Repair of Coronary Arterioles After Treatment With Perindopril in Hypertensive Heart Disease

Bodo Schwartzkopff, Michael Brehm, Markus Mundhenke, Bodo E. Strauer

Abstract—In hypertensive heart disease, no data are available on the repair of coronary resistance vessels in patients after long-term ACE inhibitor treatment. Fourteen patients with essential hypertension were studied with coronary flow reserve and with transvenous endomyocardial biopsy before and after 12 months of antihypertensive treatment with perindopril (4 to 8 mg/d, mean 5.9±2.3 mg/d). Left ventricular muscle mass index decreased by 11% (from 145±41 to 128±36 g/m², P=0.04). Maximal coronary blood flow was increased by 54% (from 170±46 to 263±142 mL·min⁻¹·100 g⁻¹, P=0.001), and minimal coronary vascular resistance was diminished by 33% (from 0.67±0.21 to 0.45±0.19 mm Hg·min·100 g·mL⁻¹, P=0.001); consequently, coronary reserve increased by 67% from 2.1±0.6 to 3.5±1.9 (P=0.001). Structural analysis revealed regression of periarteriolar collagen area by 54% (from 558±270 to 260±173 μm², P=0.04) and of total interstitial collagen volume density by 22% (from 5.5±3.8 Vv% to 4.3±3.2 Vv%, P=0.04), whereas arteriolar wall area was slightly but not significantly reduced. Long-term therapy with the ACE inhibitor perindopril induces structural repair of coronary arterioles that is mainly characterized by the regression of periarteriolar fibrosis and associated with a marked improvement in coronary reserve. These findings indicate the beneficial reparative effects of ACE inhibition on coronary microcirculation in hypertensive heart disease. (Hypertension. 2000;36:220-225.)

Key Words: arterioles ■ collagen ■ hypertension, arterial ■ angiotensin-converting enzyme inhibitors ■ coronary reserve

Arterial hypertension is the most common cause of pressure overload of the left ventricle, and left ventricular (LV) hypertrophy (LVH) is its common sequelae. Furthermore, LVH is a strong independent risk factor for cardiovascular morbidity and mortality.¹ Potential mechanisms that might account for this observation include increased vulnerability of the hypertrophied myocardium to ischemic damage and enhanced arrhythmogenesis.² Moreover, it is increasingly recognized that patients with arterial hypertension and LVH have symptoms and signs of myocardial ischemia despite angiographically normal coronary arteries, and this was found to be related to impaired coronary flow reserve.³ Functional and structural abnormalities of the coronary microcirculation have been described in hypertensive heart disease.⁴–⁶ Thus, an adequate increase in myocardial blood flow may be prevented in response to increased metabolic demand and may precipitate myocardial ischemia in these patients.⁷

Important structural components of impaired coronary reserve are thickening of the media wall with reduced lumen size and accumulation of collagen in the periarteriolar region.⁴,⁵ The thickening and hardening of arterioles have been called arteriolosclerosis and are characteristic of pathological hypertensive hypertrophy.⁸,⁹

Antihypertensive treatment has been shown to normalize blood pressure and to reverse LVH in hypertensive patients.¹⁰,¹¹ However, to date, there are no reports that evaluate the effects of antihypertensive drugs on myocardial perfusion in regard to their cardioreparative effects on coronary arterioles in humans. This issue is particularly interesting because the renin-angiotensin-aldosterone system (RAAS) is increasingly seen as being important in the process of pathological hypertensive remodeling of the heart and the coronary circulation.¹² Accordingly, our objective in the present investigation was to examine under clinical conditions the extent to which long-term antihypertensive treatment with an ACE inhibitor can reverse arteriolar remodeling and sclerosis and improve coronary reserve in patients with arterial hypertensive heart disease.

Methods

Study Design
The study design was prospective and open. Inclusion criteria for the study were primary arterial hypertension, a coronary angiogram with no or <40% stenoses, clinical symptoms of either angina pectoris according to the Canadian Cardiovascular Society (CCS) classification of ≥2 or dyspnea according to the New York Heart Association (NYHA) classification of ≥2, and LVH with an LV mass index of >120 g/m².
Patients with valvular heart disease, dilated cardiomyopathy (ejection fraction <0.45), hypertrophic obstructive cardiomyopathy, left or right bundle-branch block, atrial fibrillation, diabetes mellitus, alcoholism, hypothyroidism or hyperthyroidism, renal insufficiency, or pulmonary disease with impairment of ventilation or gas exchange were excluded. Secondary forms of arterial hypertension and previous ACE inhibitor therapy were also exclusion criteria.

The diagnosis of arterial hypertension had to be confirmed with ≥3 consecutive blood pressure measurements within 3 weeks with a systolic blood pressure of >150 mm Hg or a diastolic blood pressure of >90 mm Hg, or both, after resting for 15 minutes in the supine position.

Patients with arterial hypertension had discontinued any preexisting cardiovascular medication for at least 5 days. At baseline, 12-lead ECG, exercise tolerance test (bicycle), echocardiography, right ventricular catheterization, right septal endomyocardial biopsy, and coronary flow measurement were undertaken. The same measurements were performed 12 months later, after a 1-week washout period.

Regular laboratory investigations at the visits included creatinine, glucose, cholesterol, and triglyceride levels; blood cell count; and electrolytes.

**Patients**

Of the 20 patients who were screened, 17 patients who fulfilled the inclusion criteria were enrolled in the study protocol. Nine patients had never received antihypertensive therapy, and 5 had inadequate blood pressure lowering with a calcium channel blocker (n=1) or β-blocker (n=4). Three of the 17 patients were excluded from the study due to a rash (n=1), the complaint of a dry cough (n=1), and refusal to undergo the second coronary flow reserve measurement (n=1). Thus, 14 hypertensive patients (6 men, 8 women) completed the study protocol.

The mean patient age was 58±5 years. Mean systolic blood pressure was 164±11 mm Hg, and mean diastolic blood pressure was 90±6 mm Hg. To achieve effective blood pressure lowering to a systolic blood pressure of <150 mm Hg and a diastolic blood pressure of <90 mm Hg, ACE inhibitor treatment with perindopril was started at a dosage of 4 mg/d. To check patient compliance, tablet counts were made each visit every 6 weeks within the first 6 months and then every 3 months. The dosage was gradually increased to a maximum of 8 mg/d to reach the target blood pressure. The mean perindopril dosage over the entire study period was 5.86±2.28 mg/d (range 4 to 8 mg/d). In 4 patients, a diuretic (50 mg hydrochlorothiazide) was also administered to control blood pressure.

**Echocardiography**

Transthoracic M-mode echocardiographic measurements were made by 1 investigator who was unaware of the patients’ data. The LV mass index was calculated according to the recommendations of the American Society of Echocardiography.13

**Right Ventricular and Pulmonary Artery Catheterization**

At the time of coronary blood flow measurements, the right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were measured with a Swan-Ganz floating catheter. Cardiac output was determined with the thermodilution technique.

**Coronary Blood Flow Measurements**

Coronary blood flow was quantitatively measured with the inert chromatographic argon method under baseline conditions and after pharmacological vasodilatation with dipyridamole (0.5 mg/kg body wt) over a period of 4 minutes. The aortic pressure was measured with a fluid-filled multipurpose catheter in the descending aorta. Coronary vascular resistance was calculated as the coronary perfusion pressure (coronary perfusion pressure equals mean systemic arterial pressure minus mean right arterial pressure) divided by coronary blood flow. The coronary vasodilator capacity (ie, the coronary reserve) was calculated as the ratio of coronary resistance under baseline conditions to coronary resistance after dipyridamole-induced coronary vasodilatation. Myocardial oxygen consumption was determined from the product of aortocoronary venous (sinus) oxygen difference and baseline coronary blood flow per unit weight of myocardium. The advantages and disadvantages of the method have been discussed previously.14

**Morphological Investigation**

A transvenous endomyocardial biopsy was performed under biplane fluoroscopic control to gain ≥3 to 5 samples from the right basal septum of each patient. Samples were immediately fixed in 4% buffered formalin, embedded in paraffin, and numbered. Paraffin blocks of tissue were randomly cut to generate isotropic conditions. Morphometric measurements were performed in a blinded way for the investigator and included (1) myocyte diameter across the nucleus (μm), (2) mean volume density (Vv%) of total interstitial collagen, and (3) quantification of the total wall area (μm²) and diameter of mostly circular arteriolar profiles (μm) and perivascular collagen (adventitia) area (μm²).

Reproducibility of morphometric data has been extensively investigated, and measurements were made according to a previously reported protocol from our group.5,13,16

**Statistical Analysis**

Descriptive data are expressed as mean±SD values. The pretherapy and posttherapy results were tested with a nonparametric, two-tailed Wilcoxon’s test at a value of P<0.05. The analysis was made with the SPSS-PC package (Version 8.0).

The procedures were in accordance with institutional guidelines, and the study protocol was approved by the Ethics Committee of the Heinrich-Heine University of Dusseldorf. Informed consent was obtained from all patients before each investigation. There were no significant complications and no prolonged clinical stays.

**Results**

**Clinical Symptoms**

At the beginning of the study, all patients had either angina pectoris at rest (n=1) or under exercise (n=5), exertional dyspnea (n=10), or a pathological exercise tolerance test (n=5). Patients reported a tendency toward improvement in symptoms according to the CCS classification from 1.71±0.91 to 1.35±0.63 (P=0.057). NYHA class significantly improved from 2.0±0.87 to 1.4±0.65 (P=0.017). Laboratory values did not change significantly during the course of the study.

**Arterial Blood Pressure**

Three months after the initiation of therapy with perindopril, systolic blood pressure was reduced from 164±11 to 141±12 mm Hg (P=0.043) and diastolic blood pressure was reduced from 90±6 to 82±6 mm Hg (P=0.054) under ambulatory conditions. At the end of the antihypertensive treatment period, systolic blood pressure was 132±9 mm Hg (P=0.001) and diastolic blood pressure was 80±7 mm Hg (P=0.001) under ambulatory conditions.

**LV Muscle Mass**

The LV muscle mass index decreased by 11% from 145±41 to 128±36 g/m² (P=0.04), and interventricular septal thickness decreased from 12.5±1.14 to 11.3±1.05 mm (P=0.004). LV posterior wall thickness (11.0±0.84 versus 10.4±0.47 mm, NS) and LV end-diastolic diameter.
Central Hemodynamics
After long-term perindopril therapy, the mean pulmonary artery wedge pressure (8.4 ± 2.5 versus 6.2 ± 2.4 mm Hg, \( P = 0.007 \)) was significantly lower, whereas the pulmonary artery pressure (25.0 ± 4.2 versus 23.7 ± 4.5 mm Hg, NS), cardiac index (2.9 ± 0.3 versus 3.0 ± 0.5 L \( \cdot \) min \(^{-1} \) \( \cdot \) m\(^2\)), and stroke volume index (47 ± 8 versus 50 ± 5 mL/m\(^2\), NS) did not change significantly.

Coronary Hemodynamics
Baseline Conditions
Baseline coronary blood flow (85.5 ± 18.4 versus 79.5 ± 18.2 mL \( \cdot \) min \(^{-1} \) \( \cdot \) 100 g \(^{-1} \)) and coronary resistance (1.3 ± 0.34 versus 1.3 ± 0.27 mm Hg \( \cdot \) min \(^{-1} \) \( \cdot \) 100 g \(^{-1} \)) were identical before and after perindopril therapy.

After Dipyridamole Administration
After treatment with perindopril, the maximal achieved coronary blood flow after dipyridamole (0.5 mg/kg body wt) was increased by 54% (170 ± 46 to 263 ± 142 mL \( \cdot \) min \(^{-1} \) \( \cdot \) 100 g \(^{-1} \), \( P = 0.001 \)), and the minimal coronary vascular resistance, as the reciprocal parameter of coronary artery conductance, was reduced by 33% (0.67 ± 0.21 to 0.45 ± 0.19 mm Hg \( \cdot \) min \(^{-1} \) \( \cdot \) 100 g \(^{-1} \) \( \cdot \) mL\(^{-1} \), \( P = 0.001 \)). Consequently, the calculated coronary reserve increased by 67% from 2.1 ± 0.6 to 3.5 ± 1.9 (\( P = 0.001 \)) (Figure 1). The acute hemodynamic effects of dipyridamole were similar before and after perindopril therapy. Detailed information on mean aortic pressure, heart rate, and myocardial oxygen consumption is provided in the Table.

Morphological Parameters
The mean myocyte diameter showed slightly, but not significantly, smaller values (16.1 ± 2.21 to 14.8 ± 2.1 μm, \( P = 0.14 \)), and the total interstitial volume density of collagen decreased by 22% (5.5 ± 3.8 to 4.3 ± 3.2 Vv%, \( P = 0.04 \)) during treatment with perindopril. Periarteriolar fibrosis was significantly reduced by 53% (558 ± 270 to 260 ± 173 μm\(^2\), \( P = 0.04 \)). The mean arteriolar wall area was slightly, but not significantly, reduced from 384 ± 211 to 295 ± 112 μm\(^2\) (Figure 2).

Discussion
In the present study, therapy with the ACE inhibitor perindopril in hypertensive patients was associated with a marked increase in coronary vasodilator reserve and a significantly lower pharmacologically achieved minimal coronary resis-

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**Figure 1.** Individual changes in coronary hemodynamics before and after therapy.

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**Coronary Blood Flow Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Before Therapy (n=14)</th>
<th>After Therapy (n=14)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure, mm Hg</td>
<td>109 ± 14</td>
<td>101 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Vcor, mL ( \cdot ) min (^{-1} ) ( \cdot ) 100 g (^{-1} )</td>
<td>85.5 ± 18.4</td>
<td>79.5 ± 18.2</td>
<td>NS</td>
</tr>
<tr>
<td>Rcor, mm Hg ( \cdot ) min (^{-1} ) ( \cdot ) 100 g (^{-1} ) ( \cdot ) mL(^{-1} )</td>
<td>1.3 ± 0.34</td>
<td>1.3 ± 0.27</td>
<td>NS</td>
</tr>
<tr>
<td>MVo2, mL ( \cdot ) min (^{-1} ) ( \cdot ) 100 g (^{-1} ) ( \cdot ) mL(^{-1} )</td>
<td>10.3 ± 2.9</td>
<td>10.3 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73.0 ± 14</td>
<td>72.0 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td><strong>After dipyridamole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure, mm Hg</td>
<td>106 ± 13</td>
<td>97 ± 11</td>
<td>0.006</td>
</tr>
<tr>
<td>Vcor, mL ( \cdot ) min (^{-1} ) ( \cdot ) 100 g (^{-1} )</td>
<td>170 ± 46</td>
<td>263 ± 142</td>
<td>0.001</td>
</tr>
<tr>
<td>Rcor, mm Hg ( \cdot ) min (^{-1} ) ( \cdot ) 100 g (^{-1} ) ( \cdot ) mL(^{-1} )</td>
<td>0.67 ± 0.21</td>
<td>0.45 ± 0.19</td>
<td>0.140</td>
</tr>
<tr>
<td>MVo2, mL ( \cdot ) min (^{-1} ) ( \cdot ) 100 g (^{-1} ) ( \cdot ) mL(^{-1} )</td>
<td>12.3 ± 2.4</td>
<td>15.7 ± 5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>83 ± 18</td>
<td>82 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary reserve</td>
<td>2.1 ± 0.6</td>
<td>3.5 ± 1.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Vcor indicates coronary blood flow; Rcor, coronary resistance; MVo2, myocardial oxygen consumption; and HR, heart rate.
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Figure 2. Morphological changes before and after therapy.

Periarteriolar Collagen Area

Total Interstitial Collagen

Arteriolar Diameter

Arteriolar Wall Area

Pre-Treatment Post-Treatment

Perindopril had no effect, indicating that blood pressure reduction was not the decisive factor. These results confirmed the observations by Schiffrin et al.22 for the ACE inhibitor cilazapril.

In experimental models of arterial hypertension, it was demonstrated that in addition to LVH, mediated by myocyte hypertrophy, progressive myocardial fibrosis occurs.23–25 Myocardial fibrosis accounts for the development of LV diastolic dysfunction25 and for the impairment of coronary vasodilator reserve.4,5,26 The development of reactive myocardial fibrosis in hypertension is related to a stimulated RAAS that was finally proved at the cellular level where angiotensin II stimulates fibroblast-mediated collagen synthesis in a dose-dependent manner and suppresses collagenase activity, synergistically leading to progressive collagen accumulation within the cardiac interstitium.27,28

Perivascular fibrosis is seen in both the right and left ventricles and extends to the adjacent interstitial space to rise to interstitial fibrosis after angiotensin II treatment,29 accompanied by a cellular response of myocytes and macrophages in the media.30 The observed regression of periarteriolar fibrosis on ACE inhibitor treatment in our study highlights the dynamic nature of perivascular reactive fibrosis and implicates the importance of the RAAS. This becomes even more evident because beneficial effects were seen in the non–pressure-overloaded right ventricle, indicating that cardioreparation was not accounted for by LV pressure reduction alone. This is further supported by the fact that there was no significant influence on right ventricular myocyte diameter, which normally correlates with pressure load. Mukherjee and Sen31 reported the effect on increased blood pressure and myocardial collagen of antihypertensive therapy with the ACE inhibitor captopril in comparison with therapy with the vasodilator hydralazine. Although both drugs controlled blood pressure to the normotensive level, only captopril corrected the altered distribution of myocardial collagen phenotypes I and III. It should also be kept in mind that other humoral and paracrine mechanisms, such as catecholamines and endothelin, that might have been positively influenced by treatment, are also involved in the generation of interstitial collagen.32,33

The importance of periarteriolar collagen for coronary reserve was further elucidated by Isoyama et al26 in experimental hypertension. In the rat, the normalization of blood pressure after debanding of the aorta induced regression of media hypertrophy, but the normalization of coronary reserve was achieved only after the additional inhibition and reversal of collagen accumulation in the adventitia with β-aminopropionitrile.

The mechanisms that are involved in the degradation of collagen are complex, as collagen synthesis and degradation are both continuous processes and an abnormal rate in terms of increased synthesis as well as reduced degradation can lead to the accumulation of collagen in the myocardium. Recently, Laviades et al.34 reported in hypertensive patients a decreased serum concentration of free matrix metalloproteinase-1 and an increased free serum concentration of tissue inhibitor metalloproteinases, indicating diminished collagenase activ-
ity. With the ACE inhibitor lisinopril, there was an increase in and normalization of systemic extracellular degradation of collagen type I.

These data support the concept that pathological collagen content can be regressed in hypertensive patients. For the first time, we can demonstrate that the regression of fibrosis manifests in the periarteriolar region with ACE inhibitor treatment, and this might be one of the determinants of coronary reserve improvement, perhaps through augmentation of the distensibility of these resistance vessels.

In addition to repair of the structural factors of coronary resistance vessels, additional beneficial effects on the coronary circulation may have contributed to the improvement in coronary reserve. After acute administration of the ACE inhibitor perindopril in hypertensive patients, Antony et al reported a restored response to sympathetic activation, tested with the cold pressor test. They also reported that the endothelium-mediated epicardial coronary flow-dependent dilation was normalized.

The synergistic effects of restored endothelial and sympathetic factors in the context of the observed repair of structural factors of the coronary microcirculation remain to be elucidated with further studies.

Study Limitations
The present study was limited by the absence of a control group because we renounced the investigation of a control group for ethical reasons and control data have already been published. On the basis of our data, it seems reasonable that the observed repair of the non-pressure-overloaded right septal myocardium gives information independent of direct pressure overload. Nevertheless, structural regression could be even more pronounced in the LV myocardium. We did not compare other antihypertensive regimens, so the effect of different antihypertensive regimens is unclear. Furthermore, our data are limited by the immersion fixation of biopsy specimens, which does not allow us to investigate remodelling and wall/lumen ratio of maximally dilated arterioles, but arteriolar wall thickness can be estimated adequately with our measurements.

Conclusion
In hypertensive heart disease, long-term treatment with the ACE inhibitor perindopril induced the regression of periarteriolar fibrosis of resistance vessels and of interstitial collagen. This was accompanied by a marked improvement in coronary reserve. These findings emphasize the importance of structural alterations and the beneficial effects of ACE inhibition on repair of the coronary microcirculation.

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References


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