# Effects of Perindopril and Carvedilol on Endothelium-Dependent Vascular Functions in Patients With Diabetes and Hypertension

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**OBJECTIVE** — To compare the effects of the ACE inhibitor perindopril and the β-blocker carvedilol on blood pressure and endothelial functions in NIDDM patients with hypertension.

**RESEARCH DESIGN AND METHODS** — We conducted a double-blind randomized trial in 26 patients with NIDDM and mild hypertension. A 4-week run-in placebo period preceded the active 12-week treatment with perindopril (4–8 mg daily) or carvedilol (25–50 mg daily). Endothelial functions were assessed by evaluating the hemodynamic (mean blood pressure, leg blood flow) and rheological (platelet aggregation, blood viscosity, and blood filterability) responses to an intravenous bolus of 3 g L-arginine, the natural precursor of nitric oxide.

**RESULTS** — Both perindopril and carvedilol significantly reduced mean blood pressure ($P < 0.001$) and increased leg blood flow ($P < 0.05$) to the same extent; blood filterability remained unchanged in both perindopril- and carvedilol-treated groups. Carvedilol reduced platelet aggregation and blood viscosity significantly ($P < 0.05$) but perindopril did not. Before treatment, the hemodynamic and rheologic responses to L-arginine were significantly lower in patients ($P < 0.05$–$0.01$) than in 20 nondiabetic nonhypertensive control subjects. After 12 weeks of treatment, both drugs normalized the hemodynamic responses to L-arginine. Platelet aggregation response to L-arginine was ameliorated by carvedilol and remained unchanged in the perindopril group.

**CONCLUSIONS** — At the doses used, both drugs effectively reduce blood pressure and normalize the hemodynamic responses to L-arginine. The implications of the ameliorated endothelial function for the poor cardiovascular outlook of the NIDDM hypertensive patient need further assessment.

Endothelial cells have an important protective role in maintaining the normal physiological function of the vascular wall by releasing vasoactive mediators (1). Under normal conditions, the primary vasodilator mediator released is nitric oxide (NO). This agent not only acts to dilate vascular smooth muscle, it also inhibits smooth muscle cell proliferation and platelet aggregation, stimulates platelet disaggregation, and inhibits the adhesion of platelets to the endothelium surface (2). This contributes to the cytoprotective effects of NO on vasculature and is believed to play an important role in the inhibitory effect of normal endothelium on the progression of atherogenesis.

Because the development of the atherosclerotic lesion is a slowly developing process, pathophysiological changes in endothelial cell function can be observed long before the development of the atherosclerotic lesion. The selective loss of endothelium-dependent vasodilatory response is called endothelial dysfunction and can be found at an early stage of human disease. Indeed, endothelial dysfunction has been demonstrated in patients with hypercholesterolemia, hypertension, and diabetes (3–5).

L-Arginine is the natural precursor of NO (2). The systemic infusion of 30 g L-arginine in normal humans mimics many of the actions currently attributed to NO: L-arginine reduces blood pressure (6–8), inhibits platelet aggregation (6,8) and blood viscosity (8), and augments blood flow in peripheral arteries (6,8). L-Arginine may therefore be a useful tool to evaluate endothelium-dependent vascular functions. We have recently shown that the intravenous bolus administration of 3 g L-arginine is simple, suitable for repetitive testing, and able to evaluate more than the control of vasodilation (9). The reversal of the L-arginine effects by $N^G$-monomethyl-L-arginine (L-NMMA), which competitively blocks NO synthase (NOS) (2), also suggests the mediation of endogenous NO.

This study was designed to compare the effects of perindopril, an ACE inhibitor, and carvedilol, a vasodilating β-blocker, on blood pressure and endothelial functions in diabetic patients with hypertension. Diabetes and hypertension are frequently seen together and strongly predispose to cardiovascular disease (10). Both drugs may influence endothelial function, increasing by different mechanisms the availability of NO for vessels and blood: perindopril slows endogenous bradykinin breakdown (11), and carvedilol scavenges superoxide anion (12). Although lowering blood pressure with drugs can normalize endothelial dysfunction in hypertensive patients (13,14), to our knowledge no study has addressed this particular aspect in hypertensive diabetic patients.

## RESEARCH DESIGN AND METHODS

### Study subjects

This research protocol was carried out in accordance with the principle of the Decla-

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**Abbreviations**: ANOVA, analysis of variance; LBF, leg blood flow; LVR, leg vascular resistance; MAP, mean arterial pressure; L-NMMA, $N^G$-monomethyl-L-arginine; NO, nitric oxide; NOS, nitric oxide synthase.

ration of Helsinki and was approved by the local review board. The study population was recruited from the outpatient departments of our institution and was consecutively chosen. Eligible patients were fully informed of the aim of the study, and their informed consent was obtained. Twenty-six patients with NIDDM and mild hypertension (diastolic blood pressure >90 and <105 mmHg on repeated measurements in the absence of any antihypertensive treatment) were recruited for the study. They were all in good general health; in particular, the patients had adequate glycemic control ($HbA_{1c}$ <9%) with diet or oral hypoglycemic agents and did not have evidence of neuropathy (by vibration perception threshold), nephropathy (by microalbuminuria), or macroangiopathy (by electrocardiogram and Doppler examination). Patients with secondary hypertension, malignant hypertension, unstable angina, myocardial infarction within the preceding 6 months, liver or renal function abnormalities, or contraindications for or already receiving β-blockers or ACE inhibitors were excluded.

More than 30% of the patients had newly diagnosed hypertension, and 3 months of nonpharmacological treatment had failed to lower blood pressure effectively. Pretreated hypertensive participants (~40%) were taken off medication for at least 4 weeks to avoid carry-over effects. Pretreatment consisted predominantly of calcium antagonists, central or peripheral antiadrenergic agents, or diuretics; there was no difference between the two groups in the use of any specific antihypertensive medication. Special care was used to ensure against the recent use of aspirin and related drugs.

## Study design

This study had a randomized double-blind design for parallel groups with either 4 mg perindopril once daily or 25 mg carvedilol once daily. A 4-week placebo run-in period during which the patients were seen on a weekly basis preceded the baseline measurements. Those patients with an average sitting blood pressure >105 mmHg or <90 mmHg after the run-in period were excluded. As described below, an L-arginine test was performed on each patient on two occasions, one before the randomization to treatment (week 0) and the second 12 weeks after treatment (week 12), approximately 20 h after the last drug intake to avoid any influence of a potential acute effect of the drug investigated. After 4 weeks, patients with a sitting diastolic blood pressure >90 mmHg that had not decreased by at least 10 mmHg had their dose of study medication doubled for the remaining 8 weeks. All patients were instructed to follow a weight-maintaining diet consisting of 50% carbohydrate, 30% protein, and 20% fat and to refrain from heavy physical exercise or activity for at least 3 days before testing. Side effects, intercurrent diseases, and compliance were checked every 4th week during treatment. Blood pressure was monitored at each clinical visit (every week) after at least 5 min rest. Blood pressure was measured in triplicate with appropriate cuff size using a sphygmomanometer with an approximation of 2 mmHg. Measurements were always taken by the same investigator, on the same arm, and at the same hour. For the purpose of comparison, an age- and sex-matched normotensive, nondiabetic group was included.

## Hemodynamic and laboratory measurements

The patients were admitted to the research center after an overnight fast and after abstaining from smoking and alcohol- or caffeine-containing beverages the night before. After their arrival to the metabolic ward, they were placed in a quiet room with a temperature of 21–24°C. Intravenous lines were inserted in a large antecubital vein of one arm for L-arginine administration and in a dorsal vein of the contralateral arm for blood sampling. The subjects were then connected to instruments for automatic measurements of blood pressure and heart rate. The study started after three consecutive measurements of blood pressure and heart rate different by <5% were recorded. L-Arginine monochloride (Damor Pharmaceuticals, Naples, Italy) was given as an intravenous bolus of 3 g (10 ml) in 60 s, with blood samples taken every 5 min until 15 min.

Heart rate and finger arterial pressure were measured with a noninvasive technique (Finapres, Ohmeda 2300, Englewood, CA); generally, finger pressure readings of systolic, diastolic, and mean blood pressure agree well with intra-arterial blood pressure measurements (15,16). Mean arterial pressure was automatically calculated as the sum of diastolic pressure plus one-third of pulse pressure. The hand connected to the Finapres was placed at the level of the heart. Blood pressure was also measured with a sphygmomanometer at selected time points (every 2.5 min) during the test. Blood flow in the femoral artery was determined by image-directed duplex ultrasonography combining B-mode imaging and pulsed Doppler beams (Apogee CX 200, Interspec ATL, Ambler, PA). Blood-flow volumes were automatically calculated as the vessel cross-sectional area multiplied by the timed average volume from five repeated measurements for each volume-flow estimation. Blood flow did not differ between the two legs, and pooled data are presented accordingly. Doppler-derived flow measurements were obtained in the basal state and at 5-min intervals after L-arginine administration. Leg vascular resistance (LVR) was calculated by dividing the mean arterial pressure (MAP; mmHg) by the leg blood flow (LBF) and expressed in arbitrary units. Platelet aggregation response induced by ADP was determined according to Born (17). Briefly, platelet-rich plasma was obtained by centrifuging each sample at 200g for 10 min, and platelet-poor plasma was prepared by centrifuging the remaining volume of blood at 2,000g for 10 min. The aggregometer was adjusted before each test, and aggregation was induced using a final concentration of 1.25 μmol/l ADP. Aliquots of blood anticoagulated with 0.77 mol/l EDTA (the ratio of blood to EDTA was 1:20) were used to assess blood viscosity at high rate of shear (225 $s^{-1}$) using a digital viscosimeter 0.8 degree cone (Brookfield Engineering, Stoughton, MA). Erythrocyte deformability was measured according to Reid et al. (18); in brief, blood was filtered through a nucleopore polycarbonate sieve containing 5 μm cylindrical channels under a pressure of 20 cm of water. Results are expressed as the volume of red blood cells filtered per minute (ml/min) according to the formula: $60 \times Ht/t$ where $t$ indicates the time used for the filtration of 1 ml of blood and Ht the hematocrit. All determinations were made in duplicate by a person blinded to treatment.

Plasma glucose was determined by the glucose oxidase method (Beckman, Fullerton, CA). Plasma insulin was determined by radioimmunoassay, as previously described (19). Commercial enzymatic methods were used in the determination of cholesterol (Monotest; Boehringer Mannheim, Germany) and triglycerides (Peridocrome; Boehringer Mannheim); $HbA_{1c}$ was measured by column chromatography (Bio-Rad, Milan, Italy) and urinary albumin excretion by an immunoturbidimetric assay of the first morning sample (Ames, Milan, Italy).

Table 1—*Demographic and metabolic variables and vascular responses to L-arginine for patients and control subjects at entry to treatment*

| Parameter | Control subjects | Carvedilol | Perindopril |
|---|---|---|---|
| Sex (M/F) | 10/10 | 6/2 | 7/6 |
| Age (years) | 52.1 ± 5.0 | 53.0 ± 7.1 | 51.3 ± 6.0 |
| BMI | 27.2 ± 2.0 | 27.7 ± 2.2 | 27.9 ± 1.9 |
| MAP (mmHg) | 99 ± 6 | 119 ± 9.5* | 117 ± 9* |
| Glucose (mmol/l) | 5.2 ± 0.6 | 8.4 ± 1.3* | 8.7 ± 1.2* |
| $HbA_{1c}$ (%) | 5.1 ± 0.6 | 7.9 ± 0.9* | 8.1 ± 1 0* |
| Cholesterol (mmol/l) | 5.1 ± 0.9 | 4 9 ± 0.8 | 5.2 ± 1.0 |
| Triglycerides (mmol/l) | 1.2 ± 0.4 | 1.3 ± 0 4 | 1.4 ± 0.4 |
| Responses to L-arginine | | | |
| MAP (mmHg) | −5 ± 1.4 | −2.8 ± 1.5* | −2.6 ± 1.2* |
| LBF (ml/min) | 40 ± 16 | 21 ± 12† | 15 ± 10† |
| Platelet aggregation (%) | −27 ± 12 | −3.6 ± 2.5* | −2.1 ± 3* |
| Blood viscosity (cp) | −0.3 ± 0.15 | −0.14 ± 0.1† | −0.2 ± 0.1† |
| Blood filterability (ml/min) | 0.05 ± 0 02 | 0.03 ± 0 01 | 0.02 ± 0.02 |

Data are means ± SD. *$P < 0.01$; †$P < 0.05$ compared with control subjects.

## Statistical analysis

Data are presented as means ± SD. One-way analysis of variance (ANOVA) was used to compare baseline data. Change was calculated as the value obtained at the end minus the value obtained at the beginning of the intervention. ANOVA was also used to assess the significance within and between groups when a significant value of $P$ was found; a one-sample $t$ test was used to compare values obtained before and after carvedilol or perindopril administration; and two-sample $t$ tests were used for between-group comparison. Responses to L-arginine were expressed as the change from baseline recorded at 10 min after the L-arginine pulse: previous studies have shown this is the time-point of maximal vascular responses to the 3 g pulse in both health and disease (9). After a preliminary ANOVA, a one-sample $t$ test was used for comparison of the response to L-arginine obtained before and after carvedilol or perindopril administration. The Pearson correlation coefficient was used to assess the relationship between changes in blood pressure after treatment and changes in vascular responses to L-arginine. A $P$ value <0.05 was considered significant.

**RESULTS** — The nondiabetic normotensive group was composed of 20 subjects (Table 1). After 4 weeks of placebo treatment, 26 patients fulfilling the inclusion criteria were entered into treatment phase and were randomly allocated to take either perindopril or carvedilol. There was no significant difference between hemodynamic parameters and laboratory data before carvedilol and perindopril administration. Six patients in the perindopril group and five patients in the carvedilol group required upward dose titration at week 4 because of inadequate response. At the end of treatment, 85% of patients in both groups had sitting diastolic blood pressure <90 mmHg. Although no subject experienced adverse effects serious enough to warrant discontinuing either drug, some side effects were manifested: dry cough, abnormal taste, or epigastric discomfort in three patients of the perindopril group and dizziness or headache in two patients of the carvedilol group.

## Blood pressure, hemodynamic, and rheological changes

There was no statistically significant difference in blood pressure and hemodynamic changes between the two study groups (Table 2). Systolic and diastolic blood pressure, MAP, and LVR were significantly decreased to the same extent with perindopril versus carvedilol treatment. LBF increased with both treatments, with no difference between groups. The heart rate was lower after carvedilol, whereas it remained unchanged after perindopril. Platelet aggregation to ADP was lower after treatment in both groups, with a significant difference in the carvedilol group only. Blood viscosity and blood filterability remained unchanged in both groups.

### L-Arginine test

Before randomization, the vascular responses to L-arginine in patients were significantly lower than those of control subjects (Table 1). In particular, MAP fall after L-arginine administration was 54% of the response seen in control subjects ($P <$ 0.01); platelet aggregation decrease was 10% ($P < 0.01$); and blood viscosity reduction was 56% ($P < 0.05$). LBF increase after L-arginine administration was 45% ($P$ < 0.05) of that observed in control subjects.

Before randomization, there was no significant difference in the vascular

Table 2—*Hemodynarnic and rheological parameters before and after treatment*

| Parameter | Carvedilol | | Perindopril | | Changes | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Carvedilol | Perindopril |
| Systolic blood pressure (mmHg) | 162 ± 12 | 150 ± 9.8* | 165 ± 14 | 153 ± 9* | −12 ± 4.5 | −12 ± 4.9 |
| Diastolic blood pressure (mmHg) | 98 ± 4.5 | 87 ± 4.7* | 96 ± 4 | 86 ± 3.5* | −11 ± 3.7 | −10 ± 3.1 |
| Heart rate (beats/min) | 73 ± 6.5 | 69 ± 5.4* | 74 ± 6.7 | 75 ± 5.6 | −4 ± 1.5 | 1 ± 1‡ |
| LBF (ml/min) | 255 ± 46 | 284 ± 50† | 271 ± 41 | 293 ± 52† | 29 ± 19 | 21 ± 16 |
| LVR | 467 ± 73 | 384 ± 57* | 431 ± 66 | 361 ± 71* | −81 ± 47 | −71 ± 49 |
| Platelet aggregation (%) | 56 ± 19 | 47 ± 16† | 50 ± 20 | 45 ± 19 | −9 ± 3 | −5 ± 4 |
| Blood viscosity (cp) | 4.4 ± 0.6 | 4.1 ± 0.7 | 4.4 ± 0.5 | 4.2 ± 0.8 | −0.3 ± 0.2 | −0.2 ± 0.1 |
| Blood filterability (ml/min) | 0.72 ± 0.12 | 0.76 ± 0.15 | 0.75 ± 0.12 | 0.76 ± 0.15 | 0.04 ± 0.01 | 0.01 ± 0.01 |

Data are means ± SD. *$P < 0.01$, †$P < 0.05$ compared with values before treatment; ‡$P < 0.05$ for differences between changes by carvedilol versus perindopril.

Table 3—*Hemodynamic and rheological responses to L-arginine before and after treatment*

| Parameter | Carvedilol | | | Perindopril | | |
|---|---|---|---|---|---|---|
| | Before | After | Change | Before | After | Change |
| MAP (mmHg) | −2.8 ± 15 | −5.1 ± 1.8* | −2.3 ± 1.0 | −2.6 ± 1.2 | −4.8 ± 1.5* | −2.2 ± 1.2 |
| Heart rate (beats/min) | 2.5 ± 1.1 | −3.7 ± 1.4* | −5.7 ± 1.8 | 3.1 ± 1 | 3.7 ± 1.5 | 07 ± 05‡ |
| LBF (ml/min) | 21 ± 12 | 39 ± 15* | 18 ± 6 | 15 ± 10 | 30 ± 9* | 15 ± 5 |
| Platelet aggregation (%) | −3 6 ± 2 5 | −9 ± 3.2† | −5.4 ± 2.2 | −3 ± 3 | −5 ± 3 | −2 ± 15 |
| Blood viscosity (cp) | −0.14 ± 0.1 | −0.18 ± 0.1 | −0.08 ± 0.04 | −0 2 ± 0.1 | −0.2 ± 0.1 | 0 ± 0.1 |
| Blood filterability (ml/min) | 0.03 ± 0.02 | 0 05 ± 0 03 | 0.02 ± 0.02 | 0.02 ± 0.01 | 0.04 ± 0.02 | 0.02 ± 0.01 |

Data are means ± SD. *$P < 0.01$, †$P < 0.05$ compared with values before treatment; ‡$P < 0.01$ for differences between changes by carvedilol versus perindopril.

responses to L-arginine between the two groups (Table 3). Blood pressure fall after L-arginine administration was significantly enhanced in both treatment groups ($P < 0.01$), with values equaling those found in control subjects. Heart-rate increase after L-arginine administration remained unchanged after perindopril treatment but was significantly decreased by carvedilol ($P < 0.01$). LBF increase after L-arginine administration was normalized by both treatments. Platelet aggregation response to L-arginine was significantly enhanced by carvedilol but was still 30% of that found in control subjects ($P < 0.01$) No significant change of platelet aggregation response to L-arginine was observed in the perindopril group. Neither blood viscosity nor blood filterability responses to L-arginine were significantly influenced by either treatment.

### Biochemical measurements

Fasting plasma glucose (carvedilol, −0.35 ± 0.7; perindopril, −0.22 ± 0.5 mmol/l), $HbA_{1c}$ (carvedilol, −0. 12 ± 0.31; perindopril, −0.1 ± 0.2%), and total cholesterol (carvedilol, −0.15 ± 0.34; perindopril, −0.05 ± 0.14 mmol/l) levels did not change significantly after treatments. Plasma insulin responses to L-arginine (peak at 10 min) were 287 ± 63 and 307 ± 53 pmol/l at baseline and did not change significantly after treatment with either perindopril (327 ± 84) or carvedilol (259 ± 70 pmol/l).

**CONCLUSIONS** — We have shown that the ACE inhibitor perindopril and the vasodilating β-blocker carvedilol result in a significant reduction of blood pressure and in a significant improvement of endothelium-dependent vascular functions in patients who have both diabetes and hypertension. To our knowledge, this is the first documentation that the drug doses administered in this study are equivalent regarding their blood pressure–lowering effect and their capacity for improving endothelial function in subjects particularly at risk of cardiovascular disease (10). Endothelial dysfunction was already present in both groups of patients before treatment; this fits with the observation that pathophysiological changes of endothelial function can be observed long before the clinical evidence of atherosclerosis. The findings apply to patients without overt vascular disease, dyslipidemia, microproteinuria, or autonomic neuropathy, factors that may independently influence vasomotor function (20,21).

The vasodilatory response to L-arginine improved after treatment at the levels found in control subjects. This suggests that endothelium-dependent vasodilation is impaired in hypertensive patients, but as a result of, rather than as a primary cause of, their blood pressure. Although treatment of hypertension with a variety of drugs can normalize the impaired basal release of NO (13,14), there is no clear consensus as to whether NO synthesis is impaired in the vascular endothelium of hypertensive patients (4). On the other hand, the antiplatelet effect of L-arginine was partially ameliorated by the drugs, with a significant effect for carvedilol only. In some patients (four in each group), the antiplatelet response to L-arginine was paradoxical, that is, the aggregation response to ADP increased after L-arginine administration. This is reminiscent of the paradoxical vasoconstriction to acetylcholine that occurs in angiographically normal epicardial arteries of patients with either hypercholesterolemia (22) or NIDDM (23). Because the antiplatelet action of NO is believed to confer an important antithrombotic property on the endothelial surface, this may explain, at least in part, the high prevalence of thrombotic events occurring in disease processes associated with endothelial dysfunction.

Our noninvasive technique enables reproducible assessment of vascular responses to the administration of L-arginine, the natural precursor of NO. Exogenous L-arginine administration, both acutely and chronically, mimics many of the actions currently attributed to NO, including vasodilation, antiplatelet activity, and amelioration of blood viscosity (6–8). We did not measure directly whether L-arginine increased NO production. However, other investigators have shown that acute L-arginine administration is associated with an increase in a number of other surrogate measures of NO production, such as nitrite, nitrate, and exhaled NO (6,7,24). Moreover, the inhibition of L-arginine effects by L-NMMA supports that the mechanism is related to increased synthesis of NO.

The mechanism whereby L-arginine enhances the production of NO is still debated. A popular view claims that the increased availability of the substrate may be implicated. However, the $K_m$ (substrate concentration at which the reaction velocity is half maximal) of the constitutive endothelial NOS for L-arginine is far below (~30- to 800-fold) the ambient intracellular L-arginine levels (25), which puts into doubt the validity of the assumption that L-arginine serves merely as a substrate for NO. L-Arginine may enhance NO release via the reversal of the inhibitory effects of physiological concentrations of L-glutamine, increasing the $K_m$ of NOS for L-arginine (26). Finally, we have recently shown that the vascular responses to L-arginine are mediated, in part, by endogenous insulin, which seems consistent with the reported effects of this hormone, namely vasodilation and antiplatelet activity (8 ).

Diabetes and hypertension are major risk factors for premature cardiovascular morbidity and mortality (27). Diabetes and hypertension have also been shown to be a state of increased free radical production

that may contribute to the oxidation of LDL and increase the oxidant stress to the vascular wall (28,29). In vessels from rats with angiotensin II–induced hypertension, for example, enhanced superoxide anion production has been described (30). Such an increase in superoxide anion likely accelerates the inactivation of NO and accounts for the apparent decrease in bioactive NO.

An increased production of endothelium-derived hyperpolarizing factor, NO, and vasodilator prostanoids is thought to contribute to the protective cardiovascular effects of ACE inhibitors (31). These effects are thought to derive, at least in part, from the accumulation of kinins in the vascular cells, as a consequence of reduced inactivation. Perindopril significantly augments the plasma kinin levels in rats when administered at concentrations that do not affect the renin-angiotensin system (32). The release of endothelial factors stimulated by kinins may play an important role in the beneficial action of ACE inhibitors on endothelial functions and may explain, at least in part, the effect of perindopril in our patients. Indeed, the endothelial dysfunction is restored by ACE inhibitors in animal models of diabetes, hypertension, and atherosclerosis (33–35).

The amelioration of endothelial dysfunction seen in patients taking carvedilol seems not related to the reduction of blood pressure, because a relationship between the blood pressure–lowering capacity of the drug and the improved endothelial function was not found. On the other hand, this lack of association does not prove that lowering of blood pressure has no effect on endothelial function. Carvedilol is a novel, nonselective β-blocker with α1-blocking properties; it produces systemic vasodilation and does not have unwanted effects on glucose and lipid metabolism (36). Carvedilol presents a novel antioxidant activity not shared by other β-blockers. In fact, it may inhibit lipid peroxidation, prevent the depletion of endogenous antioxidants (vitamin E, glutathione) from tissues subjected to oxidative stress, and scavenge superoxide anion (37). It seems therefore conceivable that carvedilol increases the availability of NO for blood vessels by scavenging superoxide anion. This also fits with accumulated evidence indicating that the impairment of endothelial vasodilatory function in atherosclerosis seems to be related to decreased bioactivity rather than reduced production of NO or alteration in NOS (38).

A further mechanism should be considered. Both NIDDM and hypertension are states of insulin resistance (39): it is possible that the vascular abnormalities seen in our patients were specifically related to resistance to NO-mediated actions of insulin (40). Although we have no direct evidence for this, as the insulin responses to L-arginine were similar before and after treatment with both drugs, ACE inhibitors and carvedilol have been found to improve peripheral insulin sensitivity in diabetic and hypertensive patients (41,42). Because an increased production of free radicals is thought to play a role in the development of insulin resistance (43), it remains possible that the improved endothelial function after treatment may be due, at least in part, to the amelioration of the vascular effects of insulin.

In summary, this double-blind randomized study of perindopril and carvedilol in patients with both NIDDM and hypertension demonstrates that at the doses used, both drugs ameliorate vascular responses to L-arginine. Indeed, the reduced vasodilating effect of L-arginine was normalized after treatment, suggesting that endothelium-dependent vasodilation is not pathogenetically related to the raised blood pressure. On the other hand, platelet aggregation and blood viscosity responses to L-arginine were not normalized after treatment, which might have relevance to the still raised cardiovascular morbidity in treated hypertensive patients. The effects of perindopril and carvedilol to ameliorate endothelial dysfunction may be related, at least in part, to increased bioactivity of endogenous NO.

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