Effect of Lisinopril and Metoprolol on Arterial Distensibility


Abstract Apart from lowering blood pressure, antihypertensive drugs may influence vessel wall function. In a randomized double-blind study, the effect of lisinopril and metoprolol on arterial distensibility was studied in 40 patients with essential hypertension. After a placebo run-in period, the patients were randomly treated with metoprolol (50, 100, or 200 mg) or lisinopril (5, 10, or 20 mg) for 10 weeks. In the lisinopril group, blood pressure decreased after 10 weeks of therapy from 173±10/102±5 to 155±10/85±3 mm Hg and in the metoprolol group from 167±12/102±4 to 153±8/84±3 mm Hg. Diameter (millimeters), relative change in diameter (percent), and distensibility (10^{-7}/kPa) of the left common carotid artery were determined after the placebo run-in period and after 6 and 10 weeks of antihypertensive therapy. A multigate Doppler system was used to measure the vessel wall movements by Doppler analysis in M-mode; blood pressure was recorded by finger plethysmography (Finapres). Neither lisinopril nor metoprolol influenced the end-diastolic diameter of the common carotid artery after 6 and 10 weeks of treatment. In the lisinopril group, a significant increase of percent change in diameter (P<.05 compared with the baseline value; P<.05 compared with the metoprolol group) and distensibility (P<.01 compared with the baseline value; P<.05 compared with the metoprolol group) was observed. The results show that lisinopril but not metoprolol improves arterial distensibility in essential hypertension. Pressure-independent effects of angiotensin converting enzyme inhibitors may be important modulators of adaptive changes in the arterial wall. (Hypertension. 1994;23[suppl 1]:I-161-I-163.)

Key Words • hypertension, essential • angiotensin converting enzyme inhibitors

The mechanical properties of the arterial wall depend on medial thickness, smooth muscle tone, and viscoelastic properties of vascular connective tissue. Therefore, pressure-independent changes of arterial distensibility during antihypertensive treatment may reflect changes in medial mass. Interestingly, drugs reducing cardiac hypertrophy similarly improve arterial distensibility, suggesting similar effects on both myocardial and vascular growth stimuli. The ominous prognostic significance of cardiac hypertrophy has been clearly defined. Vascular hypertrophy also may adversely affect the course of hypertension. Folks and colleagues convincingly demonstrated that medial hypertrophy perpetuates a vicious cycle in the development of hypertension. Therefore, the pressure-independent effects on vascular smooth muscle function and growth may attract increased attention in the evaluation of antihypertensive drugs. In the present study, mechanical properties of the arterial wall were assessed during treatment with the angiotensin converting enzyme (ACE) inhibitor lisinopril and the β-blocker metoprolol. Despite similar antihypertensive effects, both drugs differed considerably in their effects on arterial wall properties.

Methods

In a randomized double-blind study, we investigated the effect of antihypertensive therapy with metoprolol and lisinopril on arterial distensibility in 40 patients with untreated essential hypertension. The study was approved by the local ethics committee, and all patients gave their written consent before enrollment. Patients with untreated essential hypertension aged 30 to 60 years with a diastolic blood pressure between 95 and 110 mm Hg on three occasions before and after a placebo run-in period of 1 week were included in the study. The following exclusion criteria were used: hyperkalemia (>5.3 mmol/L), heart failure, myocardial infarction in the last 3 months, cerebral insult in the last 6 months, hepatic or renal disease, and valvular heart disease. Secondary hypertension was excluded by determination of serum creatinine, 24-hour urinary catecholamine excretion, serum potassium, renal sonography, and intravenous digital subtraction angiography.

Two patients of the metoprolol group were excluded from the study after the placebo run-in period because their diastolic blood pressures were lower than 95 mm Hg at that time. The metoprolol group was composed of 12 men and 6 women, aged 47.8±7.5 years; the lisinopril group was composed of 16 men and 4 women, aged 47.6±6.2 years. Body weight was similar between the groups (metoprolol group, 75.8±12.1 kg; lisinopril group, 78.9±10.3 kg).

Blood pressure measurements at the beginning of the study were based on three independent readings with a sphygmomanometer with patients seated after a rest of 10 minutes. The patients were randomly treated with metoprolol or lisinopril for 10 weeks after the placebo run-in period. Antihypertensive therapy was started with 50 mg metoprolol once daily or 5 mg lisinopril once daily; patients were followed up after 2, 6, and 10 weeks. In case of inefficient blood pressure control (diastolic >90 mm Hg), the antihypertensive therapy was increased to 100 mg metoprolol once or twice daily or 10 mg lisinopril once or twice daily. Blood pressure was effectively controlled by 5 mg lisinopril daily in 10 patients, but 50 mg metoprolol daily was sufficient in only 4 patients. In 3 patients treated with metoprolol and 3 patients treated with lisinopril, the highest dose of the antihypertensive monotherapy was required. Systolic and diastolic blood pressures after 2, 6, and 10 weeks of therapy for the metoprolol and lisinopril groups are shown in
TABLE 1. Blood Pressure Before and After Treatment With Metoprolol or Lisinopril

<table>
<thead>
<tr>
<th>Blood Pressure Before</th>
<th>Metoprolol (n=18)</th>
<th>Lisinopril (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After placebo run-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>165.1±11.3</td>
<td>171.9±11.9</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>101.8±4.2</td>
<td>101.5±5.0</td>
</tr>
<tr>
<td>After 2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>159.9±11.6</td>
<td>164.0±10.7</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>94.9±4.9</td>
<td>90.6±5.0</td>
</tr>
<tr>
<td>After 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>156.1±9.1</td>
<td>157.4±11.2</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>86.8±4.2</td>
<td>86.4±5.9</td>
</tr>
<tr>
<td>After 10 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>152.8±8.2</td>
<td>154.5±10.2</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>84.2±2.9</td>
<td>84.6±3.2</td>
</tr>
</tbody>
</table>

SAP indicates systolic arterial pressure; DAP, diastolic arterial pressure. Values are mean±SEM.

Table 1. No significant difference in blood pressure was observed between the groups.

Arterial distensibility was determined after the placebo run-in period and after 6 and 10 weeks of antihypertensive therapy. Vessel wall distensibility was determined in the left common carotid artery. Patients with sonographically proven atherosclerotic lesions in the common carotid arteries were excluded from the study. Patients were examined in the early morning before the antihypertensive therapy was taken. Non-invasive assessment of local vessel wall distensibility was performed by a multigate pulsed Doppler system. Doppler analysis of vessel wall movements was done in the M-mode. The Doppler signals in M-mode were temporarily stored by a personal computer and analyzed in data windows covering the anterior and posterior vessel walls. Vessel wall movements were continuously recorded for three heartbeats. Calculation of the above-mentioned parameters was based on the simultaneous recording of blood pressure by finger plethysmography (Finapres). In the following, average values from three subsequent cardiac cycles are reported. The end-diastolic diameter (D), the percent change in diameter (%CD=Change of Diameter dD/End-Diastolic Diameter D · 100) of the common carotid artery, and the pulse pressure (dP) were determined, and the distensibility (DS, 10⁻³/kPa) of the common carotid artery was calculated according to the formula DS=(dD/D)/dP.

Statistics

Values are given as mean±SEM. The parameters of vessel wall properties were tested for statistical significance by two-way analysis of variance with the Tukey's Studentized Range test as post-test. Statistical analysis was performed with the TESTIMATE program (version 5.1, IDV-Gauting, 1992).

Results

The end-diastolic diameter, percent change in diameter, and distensibility of the common carotid artery were not different after the placebo run-in period between the essential hypertensive groups treated with metoprolol and with lisinopril (Table 2). After 6 and 10 weeks of therapy, the end-diastolic diameter of the common carotid artery was not significantly different between the essential hypertensive groups treated with metoprolol and with lisinopril, and in both groups no change in the end-diastolic diameter was observed during antihypertensive therapy. The percent change in diameter of the common carotid artery was significantly higher after 6 and 10 weeks of therapy in the essential hypertensive group treated with lisinopril compared with the baseline value (P<.05) and with the group treated with metoprolol (P<.05, Table 2). The distensibility of the common carotid artery was also significantly increased in the lisinopril group after 6 and 10 weeks (P<.05 compared with the metoprolol group, Figure; P<.01 compared with the baseline value).

Table 2. Mechanical Properties of Common Carotid Artery Assessed by Multigate Doppler System Before and After Treatment With Metoprolol and Lisinopril

<table>
<thead>
<tr>
<th>Vessel Parameter</th>
<th>Metoprolol Group (n=18)</th>
<th>Lisinopril Group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After placebo run-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D, mm</td>
<td>7.6±0.2 (7.2-8.0)</td>
<td>7.7±0.2 (7.3-8.1)</td>
</tr>
<tr>
<td>%CD</td>
<td>5.07±0.33 (4.41-5.73)</td>
<td>5.13±0.43 (4.27-5.99)</td>
</tr>
<tr>
<td>DS, 10⁻³/kPa</td>
<td>6.2±0.4 (5.4-7.0)</td>
<td>5.6±0.5 (4.6-6.6)</td>
</tr>
<tr>
<td>After 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D, mm</td>
<td>7.8±0.1 (7.4-7.8)</td>
<td>7.7±0.2 (7.3-8.1)*</td>
</tr>
<tr>
<td>%CD</td>
<td>5.06±0.36 (4.38-5.8)</td>
<td>5.90±0.47 (4.96-6.84)††</td>
</tr>
<tr>
<td>DS, 10⁻³/kPa</td>
<td>6.0±0.4 (5.2-6.8)</td>
<td>6.9±0.6 (5.7-8.1)†‡</td>
</tr>
<tr>
<td>After 10 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D, mm</td>
<td>7.5±0.2 (7.1-7.9)</td>
<td>7.8±0.2 (7.4-8.2)*</td>
</tr>
<tr>
<td>%CD</td>
<td>4.85±0.37 (4.11-5.59)</td>
<td>5.86±0.46 (4.94-6.78)‡‡</td>
</tr>
<tr>
<td>DS, 10⁻³/kPa</td>
<td>5.9±0.5 (4.9-6.9)</td>
<td>6.9±0.5 (5.9-7.9)‡‡</td>
</tr>
</tbody>
</table>

D indicates end-diastolic diameter; %CD, percent change in diameter; and DS, distensibility. Values are mean±SEM; 95% confidence interval is shown in parentheses. For calculation of parameters, blood pressure measured by finger plethysmography was used.

*P=NS.
†P<.05, metoprolol vs lisinopril.
‡P<.05, §P<.01 vs baseline value.
The findings obtained with lisinopril are similar to those ade is known to inhibit smooth muscle proliferation. Asmar et al 16 inves-
counteract the acute effects, because /3-receptor block-
term effects of metoprolol on arterial distensibility may
lack of vasodilation with 0-blocker therapy. The long-
distensibility did not change despite a significant de-
crease in blood pressure. This may be explained by the
viscoelastic properties of the arterial wall. The find-
ments of arterial wall stiffness observed with lisinopril
antihypertensive therapy with an ACE inhibitor therefore
intrinsic properties of the arterial wall in essential hyperten-
Arterial distensibility is significantly decreased in sus-
tained systolic-diastolic hypertension and even in border-
line hypertension.13,14 The reduction in arterial disten-
sibility in hypertension seems to be induced by modifi-
cations of the arterial wall. The viscoelastic proper-
ties of the arterial wall are dependent on a passive
component due to elastic and collagenous connective
tissue and on an active component due to smooth muscle
activity.1,2 In hypertension, thickening of the arterial
results from smooth muscle hypertrophy together with
increased consistency of the fibrous connective tissue.4,5
Antihypertensive therapy may influence the passive
component of arterial wall properties by its antihyperten-
sive effect per se, but the different effects of /3-blocker and
ACE inhibitor treatments on arterial distensibility dem-
strated in the present study show that pressure-indepen-
dent drug effects may be important modulators of the
adoptive changes in the arterial wall.

Bar graph shows change of distensibility of the common carotid
artery after 10 weeks of therapy with lisinopril and metoprolol.

Discussion

The results show that antihypertensive therapy with
lisinopril but not with metoprolol can improve the
distensibility of the common carotid artery, although
both drugs lowered blood pressure effectively. The antihypertensive therapy with an ACE inhibitor there-
fore may influence intrinsic properties of the arterial
wall in essential hypertension.

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sive effect per se, but the different effects of /3-blocker and
ACE inhibitor treatments on arterial distensibility dem-
strated in the present study show that pressure-indepen-
dent effects are at least equally important. The re-
duced arterial wall stiffness observed with lisinopril may
be due to functional rather than structural changes of
vascular smooth muscle, because after 6 weeks of treat-
ment, a maximal improvement of arterial wall distensibil-
ity was observed, and no further increase was noted after
10 weeks. Both decreased levels of angiotensin II due to
inhibition of the angiotensin converting enzyme and accu-
mulation of bradykinin due to inhibition of kininase II 15
may contribute to this effect. Long-term studies are
needed to clarify whether the structural changes go in
parallel with the acute effects on arterial distensibility.

On the other hand, in the metoprolol group arterial
distensibility did not change despite a significant de-
crease in blood pressure. This may be explained by the
lack of vasodilation with /3-blocker therapy. The long-
term effects of metoprolol on arterial distensibility may
counteract the acute effects, because /3-receptor block-
ade is known to inhibit smooth muscle proliferation.
The findings obtained with lisinopril are similar to those
reported for other ACE inhibitors. Asmar et al 16 inves-
tigated the effect of perindopril on the distensibility of
the brachial artery and found a similar increase in
arterial distensibility compared with placebo. Also, af-
ter acute intravenous administration of the ACE inhib-
itor enalaprilat, pulse-wave velocity decreased, indi-
rectly indicating an increase in distensibility.17 On the
other hand, the metoprolol effects differ from those
observed with acebutolol in brachial arteries.18 Because
acebutolol, but not metoprolol, exhibits intrinsic /3,
mimetic activity, this discrepancy can be explained by
the different pharmacologic properties of both drugs.
Indeed, propranolol did not influence the mechanical
properties of large arteries.19

In summary, the present study demonstrated differ-
ext effects of lisinopril and metoprolol on arterial
distensibility. The findings imply that pressure-indepen-
dent drug effects may be important modulators of the
adaptive changes in the arterial wall.

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