Structural Alterations in Subcutaneous Small Arteries of Normotensive and Hypertensive Patients With Non–Insulin-Dependent Diabetes Mellitus

Damiano Rizzoni, MD; Enzo Porteri, MD; Daniele Guelfi, MD; Maria Lorenza Muiesan, MD; Umberto Valentini, MD; Antonio Cimino, MD; Angela Girelli, MD; Luigi Rodella, PhD; Rossella Bianchi, MD; Intissar Sleiman, MD; Enrico Agabiti Rosei, MD

Background—It is not presently known whether non–insulin-dependent diabetes mellitus (NIDDM) is associated with the presence of structural alterations in small arteries or whether the combination of hypertension and NIDDM may have an additive effect on endothelial dysfunction. Therefore, we investigated subcutaneous small arteries in 12 normotensive subjects (NT group), 18 patients with essential hypertension (EH group), 13 patients with NIDDM, and 11 patients with NIDDM and EH (NIDDM+EH group).

Methods and Results—Subcutaneous small arteries were evaluated by a micromyographic technique. The internal diameter, the media-to-lumen ratio, remodeling and growth indices, and the collagen-to-elastin ratio were calculated. Concentration-response curves to acetylcholine, bradykinin, the endothelium-independent vasodilator sodium nitroprusside, and endothelin-1 were performed. The media-to-lumen ratio was higher in the EH, NIDDM, and NIDDM+EH groups compared with the NT group. EH patients showed the presence of eutrophic remodeling, whereas NIDDM and NIDDM+EH patients showed 40% to 46% cell growth. The collagen-to-elastin ratio was significantly increased in the EH and NIDDM+EH groups compared with the NT group. The vasodilatation to acetylcholine and bradykinin was similarly reduced in EH, NIDDM, and NIDDM+EH groups compared with the NT group. The contractile responses to endothelin-1 were similarly reduced in EH, NIDDM, and NIDDM+EH patients.

Conclusions—Our data suggest that the effects of NIDDM and EH on small artery morphology are quantitatively similar but qualitatively different and that the presence of hypertension in diabetic patients has little additive effect on small artery morphology and none on endothelial dysfunction. (Circulation. 2001;103:1238-1244.)

Key Words: diabetes mellitus ■ arteries ■ structure ■ hypertrophy ■ remodeling
disease frequently observed in NIDDM (ie, ischemic heart disease, renal disease, and ocular damage).

In a previous study, no difference in subcutaneous small artery structure was observed between control subjects and patients with insulin-dependent diabetes mellitus. In contrast, forearm minimal vascular resistance (an indirect index of resistance artery structure) was greater in NIDDM patients than in normotensive (NT) controls. However, no data obtained with direct, reliable techniques are presently available on small artery structure in human NIDDM.

Remodeling of small arteries may be associated with changes in the proportion of elastin and collagen in the arterial wall and, conversely, these changes may influence the type of remodeling. In addition, an impairment of endothelial function, as evaluated by the vasodilator response to acetylcholine, has been detected in human small arteries in EH, insulin-dependent diabetes mellitus, and NIDDM. However, it is not presently known whether the simultaneous presence of hypertension and NIDDM may have a cumulative adverse effect on the endothelial function of small arteries. Given all these considerations, we aimed to investigate structural changes and the endothelial function of subcutaneous small arteries of NT and hypertensive patients with NIDDM using a precise and reliable micromyographic technique.

Methods

Twelve NT subjects, 18 patients with EH, 15 patients with NIDDM, and 15 patients with NIDDM and EH (NIDDM + EH) were included in the study. Their age ranged from 40 to 70 years. The presence of hypertension was established using International Society of Hypertension/World Health Organization guidelines, and the presence of NIDDM was established according to the Guidelines of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. The majority of the NT subjects and those with EH were not enrolled in previous studies from our group and entered the study concurrently. "Overlapping" was <15%.

Venous blood samples were taken with the participants in the supine position, after a washout period of ≥2 weeks, for standard hematology and serum biochemistry tests (including triglycerides and total cholesterol). In addition, glycated hemoglobin (Hb A1c), circulating insulin and C-peptide levels (RIA), and microalbuminuria (nephelometric method) were measured.

Echocardiography

In all subjects, a standard echocardiographic evaluation (HP Sonos 5000, Hewlett Packard) was performed. Left ventricular internal dimensions and left ventricular posterior wall and interventricular septum thicknesses were measured according to the recommendations of the American Society of Echocardiography. Left ventricular hypertrophy was considered present if the left ventricular mass index exceeded 110 g/m² in women and 131 g/m² in men. For further technical details, see the article by Muiesan et al.

Micromyography

All participants underwent a biopsy of subcutaneous fat from the gluteal region (3 cm long, 0.5 cm wide, and 1.5 cm deep). Small arteries (average diameter in relaxed conditions, ~100 to 280 μm; 2 mm long) were dissected from the subcutaneous fat of the biopsies and mounted as a ring preparation on an isometric myograph (410 A, JP Trading) by threading onto 2 stainless steel wires (46 μm in diameter). Details about the micromyographic technique of evaluating small artery morphology were previously reported.

A calculation of the remodeling and growth indices was then performed using the technique of Hagerty and coworkers. The remodeling index quantifies how much of the vascular structural alteration may be explained by a rearrangement of the same material around a narrowed lumen, without cell growth.

The vessels were then stimulated as follows. (1) Three stimulations (2 minutes for each) with physiological saline solution (PSS) replaced NaCl by KCl on an equimolar basis (K-PSS), and 2 stimulations with K-PSS contained 10 μmol/L norepinephrine. (2) Cumulative dose-response curves to acetylcholine were determined at the following concentrations (3 minutes per concentration) after preconcentration with 5 μmol/L norepinephrine: 10⁻⁷, 3·10⁻⁷, 3·10⁻⁶, 10⁻⁶, 3·10⁻⁵, 10⁻⁵, 3·10⁻⁴, 10⁻⁴, and 10⁻³ mol/L. (3) Cumulative concentration-response curves to bradykinin were determined at the following concentrations (3 minutes per concentration) after preconcentration with 5 μmol/L norepinephrine: 10⁻⁷, 10⁻⁶, 10⁻⁵, and 10⁻⁴ mol/L. (4) Concentration-response curves to sodium nitroprusside (10⁻⁶, 10⁻⁵, 10⁻⁴, and 10⁻³ mol/L) were performed (endothelium-independent vasodilatation). (5) Finally, cumulative concentration-response curves to endothelin-1 were determined at the following concentrations (7 minutes per concentration): 10⁻¹⁰, 10⁻⁹, 10⁻⁸, and 10⁻⁷ mol/L.

To obtain further information about the mechanisms underlying endothelial dysfunction in hypertension, the following procedures were performed. (1) A cumulative dose-response curve to acetylcholine was determined in the presence of Nω-nitro-L-arginine methyl ester (L-NAME; 300 μmol/L; an inhibitor of nitric oxide synthase), indomethacin (10 μmol/L; an inhibitor of cyclooxygenase), L-NAME and indomethacin, and L-NAME plus ouabain (1 mmol/L; a blocker of ATP-dependent sodium-potassium exchanger). (2) Cumulative dose-response curves to acetylcholine and bradykinin were determined after mechanical removal of endothelium (gently rubbing the internal vascular surface).

The average values obtained from 2 vessels in each experiment were considered. The responses to acetylcholine, bradykinin, and sodium nitroprusside were expressed as the percent decrease of wall tension. The responses of blood vessels to endothelin-1 were expressed as wall tension (active force divided by 2 times the segment length) and as active media stress (wall tension divided by the media thickness). References 3 and 25 provide further details. 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 followed were in accordance with institutional guidelines.

Determination of the Composition of Small Artery Walls

Composition of the media of small artery walls was studied by electron microscopy. Ultrathin sections (70 to 90 nm) were cut by a microtome (Reichert Ultracut, Leica) and stained with 0.25% phosphotungstic acid for 10 minutes (to enhance the elastin contrast), 4% uranyl acetate for 30 minutes, and lead citrate for 3 minutes. The sections were examined with a Philips CM 10 electron microscope. Vessels were divided in 4 quadrants, and 3 electron micrographs were taken randomly in each quadrant for a total of 10 to 12 electron micrographs per vessel. Electron micrographs were examined at the original magnification of 4000× and enlarged by a factor of 3 for a final magnification of 12 000×. Standard point counting was used to determine the relative area occupied by collagen and elastin fibers within the vessel tunica media (Figure 1) and to calculate the collagen-to-elastin ratio.

Statistical Analysis

All data are expressed as mean±SEM, unless otherwise stated. One-way ANOVA and Bonferroni’s correction for multiple comparisons were used to evaluate differences among groups. The relation between continuous variables was evaluated by linear regression. Two-way ANOVA for repeated measures was used for dose-response curves to acetylcholine, bradykinin, endothelin-1, and sodium nitroprusside (group×concentration). All analyses were performed with the BMDP statistical package.
Results

Demographic Data

The demographic, hemodynamic, and humoral data are reported in Table 1. As expected, systolic and diastolic blood pressures were significantly higher in patients with EH and NIDDM+EH than in NT subjects or in patients with NIDDM. Fasting glucose was higher in the 2 groups of diabetic patients compared with NT subjects or with patients with EH. Body weight and body surface area were increased in patients with NIDDM+EH compared with NT subjects. Serum cholesterol or triglycerides were not significantly different among the groups, although patients with NIDDM or NIDDM+EH tended to have higher values. No signs of renal impairment were observed. The 24-hour albuminuria level was similar in the 2 groups of diabetic patients. Left ventricular mass index was significantly greater in patients with high blood pressure (EH and NIDDM+EH) than in NT subjects. Six patients with EH, 1 patient with NIDDM, 5 patients with NIDDM+EH, and 0 NT subjects had left ventricular hypertrophy (according to the previously mentioned criteria). Patients with NIDDM and NIDDM+EH had similar values of circulating insulin and C-peptide. Circulating insulin levels were significantly greater in patients with NIDDM than in NT subjects.

Subcutaneous Small Arteries

Media-to-lumen ratio, media thickness, and wall thickness were significantly greater and the normalized internal diameter was significantly smaller in patients with EH, NIDDM, and NIDDM+EH compared with NT subjects (Table 2). Moreover, patients with NIDDM+EH had a significantly higher media-to-lumen ratio compared with those with EH and NIDDM. The media cross-sectional area was significantly greater in patients with NIDDM compared with NT subjects, whereas the difference between patients with NIDDM+EH and NT was of borderline statistical signifi-

TABLE 1. Demographic, Hemodynamic, and Humoral Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT Subjects (n=12)</th>
<th>EH Patients (n=18)</th>
<th>NIDDM Patients (n=15)</th>
<th>NIDDM+EH Patients (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±4.0</td>
<td>55±1.4</td>
<td>57±2.6</td>
<td>61±1.3</td>
</tr>
<tr>
<td>Sex</td>
<td>6M, 6F</td>
<td>11M, 7F</td>
<td>6M, 9F</td>
<td>8M, 7F</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>69±3.18</td>
<td>69±2.36</td>
<td>74±2.58</td>
<td>85±2.58†‡</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164±4.0</td>
<td>168±2.12</td>
<td>164±1.81</td>
<td>166±2.07</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.81±0.05</td>
<td>1.82±0.04</td>
<td>1.80±0.03</td>
<td>1.93±0.04§</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.55±0.22</td>
<td>5.66±0.25</td>
<td>9.88±0.62‡</td>
<td>9.83±0.80‡</td>
</tr>
<tr>
<td>Serum nitrogen, mmol/L</td>
<td>13.6±1.23</td>
<td>13.2±0.59</td>
<td>12.9±0.65</td>
<td>13.2±0.92</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>80.4±5.3</td>
<td>82.3±3.53</td>
<td>84.9±4.42</td>
<td>89.3±4.42</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.07±0.46</td>
<td>5.61±0.29</td>
<td>6.05±0.33</td>
<td>5.82±0.33</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.50±0.20</td>
<td>1.70±0.19</td>
<td>1.66±0.18</td>
<td>2.00±0.46</td>
</tr>
<tr>
<td>Haemoglobin A1c, %</td>
<td>...</td>
<td>...</td>
<td>7.64±0.69</td>
<td>6.98±0.33</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128±2.3</td>
<td>161±1.6‡</td>
<td>131±2.6</td>
<td>157±3.9‡</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79±2.0</td>
<td>98±1.6‡</td>
<td>80±0.8</td>
<td>96±2.3‡</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>92±7.2</td>
<td>120±5.7†</td>
<td>83.9±5.7</td>
<td>116±7.2*</td>
</tr>
<tr>
<td>Albuminuria, mg/24 hours</td>
<td>...</td>
<td>...</td>
<td>114±91.9</td>
<td>65.1±20.9</td>
</tr>
<tr>
<td>Circulating insulin, pmol/L</td>
<td>52±12</td>
<td>77±23</td>
<td>156±32.1*</td>
<td>103±30.1</td>
</tr>
<tr>
<td>Circulating C-peptide, ng/mL</td>
<td>2.28±0.67</td>
<td>2.88±0.49</td>
<td>3.35±0.59</td>
<td>3.25±0.30</td>
</tr>
</tbody>
</table>

Values are mean±SEM. M indicates male; F, female.

*P<0.05, †P<0.01, ‡P<0.001 vs NT subjects; §P<0.01, |P<0.001 vs EH patients.
The vasodilatation to acetylcholine and bradykinin was significantly reduced in EH patients (ANOVA, 0.06 without correction for multiple comparisons; Table 2). Patients with EH showed the presence of eutrophic remodeling, as suggested by a remodeling index close to 100%, whereas patients with NIDDM and NIDDM+EH showed a remodeling index of 40% to 46%.

A weak but statistically significant correlation between media-to-lumen ratio and levels of circulating insulin (r=0.35, P<0.05) was observed in the 30 patients with diabetes mellitus (separated r values: NIDDM, 0.32; NIDDM+EH, 0.37). No significant correlation was observed in NT and EH patients (r=0.07 and -0.03, respectively).

A significant increase in the collagen content of the media of small arteries was observed in EH, NIDDM, and NIDDM+EH patients compared with NT subjects (P<0.05). The collagen-to-elastin ratio was significantly greater in EH and NIDDM+EH patients than in NT subjects (Figure 1). Three NIDDM+EH and 4 EH patients were previously treated with calcium antagonists or ACE inhibitors for <6 months. None was treated with angiotensin II type 1 antagonists. The data obtained after the exclusion of these patients were completely superimposable to those obtained in the whole group or in the remaining patients.

**Endothelial Function**

The vasodilation to acetylcholine and bradykinin was significantly reduced in EH patients (ANOVA, P<0.01 and <0.05, respectively, versus NT subjects), NIDDM patients (ANOVA, P<0.0001 and <0.01, respectively, versus NT subjects), and NIDDM+EH patients (ANOVA, P<0.01 and <0.05, respectively, versus NT subjects; P=NS versus other groups; Figure 2). No difference among groups was observed in the responses to sodium nitroprusside (Figure 3). The contractile response to endothelin-1 was similarly reduced in EH, NIDDM, and NIDDM+EH patients (Figure 3) compared with NT subjects when expressed as active media stress (ANOVA, P<0.05 at least; Figure 3). No difference was observed in terms of wall tension among groups (maximum wall tension (N/m): NT, 1.87±0.36; EH, 2.08±0.24; NIDDM, 2.38±0.28; and NIDDM+EH, 1.92±0.19). No significant correlation between blood pressure values and indices of endothelial function was observed. In EH, NIDDM, and NIDDM+EH patients, L-NAME blocked ≈50% of the vasodilator effect of acetylcholine or bradykinin (ANOVA between curves, P<0.01 at least), and the remain-

![Image](http://circ.ahajournals.org/)

**Figure 2.** Line graphs show a concentration-response curve to acetylcholine (top) and bradykinin (bottom) in subcutaneous small arteries of NT subjects (solid line, n=12) and patients with EH (dotted line, n=18), NIDDM (long dashed line, n=15), and NIDDM+EH (short dashed line, n=15). Data are shown as mean±SEM.

**Table 2.** Morphological Characteristics of the Subcutaneous Small Arteries in the Different Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT Subjects (n=12)</th>
<th>EH Patients (n=18)</th>
<th>NIDDM Patients (n=15)</th>
<th>NIDDM+EH Patients (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media thickness, μm</td>
<td>14.4±0.79</td>
<td>21.1±0.99†</td>
<td>23.4±1.00†</td>
<td>23.7±0.83†</td>
</tr>
<tr>
<td>Wall thickness, μm</td>
<td>30.1±1.41</td>
<td>41.8±1.57†</td>
<td>43.3±1.64†</td>
<td>43.2±1.63†</td>
</tr>
<tr>
<td>Normalized internal diameter, μm</td>
<td>299±15</td>
<td>226±16*</td>
<td>245±14*</td>
<td>220±12†</td>
</tr>
<tr>
<td>Media cross-sectional area, μm²</td>
<td>1427±2363</td>
<td>1506±1714</td>
<td>2086±2190*</td>
<td>19880±1728</td>
</tr>
<tr>
<td>Media-to-lumen ratio</td>
<td>0.050±0.003</td>
<td>0.093±0.006†</td>
<td>0.100±0.004†</td>
<td>0.112±0.004†</td>
</tr>
<tr>
<td>Remodeling index, %</td>
<td>...</td>
<td>92</td>
<td>75</td>
<td>86</td>
</tr>
<tr>
<td>Growth index, %</td>
<td>...</td>
<td>6</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>% Media area of collagen</td>
<td>14.9±1.15</td>
<td>22.4±0.76*</td>
<td>21.8±0.41*</td>
<td>24.4±0.75*</td>
</tr>
<tr>
<td>% Media area of elastin</td>
<td>10.8±0.32</td>
<td>9.26±0.26</td>
<td>11.28±0.23</td>
<td>10.5±0.48</td>
</tr>
<tr>
<td>Collagen-to-elastin ratio</td>
<td>1.37±0.13</td>
<td>2.34±0.15*</td>
<td>1.95±0.07</td>
<td>2.46±0.12*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<0.05, †P<0.001 vs NT subjects; ‡P<0.05 vs NIDDM or EH patients.
ing vasodilatation was completely blocked by ouabain (Table 3). No change was observed when indomethacin was added to the organ bath (Table 3). The mechanical removal of endothelium completely abolished vasodilatation to acetylcholine or bradykinin.

The mechanical removal of endothelium completely abolished vasodilatation to acetylcholine or bradykinin.

**Discussion**

This study evaluated small artery structure in NT and hypertensive patients with NIDDM for the first time using a direct, reliable, and well-assessed technique. The main result of our study is that hypertensive and NT patients with NIDDM show the presence of structural abnormalities in the resistance arteries, as indicated by an increased media-to-lumen ratio, and that these alterations are characterized by inward hypertrophic remodeling, rather than by eutrophic remodeling, which is usually observed in patients with EH.\(^3\) However, it is not presently known whether eutrophic and hypertrophic remodeling have different underlying pathogenetic mechanisms or a different natural history or whether they are differently modified by appropriate treatment. Our data also suggest that structural alterations in the vasculature are not the sole determinant of blood pressure, because they are present in both NT and hypertensive patients with NIDDM. Similar dissociations between vascular structural alterations and blood pressure values were previously observed in animal models of genetic and experimental hypertension.\(^25,27\) A possible explanation may be that a complex interplay between structural and functional factors is needed for blood pressure rise.

The presence of hypertrophic remodeling seems to be a characteristic of patients with NIDDM, although we previously observed smooth muscle cell hypertrophy in patients with renovascular hypertension in whom a pronounced activation of the renin-angiotensin system was present.\(^2,4\) It has been suggested that insulin or other related substances may have a role in promoting vascular cell growth.\(^6\) The observation of a significant correlation between plasma insulin concentrations and the media-to-lumen ratio of subcutaneous small arteries in our patients suggests, although it does not prove, that the hormone has an important role in the genesis of vascular structural alterations in patients with NIDDM. Because we did not measure smooth muscle cell size, we cannot safely attribute hypertrophic remodeling to either cell hypertrophy or hyperplasia.

In the present study, we observed an increase in collagen deposition in small arteries of patients with EH and NIDDM+EH. Patients with NIDDM showed a greater percent wall area occupied by collagen fibers compared with NT subjects, and the collagen-to-elastin ratio tended to be increased in NIDDM patients, although the difference did not

| TABLE 3. Response to Acetylcholine in Subcutaneous Small Arteries in the Presence or Absence of L-NAME, Indomethacin, or Ouabain |
|----------------------------------|------------------|------------------|------------------|
|                                | EH Patients (n=10) | NIDDM Patients (n=9) | NIDDM+EH Patients (n=8) |
| Acetylcholine 10^−5 mol/L        | −61±6.5%          | −48±3.1%          | −54±6.4%          |
| Acetylcholine 10^−6 mol/L + indomethacin | −56±6.9%          | −52±4.2%          | −50±5.9%          |
| Acetylcholine 10^−5 mol/L + L-NAME | −34±5.3%‡         | −30±5.0%‡         | −32±5.1%‡         |
| Acetylcholine 10^−6 mol/L + indomethacin + L-NAME | −44±8.2%*         | −35±5.9%*         | −38±7.9%*         |
| Acetylcholine 10^−5 mol/L + L-NAME + ouabain | −3±2.5%‡         | −5±2.0%‡         | −4±1.9%‡         |

Values are mean±SEM.

*P<0.05, †P<0.01, ‡P<0.001 vs acetylcholine alone.
reach statistical significance. Changes in extracellular matrix components may have a relevant role in the process of vascular remodeling, and they may be triggered by different hemodynamic or humoral factors. Our data suggest that the relative proportion of collagen to elastin fibers may be modified mainly in the presence of an increased hemodynamic load. It is possible that growth factors like insulin exert a more potent effect on the cellular components of the tunica media of small arteries, whereas an increased hemodynamic load mainly influences wall mechanics and extracellular matrix composition, as expressed by changes in the relative ratio between more versus less distensible components of the media (elastin versus collagen). In this study, no increase in left ventricular mass was observed in patients with NIDDM. A possible explanation is that cardiac mass is more directly influenced by the hemodynamic load than by growth factors, whereas the opposite seems to be true for subcutaneous small arteries.

Endothelial cells have important regulatory effects on the cardiovascular system through the release of vasodilator and vasoconstrictor factors. In addition, platelet aggregation and leukocyte extravasation through the endothelium may be influenced by locally produced compounds. Therefore, endothelial damage and dysfunction may contribute to inflammatory and thrombotic vascular lesions. Hypertensive patients and patients with insulin-dependent diabetes mellitus show the presence of an impairment of endothelial function in small arteries, as evaluated by direct methods, whereas similar data in NIDDM patients are lacking. Our study demonstrated the presence of impaired dilatation to acetylcholine and bradykinin in the subcutaneous small arteries of patients with NIDDM and NIDDM + EH. However, the presence of the 2 cardiovascular risk factors together did not induce a further worsening of endothelial function. A possible explanation is that, both in hypertension and in diabetes mellitus, oxidative stress, resulting from the vascular production of free radicals and/or cyclooxygenase-dependent substances, may reduce nitric oxide bioavailability. If the pathogenetic mechanism of endothelial dysfunction is similar in the 2 conditions, no additive effect may be expected.

A second important point relates to the mechanisms of endothelial dysfunction in the small resistance arteries of hypertensive and diabetic patients. In patients with EH, vasodilator responses to acetylcholine and bradykinin infused into the brachial artery are not usually blocked by inhibitors of nitric oxide synthase (ie, L-NMMA), whereas in NT subjects, the inhibitory effect of L-NMMA is preserved. In the subcutaneous small arteries of patients with EH and in those with NIDDM or NIDDM + EH, inhibitors of nitric oxide synthase are able to block ≈50% of the vasodilator effect of acetylcholine or bradykinin, whereas the remaining vasodilatation is blocked by ouabain, thus suggesting that the production of both nitric oxide and endothelium-derived hyperpolarizing factor may be involved. No effect was observed when indomethacin was added to the organ bath; therefore, the production of cyclooxygenase-dependent substances seems to be of minor importance, at least in our experimental model.

In the present study, reduced vascular responsiveness to endothelin-1 was also observed. Similar evidence was previously available only for hypertensive patients. The result can be explained, at least in part, by downregulation of the endothelin receptors on vascular smooth muscle as a consequence of increased production or biological activity of the peptide.

In conclusion, our data suggest that the effects of diabetes mellitus and EH on small artery morphology are qualitatively similar (despite the presence of a different hemodynamic load) but qualitatively different (hypertrophic versus eutrophic remodeling) and that the presence of hypertension in diabetic patients has little additive effect on small artery morphology. An evident endothelial dysfunction has been detected in patients with NIDDM, and the simultaneous presence of EH did not seem to exert an additive effect. The contractile responses to endothelin-1 were significantly reduced. Whether appropriate antihypertensive and/or antidiabetic therapy in NIDDM and NIDDM + EH patients may be associated with a regression of the structural alterations of small subcutaneous arteries deserves further investigation.

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