase in FBF that was significantly (P<0.01) reduced in patients with essential hypertension (FBF from 3.1±0.5 to 16.2±4.5 mL/100 mL of forearm tissue per min; maximum, 422±36%) when compared with healthy controls (FBF from 3.2±0.5 to 25.0±6.1 mL/100 mL of forearm tissue per min; maximum, 687±38%). The L-NMMA infusion blunted the response to acetylcholine in control subjects (FBF from 1.8±0.4 to 6.9±2.1 mL/100 mL of forearm tissue per min; maximum, 275±25%; P<0.01 versus saline), but it was not effective in hypertensive patients (FBF from 2.3±0.5 to 11.6±2.6 mL/100 mL of forearm tissue per min; maximum, 386±28%). The response to sodium nitroprusside was similar in hypertensive patients (FBF from 3.2±0.5 to 13.2±2.5 mL/100 mL of forearm tissue per min; maximum, 318±21%) and in controls (FBF from 3.1±0.3 to 13.4±1.0 mL/100 mL of forearm tissue per min; maximum, 334±20%; P=NS).

TAK-044 caused a small degree of vasodilation in normotensive subjects (FBF from 3.4±0.4 to 4.0±0.7 mL/100 mL of forearm tissue per min; maximum, 17±10%). It caused more pronounced vasodilation in hypertensive patients (FBF from 3.1±0.5 to 5.6±1.3 mL/100 mL of forearm tissue per min; maximum, 77±9%) (Figure 2).

In hypertensive patients, treatment with candesartan cilexetil significantly lowered blood pressure values and increased plasma renin activity and plasma angiotensin II levels (Table). Plasma ET-1 concentrations were 2.49±1.32 pg/mL in normotensive subjects and 2.61±1.06 pg/mL in hypertensive patients. Candesartan cilexetil significantly reduced plasma ET-1 concentrations in patients with essential hypertension (2 months: 1.61±0.88 pg/mL, P<0.05 versus baseline; 12 months: 0.72±0.53 pg/mL, P<0.01 versus baseline). Lipid and glycemic profiles did not change during the 12-month observation period (Table).

### Behavior of Hemodynamic and Humoral Parameters During the Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Candesartan (2 months)</th>
<th>Candesartan (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>152.3±7.1</td>
<td>135.2±4.8*</td>
<td>131.1±6.7*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>102.6±4.1</td>
<td>85.3±3.6*</td>
<td>82.6±4.9*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>77.9±4.4</td>
<td>74.7±4.4*</td>
<td>70.7±5.5*</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.29±0.60</td>
<td>5.51±0.79</td>
<td>5.09±0.66</td>
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<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.28±0.32</td>
<td>1.10±0.35</td>
<td>1.24±0.30</td>
</tr>
<tr>
<td>PRA†</td>
<td>0.74±0.53</td>
<td>1.27±1.13</td>
<td>1.50±1.93</td>
</tr>
<tr>
<td>Angiotensin II, pg/mL</td>
<td>5.02±2.02</td>
<td>6.65±2.82</td>
<td>8.96±2.53*</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; and PRA, plasma renin activity.

*P<0.01 versus baseline values.

†As measured by ng of angiotensin I per mL per hour.
Vasoconstriction with L-NMMA was significantly enhanced after both 2 (FBF from 3.4±0.6 to 2.1±0.4 mL/100 mL of forearm tissue per min; maximum, −37±2%; \( P<0.05 \)) and 12 months of therapy (FBF from 3.3±0.4 to 1.9±0.4 mL/100 mL of forearm tissue per min; maximum, −42±2%; \( P<0.001 \)), but the response to norepinephrine remained unchanged (2 months: FBF from 3.2±0.5 to 2.2±0.5 mL/100 mL of forearm tissue per min; maximum, −33±3%; 12 months: FBF from 3.3±0.4 to 2.2±0.3 mL/100 mL of forearm tissue per min; maximum −34±3%) (Figure 1).

After 2 months of candesartan treatment, the response to acetylcholine was unchanged (FBF from 3.4±0.7 to 16.9±4.7 mL/100 mL of forearm tissue per min; maximum, 404±34%), as was the effect of L-NMMA on the acetylcholine response (at 2 months, FBF from 2.1±0.4 to 10.1±2.8 mL/100 mL of forearm tissue per min; maximum, 380±31%). After 12 months, the response to acetylcholine at the highest infusion rate was significantly (\( P<0.05 \)) enhanced when compared with baseline (FBF from 3.2±0.4 to 18.2±4.1 mL/100 mL of forearm tissue per min; maximum, 480±35%). However, L-NMMA was still ineffective on the vasodilation induced by acetylcholine (FBF from 1.9±0.4 to 10.8±2.9 mL/100 mL of forearm tissue per min; maximum, 474±32%). Moreover, the response to sodium nitroprusside, although unchanged after 2 months of treatment (FBF from 3.4±0.64 to 13.1±3.2 mL/100 mL of forearm tissue per min; maximum, 295±19%), was also significantly enhanced after 12 months (FBF from 3.2±0.5 to 11.3±1.8 mL/100 mL of forearm tissue per min; maximum, 374±25%; \( P<0.05 \) versus baseline).

Finally, vasodilation with TAK-044 was significantly (\( P<0.0001 \)) reduced after 2 months (FBF from 3.4±0.6 to 3.9±0.8 mL/100 mL of forearm tissue per min; maximum, 17.3±3.2%), and it was almost abolished after 1 year (FBF from 3.3±0.4 to 3.5±0.5 mL/100 mL of forearm tissue per min; maximum, 5.9±1.8%) of treatment with candesartan cilexetil.

**Discussion**

The present study confirms the presence of endothelial dysfunction in essential hypertension and demonstrates that treatment with the AT-1 receptor blocker candesartan increases tonic NO release and reduces the vasoconstricting effect of endogenous ET-1 in the forearm of patients with essential hypertension.

In accordance with previous reports, hypertensive patients showed blunted vasoconstriction with L-NMMA compared with normotensive subjects, whereas vasoconstriction to norepinephrine was only slightly reduced, confirming the presence of impaired tonic NO release. Moreover, vasodilation to acetylcholine, but not to sodium nitroprusside, was reduced in patients with essential hypertension when compared with normotensive controls. Because the impaired response to acetylcholine was also resistant to the inhibiting effect of L-NMMA, these results further confirm the presence of a curtailed agonist-induced endothelium-dependent vasodilation in essential hypertension, which is attributable to impaired NO availability. In agreement with preliminary results, TAK-044, an ET A/B receptor antagonist, showed a greater vasodilating effect in hypertensive patients compared with normotensive subjects, which suggests that endogenous ET-1 may possibly play a pathophysiological role in essential hypertension.

In hypertensive patients, 2 months of candesartan cilexetil treatment significantly increased vasoconstriction with L-NMMA. This effect was more pronounced after 12 months: then, the response to the NO-synthase inhibitor was no longer different than that in normotensive controls. Because the vasoconstrictor effect of norepinephrine was unchanged by pharmacological treatment, these results indicate that AT-1 receptor blockade with candesartan can restore tonic NO release. Whether this beneficial effect is related to the mechanism of action of the drug or to mere blood pressure reduction cannot be established by the present experimental design. Previous evidence indicates that antihypertensive treatment for 6 weeks with the angiotensin-converting enzyme (ACE) inhibitor enalapril (10 mg/day, taken orally) or the calcium-antagonist amlodipine (5 mg/day, taken orally) also increases blunted vasoconstriction to L-NMMA in patients with essential hypertension. However, the latter study likewise provides no information regarding whether the beneficial action of these compounds on basal NO release is related to blood pressure normalization or a specific pharmacological interaction.

Regarding the vasodilating effect of acetylcholine, candesartan was ineffective after 2 months of treatment, but it slightly enhanced the response to the highest infusion rate of the muscarinic agonist after 12 months of administration. However, this effect is probably nonspecific because it was also observed with sodium nitroprusside. Thus, in patients with essential hypertension, long-term treatment with the AT-1 receptor antagonist may improve peripheral vascular structure but not agonist-induced endothelial activation. This hypothesis is further supported by the following considerations. First, the increased response to acetylcholine after long-term candesartan cilexetil treatment was still resistant to L-NMMA, indicating that the potentiating vascular effect of the muscarinic agonist is not dependent on the restoration of NO availability. Second, the present results agree with previous evidence obtained with ACE inhibitors. The administration of captopril and enalapril for 7 to 8 weeks or cilazapril for 5 months did not affect the vasodilation caused by methacholine and acetylcholine, respectively, in the forearms of patients with essential hypertension. Only 1 year of treatment with lisinopril could increase the vasodilating effect of acetylcholine, an effect shared by sodium nitroprusside. Because in the latter study lisinopril also reduced minimal forearm vascular resistances, an index of structural alterations, the results in the cited study were interpreted as evidence that long-term treatment with the ACE inhibitor can improve peripheral vascular structural alterations but not endothelium-dependent vasodilation to acetylcholine. Finally, the lack of effect of candesartan cilexetil treatment on the response to acetylcholine confirms that mere blood pressure normalization is not sufficient to restore agonist-evoked endothelium-dependent vasodilation.
The most important finding of this study is that candesartan treatment can reduce the vasodilating effect of TAK-044, an antagonist for the ET A/B receptor, in hypertensive patients. Because the vasoconstrictor tone of endogenous ET-1 is increased in essential hypertension,\textsuperscript{1,12} this evidence demonstrates that AT-1 receptor blockade can blunt the altered ET-1 effect on vascular tone. However, it is important to note that the present experimental design has 2 major limitations. First, no evidence exists regarding whether the TAK-044 infusion time (5 minutes for each dose) is sufficient to reach the plateau of the vascular effect induced by the compound. However, the finding that the maximal vasodilation obtained in both normotensive subjects and patients with essential hypertension is similar to previous results obtained with ET A/B receptor blockade\textsuperscript{11,25} supports the possibility that the TAK-044 effect observed in our experimental conditions was almost maximal. Second, the present experimental design, without a placebo control treatment or an alternative therapy, cannot distinguish between an effect specifically related to AT-1 receptor blockade or a nonspecifically determined effect caused by blood pressure reduction. Despite this, the former possibility can be supported by the experimental evidence indicating that angiotensin II is a potent inducer of ET-1 production and release, an effect that is mediated by the AT-1 receptor subtype. Thus, in cultured endothelial cells, angiotensin II activates ET-1 synthesis and release.\textsuperscript{18,19}

Finally, although plasma ET measurement is not considered a sensitive marker for tissue production of the peptide because only \(\approx 20\%\) of generated ET is secreted luminally and the greater portion of the peptide is secreted toward the adjacent smooth muscle,\textsuperscript{36} it is of interest that in the present study, candesartan cilexetil treatment reduced circulating ET-1 levels in patients with essential hypertension. Again, this beneficial effect of treatment with the AT-1 receptor antagonist could be related either to the decreased effect of the stimulation of angiotensin II on ET-1 production or to a nonspecific effect related to blood pressure normalization. It is also worth noting that the above-discussed improvement in vascular structure exerted by candesartan cilexetil could be related to the decreased production and/or activity of ET-1.\textsuperscript{1,3}

In conclusion, this study underlines the complexity of endothelial dysfunction in essential hypertension. Patients with essential hypertension are characterized by reduced basal NO release, impaired agonist-evoked endothelium-dependent vasodilation, and increased endogenous ET-1 vasocostrictor activity. Taken together, these alterations can contribute to the development of vascular functional and structural alterations that characterize patients with essential hypertension. AT-1 receptor blockade can partially improve endothelial function by increasing tonic NO release and reducing the vasoconstrictor effect of endogenous ET-1. This positive effect of candesartan could be relevant to the vascular protection of patients with essential hypertension.

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