Effect of Treatment With Candesartan or Enalapril on Subcutaneous Small Artery Structure in Hypertensive Patients With Noninsulin-Dependent Diabetes Mellitus

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Abstract—Structural alterations of subcutaneous small resistance arteries are associated with a worse clinical prognosis in hypertension and noninsulin-dependent diabetes mellitus (NIDDM). However, no data are presently available about the effects of antihypertensive therapy on vascular structure in hypertensive patients with NIDDM. Therefore, we have investigated the effect of an angiotensin-converting enzyme inhibitor, enalapril, and a highly selective angiotensin receptor blocker, candesartan cilexetil, on indices of subcutaneous small resistance artery structure in 15 patients with mild hypertension and NIDDM. Eight patients were treated with candesartan (8 to 16 mg per day) and 7 with enalapril (10 to 20 mg per day) for 1 year. Each patient underwent a biopsy of the subcutaneous fat from the gluteal region at baseline and after 1 year of treatment. Small arteries were dissected and mounted on a micromyograph and the media-to-internal lumen ratio was evaluated; moreover, endothelium-dependent vasodilation to acetylcholine was assessed. A similar blood pressure-lowering effect and a similar reduction of the media-to-lumen ratio of small arteries was observed with the 2 drugs. Vascular collagen content was reduced and metalloproteinase-9 was increased by candesartan, but not by enalapril. Changes of circulating indices of collagen turnover and circulating matrix metalloproteinase paralleled those of vascular collagen. The 2 drugs equally improved endothelial function. In conclusion, antihypertensive treatment with drugs that inhibit the renin-angiotensin-aldosterone system activity is able to correct, at least in part, alterations in small resistance artery structure in hypertensive patients with NIDDM. Candesartan may be more effective than enalapril in reducing collagen content in the vasculature. (Hypertension. 2005; 45[part 2]:659-665.)

Key Words: arteries ■ diabetes mellitus ■ hypertrophy ■ remodeling
sive drugs maintained a media-to-lumen ratio of subcutaneous
ous arteries significantly greater than normotensive subjects
and nondiabetic hypertensive patients,15 thus suggesting that
vascular remodeling in hypertensive patients with NIDDM
may be particularly difficult to correct. However, no prospec-
tive randomized study about the effect of a single antihyper-
tensive drug on small artery remodeling or on extracellular
matrix in hypertensive patients with NIDDM has been per-
formed so far.

It has been previously demonstrated that the measurement
of the circulating levels of some peptides might give impor-
tant information about collagen turnover in the cardiovascular
system. In particular, N-terminal propeptide of type I colla-
gen (PINP) is a marker of collagen synthesis,16,17 whereas
C-terminal telopeptide of type I collagen (ICTP) is a marker
of collagen degradation;18 N-terminal propeptide of type III
procollagen may reflect both synthesis and degradation.
These markers were previously shown to be related to
cardiac,16,17,19 and possibly also to vascular, fibrosis. It has
been also demonstrated that circulating levels of metallopro-
teinases (MMPs), which are catabolic enzymes involved in
the degradation of extracellular matrix proteins (namely
collagen), are decreased in hypertensive patients (especially
in those with left ventricular hypertrophy) compared with
controls and are increased by drugs that are able to reduce
cardiovascular fibrosis.18 Changes in MMP-1 serum levels
parallel those of circulating ICTP, whereas changes in circu-
lating PINP move in the opposite direction.18

Given all these considerations, we aimed to investigate the
structure of subcutaneous small arteries of hypertensive
patients with NIDDM, before and after long-term treatment
with the angiotensin II type 1 receptor blockers candesartan
and the ACE inhibitor enalapril, using a precise and reliable
micromyographic technique. We have also focused our atten-
tion on changes in vascular extracellular matrix, as well on
circulating indices of extracellular matrix turnover.

Patients and Methods

Fifteen patients with diagnoses of mild essential hypertension
(sitting diastolic blood pressure between 90 and 99 mm Hg and/or
sitting systolic blood pressure between 140 and 159 mm Hg at
the end of a 2-week placebo run-in period), aged between 30 and 70
years, and with a previous diagnosis of NIDDM, with or without
ongoing oral hypoglycemic therapy, were included in the study.
Patients were previously untreated for hypertension (n=5) or treated
for ≤1 month in the 3 months preceding the enrollment (n=10).
Among the previously treated patients, only those who did not
tolerate and/or did not respond to their previous antihypertensive
medication were enrolled. Patients previously treated with ACE
inhibitors and angiotensin receptor blockers, as well as patients with
secondary forms of hypertension or with any disease that could have
interfered with the study protocol, were excluded. Characteristics of
previous antihypertensive therapy were similar in the 2 groups.
The presence of NIDDM was established according to the Guidelines
of the Expert Committee on the Diagnosis and Classification of
Diabetes Mellitus.20 Patients were randomized to 1 of the 2 active
treatments (candesartan 8 mg once daily or enalapril 10 mg once
daily). After 6 weeks of active treatment, if blood pressure was
≥130/85 mm Hg, the dose of candesartan and enalapril was doubled
(16 mg once daily and 20 mg once daily, respectively). Target blood
pressure values were established according to available guidelines.21
If blood pressure was still uncontrolled after 12 weeks of active
therapy, a diuretic was added (hydrochlorothiazide 12.5 mg once
daily). After 18 weeks of treatment, if blood pressure was still
uncontrolled, the dosage of diuretic was doubled (hydrochlorothia-
zide 25 mg once daily). Patients were then re-evaluated at 6 and 12
months after enrollment. Venous blood samples were taken with the
participants in the supine position, after a washout period of at least
2 weeks, for standard hematology and serum biochemistry tests
(including triglycerides and total cholesterol), at baseline, 6 months,
and 12 months after enrollment. The study was comparative,
randomized, and double-blind.

Micromyography

At baseline and at the end of the study (12 months), all participants
underwent a biopsy of subcutaneous fat from the gluteal region
(3-cm long, 0.5-cm wide, 1.5-cm deep).6,6 Small arteries (~100 to
280 μm of average diameter in relaxed conditions, 2-mm-long) were
dissected from the subcutaneous fat of the biopsy samples and
mounted as a ring preparation on an isometric myograph (410 A; JP
Trading, Aarhus, Denmark) by threading onto 2 stainless steel wires
(40-μm diameter). Details about the micromyographic technique of
evaluation of small artery morphology were previously
reported.5,22–24

The following functional evaluations were performed: a cumula-
tive dose-response curve to acetylcholine at the following concen-
trations: (10⁻⁹, 10⁻⁸, 10⁻⁷, 10⁻⁶, 10⁻⁵ mol/L), 3 minutes per concen-
tration, after preconstriction with norepinephrine 5 μmol/L; and a
concentration-response curve to sodium nitroprusside (10⁻⁷, 10⁻⁸,
10⁻⁹, 10⁻¹⁰ mol/L) (endothelium-independent vasodilatation).
The average values obtained from 2 vessels in each experiment
were considered. The response to acetylcholine and sodium nitro-
prusside was expressed as the percent decrease of the wall tension.

The protocol of the study was approved by the ethics committee of
our institution (Medical School, University of Brescia), and informed
consent was obtained from each participant. The procedures fol-
lowed were in accordance with institutional guidelines.

Determination of the Composition of Small Artery Walls

Human arteries obtained from subcutaneous biopsies were isolated
and fixed in paraformaldehyde 4% for 24 hours. The vessels were
washed in phosphate buffer 0.12 mol/L for 24 hours, dehydrated in
a series of alcohol, embedded in paraffin, and cut on a microtome at
5-μm-thickness section. After deparaffinization and hydration, the
sections were stained for 5 minutes in 1% acid phosphomonolobic
aqueous solution and then stained for 3 minutes in 6% Sirius red in
an aqueous solution. After dehydration in alcohol series and clarifi-
cation with xylene, the slides were mounted in depex. All sections
were then analyzed using a light microscope under normal and
polarized light. Tissue sections were examined under green filtered
light at a magnification of 40×. Five patients from each group were
used to study collagen content in the arteries. Measurement of 10
areas per artery was performed. The percentage of total collagen
occupying the media layer of vessels was calculated using an image
analyzer (ImageproPlus; Immagini e Computer, Milan, Italy). The
same sections were examined using polarized light microscopy.
Under these conditions, collagen fibers of different thickness are
differently colored. The thick and denser type I collagen fibers are
detected as orange to red, whereas the thinner type III collagen fibers
appear yellow to green.24 The percentage of the different types of
collagen occupying the media layer was evaluated with the same
automated image analyzer.

Zymographic Analysis

Gelatinase activity in subcutaneous small arteries was assessed by
gelatin zymography. Gelatin zymographic analysis of protein extract
from the vessels revealed a lytic band, consistent with the presence
of proform of MMP-9 at 92 kDa. MMP-9 activity was expressed as
absolute units. The method was described in detail previously.26
**Echocardiography**

In all subjects, a standard echocardiographic evaluation (HP Sonos 5000; Hewlett Packard, Andover, Mass) was performed. Left ventricular internal dimensions, left ventricular posterior wall, and interventricular septum thickness were measured according to the recommendations of the American Society of Echocardiography. The diagnosis of left ventricular hypertrophy was considered if left ventricular mass index exceeded 110 g/m² in females and 131 g/m² in males.

**Circulating Indices of Extracellular Matrix**

We have also evaluated some circulating indices of collagen turnover: PINP, ICTP, and N-terminal propeptide of type III procollagen by radio-immuno assay (Orion Diagnostica, Espoo, Finland) at baseline and after 6 months and 12 months of treatment. We also evaluated MMP-1, MMP-2, and MMP-9 serum levels by enzyme-linked immunosorbent assay (Chemicon, Temecula Calif) at baseline and after 6 months and 12 months of treatment.

**Statistical Analysis**

All data are expressed as mean±SD, unless otherwise stated. One-way analysis of variance (ANOVA) and Bonferroni correction for multiple comparisons were used to evaluate differences among groups. Two-way ANOVA for repeated measures was used for dose-response curves to acetylcholine and sodium nitroprusside (group×concentration). All analyses were performed with the BMDP statistical package (BMDP software programs 7D, 8D, 1V, 2V; BMDP Statistical Software Inc, Los Angeles, Calif). The study had 80% power to detect a difference between groups in the media-to-lumen ratio of 0.01 at 5% of significance level.

### Results

**Demographic Data**

Fifteen hypertensive patients with NIDDM were randomized, 8 to treatment based on candesartan, 7 to treatment based on enalapril. In 1 patient in the candesartan group and in 1 in the enalapril group, hydrochlorothiazide was added to further reduce blood pressure. The 2 groups were well-balanced at baseline (Table 1). Average body mass index was in the overweight range. No significant change in fasting glucose was observed during the treatment period. Systolic and diastolic blood pressures were significantly and equally reduced by both treatments (Table 1); 75% of the patients in the candesartan group and 86% in the enalapril group had a final blood pressure ≤140/90 mm Hg, whereas 38% and 43%, respectively, had a final blood pressure ≤130/80. No signs of renal impairment were present in any patient (Table 1), and proteinuria, evaluated by 2 consecutive overnight urine sample collections (9 hours, nephelometry), was in the normal or in the microalbuminuric range in all patients (Table 1).

**Echocardiography**

Changes in left ventricular mass index were modest, because no patients had left ventricular hypertrophy at baseline (Table 1). Enalapril was slightly more effective than candesartan in reducing left ventricular mass index (enalapril: P<0.05 versus basal values; candesartan: no significant difference).

**Morphology of Subcutaneous Small Arteries**

Media-to-lumen ratio was significantly reduced and normalized internal diameter was significantly increased by treatment with candesartan (Table 2, Figure 1), whereas enalapril induced a similar reduction in the media-to-lumen ratio but had no significant effect on internal diameter (Table 2). A significant decrease in the total and type I collagen content of the media of small arteries was observed in patients treated with candesartan (Figure 2, Table 2), whereas no change was observed in the enalapril group. Neither candesartan nor enalapril showed any effect on type III collagen (Table 2).

**Zymographic Analysis**

MMP-9 activity was significantly increased after treatment with candesartan (Table 2), whereas no statistically significant change was observed with enalapril.

**Circulating Indices of Collagen Turnover and MMPs**

Circulating indices of collagen turnover pointed toward reduced synthesis of collagen in patients treated with candesartan, as suggested by a reduction in PINP and in PINP/ICTP.

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**TABLE 1. Demographic, Hemodynamic, and Echocardiographic Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Candesartan</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±9</td>
<td>58±4</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>6M/2F</td>
<td>5M/2F</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>90±19</td>
<td>79±7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174±10</td>
<td>167±7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29±9</td>
<td>28.5±2.80</td>
</tr>
<tr>
<td>Known duration of diabetes, y</td>
<td>2.1±1.3</td>
<td>1.9±1.6</td>
</tr>
<tr>
<td>Known duration of hypertension, y</td>
<td>1.3±1.8</td>
<td>1.1±1.6</td>
</tr>
<tr>
<td>Hemoglobin A₁₀, %</td>
<td>6.8±0.3</td>
<td>7.1±0.4</td>
</tr>
<tr>
<td>No. of patients on oral hypoglycemic therapy</td>
<td>7/8</td>
<td>6/7</td>
</tr>
<tr>
<td>No. of patients on lipid-lowering agents</td>
<td>4/8</td>
<td>4/7</td>
</tr>
<tr>
<td>Albumin excretion rate, µg/min</td>
<td>55.0±188</td>
<td>47.9±151</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>9.27±2.57</td>
<td>9.21±2.18</td>
</tr>
<tr>
<td>Basal</td>
<td>10.4±3.68</td>
<td>9.49±2.57</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>9.15±3.24</td>
<td>9.43±1.84</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>12.2±12.2</td>
<td>87.4±11.8</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>8.8±1.1</td>
<td>8.65*</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>8.65*</td>
<td>6.10±0.70</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.48±0.38</td>
<td>1.50±0.43</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>175±13.1</td>
<td>151±14.9</td>
</tr>
<tr>
<td>Basal</td>
<td>148±13.1</td>
<td>151±14.9</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>137±9.90*</td>
<td>129±16.4*</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>139±13.3*</td>
<td>131±7.01*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>176±6.94</td>
<td>94.9±5.24</td>
</tr>
<tr>
<td>Basal</td>
<td>91.3±6.94</td>
<td>94.9±5.24</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>84.3±6.98†</td>
<td>81.6±4.89†</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>83.9±6.94*</td>
<td>81.7±8.65*</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>86.3±28.3</td>
<td>94.8±26.1</td>
</tr>
<tr>
<td>Basal</td>
<td>83.2±25.0</td>
<td>86.1±15.8</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>82.3±27.6</td>
<td>78.7±18.1*</td>
</tr>
</tbody>
</table>

F indicates female; M, male.

*P<0.05; †P<0.01 vs basal.
Media-to-lumen ratio (Table 3). Again, no change was observed in patients treated with enalapril (Table 3).

Similarly, serum levels of MMP-2 and MMP-9 were increased during treatment with candesartan, whereas no change was observed during treatment with enalapril (Table 3). MMP-1 showed a similar trend, but differences did not reach statistical significance (Table 3).

Endothelial Function

The vasodilatation to acetylcholine was significantly improved by both treatments (ANOVA $P<0.05$) (Figure 2). No difference among groups was observed in the responses to sodium nitroprusside (Figure 3).

Discussion

For the first time to our knowledge, this study has evaluated small artery structure in hypertensive patients with NIDDM in a prospective study before and after treatment using a direct, reliable, and well-assessed technique. The main result of our study is that enalapril and candesartan proved to be equally effective in correcting small resistance artery remodeling (ie, media-to-lumen ratio), but candesartan seemed to have some advantages in reducing alterations of extracellular matrix. In fact, candesartan decreased total and type I collagen, which is the collagen subtype mostly represented in adult vessels.

It has been shown previously that hypertensive patients with NIDDM have marked structural abnormalities in the resistance arteries, as indicated by an increased media-to-lumen ratio, together with an increased collagen content in the media layer. It has been also suggested that an impaired myogenic responsiveness of subcutaneous small arteries, with increased wall stress for a given intraluminal pressure, may be the stimulus responsible for vascular hypertrophy in these patients, possibly in association with high levels of circulating trophic factors, such as insulin or insulin-like growth factor-1.

Changes in extracellular matrix components may have a relevant role in the process of vascular remodeling and may also be triggered by different hemodynamic or humoral factors. Our data suggest that the collagen content of the vascular wall may be modified by angiotensin II type-1 receptor blocker treatment more than by ACE inhibitor treatment. The reasons may be related to a more extensive inhibition of the renin-angiotensin system, particularly of angiotensin II-mediated effects. Angiotensin II and aldosterone are deeply involved in the genesis of extracellular matrix alterations via a profibrotic effects. The observation of more evident changes in vascular collagen content with candesartan treatment, as evaluated by direct morphological

![Figure 1](https://hyper.ahajournals.org/)

Figure 1. Media-to-lumen ratio of subcutaneous small resistance arteries before and after treatment with candesartan (full circles, solid line) and enalapril (full squares, dotted line) in the single patients.

![Figure 2](https://hyper.ahajournals.org/)

Figure 2. Polarized light images of subcutaneous small arteries of a hypertensive patient with NIDDM before (A) and after treatment with candesartan (B). Type 1 collagen fibers in orange–red, collagen type III fiber in yellow–green. Bar=50 μm.
Table 3. Circulating Indices of Collagen Turnover and Metalloproteinases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Candesartan n=8</th>
<th>Enalapril n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINP, µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>39.7±10.8</td>
<td>43.4±19.4</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>31.1±8.66†</td>
<td>35.3±15.2</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>32.3±7.05*</td>
<td>32.8±11.5</td>
</tr>
<tr>
<td>ICTP, µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>4.13±1.17</td>
<td>3.80±1.15</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>4.10±0.85</td>
<td>3.71±1.31</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>4.16±0.92</td>
<td>4.19±1.34</td>
</tr>
<tr>
<td>PIINP, µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>3.60±1.54</td>
<td>3.35±0.70</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>3.72±1.50</td>
<td>3.67±1.43</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>3.76±0.88</td>
<td>3.17±0.88</td>
</tr>
<tr>
<td>PINP/ICTP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>9.98±2.66</td>
<td>11.4±3.01</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>7.73±1.87*</td>
<td>9.91±3.09</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>7.84±1.51*</td>
<td>8.48±3.13</td>
</tr>
<tr>
<td>MMP-1, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>3.69±0.52</td>
<td>3.03±0.94</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>4.01±0.57</td>
<td>3.34±0.95</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>4.65±0.83</td>
<td>3.28±0.74</td>
</tr>
<tr>
<td>MMP-2, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>35.6±3.78</td>
<td>47.8±3.40</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>44.3±4.87</td>
<td>41.0±5.14</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>54.9±4.37††</td>
<td>35.9±5.40</td>
</tr>
<tr>
<td>MMP-9, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>149±13.5</td>
<td>155±12.4</td>
</tr>
<tr>
<td>After 6 months of treatment</td>
<td>165±9.36</td>
<td>160±8.03</td>
</tr>
<tr>
<td>After 12 months of treatment</td>
<td>174±8.61*</td>
<td>160±13.3</td>
</tr>
</tbody>
</table>

ICTP indicates C-terminal telopeptide of type I collagen; PIINP, N-terminal propeptide of type III procollagen; PINP, N-terminal propeptide of type I collagen.

†P<0.01 vs basal.
††P<0.05 vs enalapril.

Figure 3. Line graphs show a concentration-response curve to acetylcholine (top) and sodium nitroprusside (SNP) (bottom) in subcutaneous small arteries of hypertensive patients with NIDDM before and after treatment with enalapril (n=7) or candesartan (n=8). Data are shown as mean±SEM. Maximum vasodilation to acetylcholine (% reduction in wall tension with acetylcholine 10^{-10} mol/L) observed in normotensive and normoglycemic control subjects (historic data): -98±6%.

Techniques, is strengthened by the detection of more pronounced changes in circulating indices of collagen turnover, particularly of PINP, although they may be a reflection of changes of collagen content in different organs, namely in the heart. In our study, however, changes in left ventricular mass were modest and, in any case, in the opposite direction (ie, enalapril slightly more effective than candesartan). The observation of an increased activity of MMP-9 in subcutaneous small arteries after treatment with candesartan may partially explain differences in the effect on vascular collagen between the 2 drugs. In our study, no change in circulating ICTP levels was observed with candesartan. It was, however, suggested that the ratio between indices of synthesis and degradation of collagens may be more informative that absolute values of the single components of the ratio. It should also be noted that some differences in baseline values of type 1 collagen content and circulating MMP-2 are present, despite a proper randomization of patients. It cannot be completely ruled out that more evident effects of candesartan on vascular fibrosis may be partly explained by more pronounced alterations in the extracellular matrix in this group.

Hypertensive patients with NIDDM show the presence of an impairment of endothelial function in subcutaneous small arteries, as evaluated by an altered dilatation to acetylcholine and bradykinin. According to Schofield et al, part of the endothelial dysfunction may be related to the presence of an abnormal lipid profile. In our study, a significant improvement of endothelium-dependent vasodilation was observed. No significant change in serum triglycerides and cholesterol was detected (data not shown); however, a statistically significant reduction in blood pressure values was obtained. Therefore, it may be speculated that improvement of endothelial function may be related either to the hemodynamic effect of the 2 drugs or to a possible reduction of oxidative stress, consequent to the inhibition of the renin-angiotensin-aldosterone system activity. Again, pro-oxidative properties of angiotensin II have been well-documented previously.
Limitations of the Study

The number of patients evaluated in our study is relatively small—albeit it is similar to that of previous studies in essential hypertensive patients10–15—because of the invasive-ness of the biopic procedure and the complexity of the methods used. Patients evaluated in our study were relatively uncomplicated, without any evident cardiac or renal impairment. We do not know, at present, which are the functional or clinical consequences of the reduction of collagen content in the vascular extracellular matrix and, therefore, which clinical significance may be attributed to the different effects of the 2 drugs observed in the present study. Finally, a partially surprising finding of our study was the observation of an increase in the media cross-sectional area and of media thickness of subcutaneous small vessels after treatment with candesartan, whereas no significant change was observed with enalapril. A heterogeneity in vessel diameter may result from sampling vessels at random points in the vasculature; therefore, we have focused our attention to the media to lumen ratio, which is independent from the dimensions of the vessels10 and thus more reliable than the media thickness or the media cross-sectional area when comparisons among groups are concerned. In fact, it has been previously demonstrated that media-to-lumen ratio is the only structural parameter that is independent from the vessel’s dimension, remaining constant for a wide range of diameters (at least in human small resistance arteries of 150 to 300 μm);31 therefore, it is not affected by a possible sampling bias. In addition, it was previously demonstrated in the absence of a time effect in the evaluation of subcutaneous small resistance artery structure, because no difference in the media-to-lumen ratio was observed when biopsies of subcutaneous tissue were repeated in normotensive subjects after 1 year.32

Perspectives

Our data suggest: (1) effective antihypertensive treatment with candesartan or enalapril may partially and equally correct subcutaneous small resistance artery remodeling; (2) candesartan may induce a more pronounced reduction in the vascular collagen content; and (3) endothelial dysfunction may be similarly improved (although not completely normalized) by treatment with candesartan or enalapril. However, a complete normalization of vascular structure in hypertensive patients with NIDDM probably needs additional and different therapeutic strategies, including inhibition of growth factors (insulin, insulin-like growth factors-1), a more pronounced blood pressure reduction, and tighter metabolic control. In particular, combination therapies, including statins, aldosterone antagonists, peroxisome proliferator-activated receptor agonists, and drugs reducing oxidative stress are needed and would be the next step to reduce the risk in these patients. Also, a combination between ACE inhibitors and angiotensin receptor blockers may provide additional benefits.

Acknowledgments

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References


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