Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries

DIETER OEPHERK, M.D., GERHARD MALL, M.D., HORST ZEBE, M.D., FRANZ SCHWARTZ, M.D., EBERHARD WEIHE, M.D., JOACHIM MANTHEY, M.D., AND WOLFGANG KÜBLER, M.D.

ABSTRACT The pathogenesis of angina pectoris in patients with left ventricular hypertrophy secondary to arterial hypertension and with normal coronary arteries remains uncertain. We measured coronary blood flow (argon method) in 12 control subjects and in 16 patients with arterial hypertension at rest and after intravenous administration of dipyridamole (0.5 mg/kg). In the patients with arterial hypertension, coronary blood flow response to dipyridamole was markedly reduced (p < .001 as compared with control values). During coronary vasodilation there was a linear correlation between coronary resistance and left ventricular end-diastolic pressure (r = .67, p < .001). Left ventricular catheter biopsy specimens did not reveal alterations in myocardial microvasculature. These findings suggest that reduction of coronary reserve may be an important contributor to the pathogenesis of angina pectoris in these patients.


THE PARADOX of patients suffering from typical stress-induced angina despite the presence of normal coronary and left ventricular angiographic findings has been reported in recent studies.1-5 However, patients with essential hypertension have been excluded from these studies despite the fact that they often have symptoms of ischemic heart disease without evidence of coronary artery disease.

The mechanism responsible for the development of angina pectoris in patients with normal coronary arteries and left ventricular hypertrophy secondary to arterial hypertension has not yet been identified. A variety of possible causes have been suggested: a reduction in coronary reserve, an occlusive disease of small coronary arteries not visualized by coronary arteriography, an inadequate growth of the coronary microvasculature, or an augmentation of the extravascular component of coronary resistance.6-13

To further evaluate hypertensive patients with angina but with normal coronary arteriograms, the following studies were performed in addition to left ventricular and coronary angiography: (1) coronary blood flow (CBF) was measured at rest and during dipyridamole-induced coronary vasodilation and (2) biopsy specimens were taken from left ventricular myocardium for microscopic evaluation of intramyocardial vessels and of the myocardial cells.

Materials and methods

Group A (control subjects) consisted of 12 patients (seven men, five women; mean age 44.8 years) without detectable heart disease. These patients suffered from recurrent atypical chest pain and they were referred for coronary arteriography to exclude an organic cause of the symptoms. All patients in this group had normal electrocardiograms (ECGs) at rest and during exercise and normal coronary and left ventricular angiograms.

Group B comprised 16 patients (11 men, five women; mean age 51.4 years) with arterial hypertension class I or II.14 The history of hypertension varied from 4 to more than 20 years (average 9.5 ± 6.2 years). Patients were treated in addition to thiazide-type diuretics with β-adrenergic blocking agents (n = 12) and/or hydralazine (n = 3) or prazosin (n = 3). All patients had typical stress-induced angina pectoris that could be promptly relieved by nitroglycerin. The ECG showed evidence of left
ventricular hypertrophy,\textsuperscript{15} and sinus rhythm was present in all cases. Congestive heart failure, valvular heart disease, and coronary heart disease as well as echocardiographic signs of hypertrophic cardiomyopathy and/or asymmetric septal hypertrophy\textsuperscript{16} were not present in these patients. After the patients gave informed consent, antihypertensive treatment was withheld for at least 12 hr before cardiac catheterization. All patients were premedicated with 10 mg of oral diazepam and were in the fasting state.

**Determination of CBF.** CBF was determined after right and left heart catheterization by the argon method,\textsuperscript{17-20} which uses an improved inert gas saturation technique. The patient spontaneously inspires a gaseous mixture (79% argon and 21% oxygen) over a period of 5 min. Simultaneously, arterial blood samples (obtained with a Fa Cordis multipurpose catheter in the descending aorta) and coronary venous blood samples (obtained with a multipurpose catheter inserted at least 20 mm within the coronary sinus) were continuously collected with a special motor pump unit. For both catheters, two special glass syringes (5 ml) adapted by a y-connector were used. Aragon analyses were carried out by gas chromatography. The reproducibility of argon analyses in samples of argon in water varied less than \( \pm 3\% \).

According to the formula of Kety,\textsuperscript{21} CBF is proportional to the tissue concentration of the indicator divided by the mean arterial-coronary-venous difference of the indicator. Tissue concentration of the myocardium results from the coronary venous concentration at the end of the saturation period multiplied by the tissue partition coefficient of the indicator (argon = 1.1). From the results of control experiments in our laboratory, this technique allows accurate estimation \((r = \cdot.957)\) of CBF rates of more than 360 ml/100 g/min.\textsuperscript{22} Measurements of CBF were carried out under resting conditions and during coronary vasodilation. The latter was achieved by the intravenous injection of 0.5 mg/kg dipyridamole administered over a period of 10 min. Immediately thereafter, arterial-coronary-venous blood sampling was started.

Coronary resistance was calculated as:

\[
\frac{\text{diastolic MAP} - \text{RAP (mm Hg)}}{\text{CBF (ml/100 g/min)}}
\]

where MAP = mean aortic pressure and RAP = right atrial pressure. Oxygen content of arterial and coronary venous blood samples was determined with a Lex O\textsubscript{2} Con analyzer. Myocardial oxygen consumption (MV\textsubscript{O\textsubscript{2}}\text{r}) was calculated as arterio-cor-nary sinus content difference (ml/100 ml) \( \times \) CBF (ml/100 g/min).

**Transarterial left ventricular endomyocardial biopsy.** With a King’s College biotome and a St. Thomas sheath,\textsuperscript{23} biopsy specimens of seven patients in group B were taken from left ventricular myocardium and immediately fixed by immersion with a 1.5% glutaraldehyde, 1.5% formaldehyde mixture in 0.2M phosphate buffer. The tissue was embedded and oriented in block in such a way that endocardium, Purkinje fibers, and myocardium could be clearly identified by light and electron microscopic analysis. The amount of interstitial fibrous tissue was determined morphometrically\textsuperscript{24} by means of point counting (10 to 20 test areas per patient, 36 test points per test area) at a magnification of 160-1.

The morphometric diameter of muscle fiber was determined on cross sections studied on projected light microscopic negatives or directly in the light microscope with a MOP AM03 (Kontron) morphometric device. To quantify the degree of cardiac hypertrophy, cell diameters of more than 300 cross-sectioned cardiac muscle cells were measured in each sample.

**Coronary and left ventricular angiography.** Selective coronary arteriography was performed with multiple views of the right (at least three projections) and left (at least six projections) coronary arteries, including hemi-axial projections. Intra-cardiac pressures were obtained by means of a fluid-filled catheter, pressure-transducer system. End-diastolic and end-systolic volumes were calculated from the monoplane angiogram in a 30 degree right anterior oblique projection. A representative measurement of left ventricular wall thickness was made from a right anterior oblique projection of the ventriculogram in end-diastole in the area approximately halfway between the apex and the aortic valve. Left ventricular mass was calculated according to the method of Rakaley et al.\textsuperscript{25}

Statistical analyses of the data were performed with the t test for paired and unpaired analysis when appropriate. Statistical significance was accepted at the p < .05 level.

**Results**

CBF. CBF was 78 ml/100 g/min in group A subjects and 88 ml/100 g/min in group B patients (table 1; \( p = \text{NS} \)) under resting conditions. After administration of dipyridamole, however, the rise of CBF in group B patients was markedly reduced to 168 ml/100 g/min as compared with 301 ml/100 g/min in controls (table 1; \( p < .001 \)). Under resting conditions, coronary resistance was 1.03 mm Hg/ml/100 g/min in group A and 1.14 mm Hg/ml/100 g/min in group B (\( p = \text{NS} \)). After dipyridamole, coronary resistance declined to 0.23 mm Hg/ml/100 g/min in group A and was significantly increased in group B (0.50 mm Hg/ml/100 g/min; \( p < .001 \)) (table 1, figure 1).

MV\textsubscript{O\textsubscript{2}}\text{r}, under resting conditions was 9.4 ml/100 g/min in group A and 10.7 ml/100 g/min in group B (\( p = .
### TABLE 1

Hemodynamic and angiographic data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>LVEDP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>AOP (mm Hg)</th>
<th>CBF (ml/100 g/ min)</th>
<th>CR (mm Hg/ml/ 100 g/min)</th>
<th>MViO2 (ml/100 g/ min)</th>
<th>EF (%)</th>
<th>LV mass (g/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>D</td>
<td>R</td>
<td>D</td>
<td>R</td>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>51</td>
<td>4</td>
<td>79</td>
<td>76</td>
<td>85</td>
<td>70</td>
<td>85</td>
<td>241</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>3</td>
<td>84</td>
<td>98</td>
<td>100</td>
<td>100</td>
<td>82</td>
<td>333</td>
<td>1.05</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>9</td>
<td>74</td>
<td>95</td>
<td>85</td>
<td>75</td>
<td>79</td>
<td>382</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>4</td>
<td>68</td>
<td>108</td>
<td>90</td>
<td>82</td>
<td>91</td>
<td>324</td>
<td>0.85</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>8</td>
<td>82</td>
<td>135</td>
<td>95</td>
<td>90</td>
<td>91</td>
<td>348</td>
<td>0.97</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>12</td>
<td>65</td>
<td>82</td>
<td>98</td>
<td>90</td>
<td>77</td>
<td>301</td>
<td>1.10</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>5</td>
<td>60</td>
<td>68</td>
<td>93</td>
<td>70</td>
<td>71</td>
<td>206</td>
<td>1.13</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>6</td>
<td>95</td>
<td>102</td>
<td>90</td>
<td>77</td>
<td>85</td>
<td>237</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>7</td>
<td>62</td>
<td>71</td>
<td>80</td>
<td>70</td>
<td>64</td>
<td>261</td>
<td>1.28</td>
</tr>
<tr>
<td>10</td>
<td>41</td>
<td>10</td>
<td>82</td>
<td>90</td>
<td>72</td>
<td>70</td>
<td>66</td>
<td>411</td>
<td>0.98</td>
</tr>
<tr>
<td>11</td>
<td>29</td>
<td>8</td>
<td>59</td>
<td>114</td>
<td>82</td>
<td>75</td>
<td>75</td>
<td>324</td>
<td>1.06</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
<td>6</td>
<td>66</td>
<td>89</td>
<td>95</td>
<td>75</td>
<td>71</td>
<td>244</td>
<td>1.16</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>45.3</td>
<td>6.8</td>
<td>73</td>
<td>94</td>
<td>89</td>
<td>79</td>
<td>78</td>
<td>301</td>
<td>1.03</td>
</tr>
<tr>
<td>± SD</td>
<td>8.9</td>
<td>2.7</td>
<td>11.4</td>
<td>19.2</td>
<td>8.0</td>
<td>9.8</td>
<td>9.0</td>
<td>63.6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

- p value (R vs D) <.005 <.001 <.001 <.001 <.001
- p value (group A vs B) <.05 <.001 NS NS <.001 <.001 <.001 <.001 <.001

LVEDP = left ventricular end-diastolic pressure; HR = heart rate; AOP = mean aortic pressure; CR = coronary resistance; EF = left ventricular ejection fraction; LV mass = left ventricular mass; R = resting conditions; D = dihydralidine (0.5 mg/kg iv).

NS). During coronary vasodilation by dipyridamole, MViO2 increased in group A to 13.7 ml/100 g/min (p < .001) and to 13.0 ml/100 g/min in group B (table 1; p < .005). In group B, left ventricular end-diastolic pressure and mean aortic pressure were significantly higher than control values (p < .001 for both). Regression analysis in group B patients indicated that left ventricular end-diastolic pressure was positively related to coronary resistance during coronary vasodilation (r = .67, p < .001). Heart rates were comparable in groups A and B.

**Coronary and left ventricular angiography.** The coronary arteries and their subbranches were found to be free of even minor luminal irregularities in all subjects. Mean ejection fraction was 72% in group A and 73% in group B (p = NS). Left ventricular mass averaged 73 ± 12.7 g/m² in group A and 118 ± 44 g/m² in group B (p < .005).
Left ventricular biopsy. In group B patients, light and electron microscopic examination of specimens taken from left ventricular myocardium showed hypertrophy of the muscle fibers. The mean diameter of muscle fibers was 24.1 ± 5.6 μm (range 17.2 to 29.4). No lesions of small vessels ranging in external diameter from 5 to 50 μm were found (figures 2 and 3). Approximately 10 to 15 arterioles, metarterioles, capillaries, and venules from each patient could be analyzed.

None of the biopsy specimens had significant interstitial fibrosis. The morphometrically determined average volume fraction of collagenous tissue of all patients was 4 vol% and exceeded 5 vol% in only one patient (No. 7, 13%), who showed slight focal fibrosis. In four patients (Nos. 7, 9, 12, and 13) a focal loss of myofibrils indicating degeneration of myofibers was observed.

Discussion

The major observation of this study confirming similar results published by Strauer is the reduction of dipyridamole-induced coronary vasodilation in patients with arterial hypertension, angina pectoris, and normal coronary arteries. Such a reduction of coronary reserve has been previously described in patients with coronary artery disease, in patients with normal coronary arteries and left ventricular hypertrophy secondary to aortic valve disease, and in patients with syndrome X.

Since obstructive coronary lesions were not present in our patients, the reduced coronary reserve in group B may be attributed to abnormalities of small intramyocardial vessels not visualized by coronary arteriography, i.e., small vessel disease. This possibility was excluded because structural changes of the intramyocardial vessels (arterioles, metarterioles, capillaries, and venules) were not found in the specimens taken from left ventricular myocardium.

The observed degenerative changes of myofibers are common findings in long-standing cardiac hypertrophy secondary to aortic valve disease, congenital heart disease, and dilated cardiomyopathy. They are considered to be representative of Meerson’s third stage of hypertrophy, i.e., cellular exhaustion.

A second possible cause for the reduction in coronary reserve in group B patients could be an increase of extravascular component of coronary resistance due to augmentation of myocardial tissue pressure during diastole. Experimental studies in animals have shown that enhanced left ventricular filling pressures during maximal coronary vasodilation reduce the vascular capacitance of the resistance vessels. The positive coro-
relation found in this study between coronary resistance during coronary vasodilation and left ventricular end-diastolic pressure indicates that this mechanism also applies to the human heart. The increase in left ventricular end-diastolic pressure in group B, however, seems insufficient to account for the reduction in coronary reserve by more than 40%.

A third mechanism that may have caused a reduction of coronary reserve in group B patients relates to the adaptation of coronary microcirculation to myocardial hypertrophy. If the growth of coronary resistance vessels does not keep pace with the increase in left ventricular mass, the minimal resistance of coronary vessels per unit mass of weight increases. Experimental\textsuperscript{10-12} and clinical studies\textsuperscript{13,26} have demonstrated that an increase in "minimal" coronary resistance occurs in association with left ventricular hypertrophy. However, although group B patients had an increased left ventricular mass, no significant correlation was found between coronary resistance during vasodilation and left ventricular mass.

Finally, a functional increase in the tone of coronary

\textbf{FIGURE 3.} Small artery without pathologic structural changes. \textit{M =} muscle cell layer; \textit{E =} endothelial cell layer. Normal basement membrane and lamina elastica interna. (Electron micrograph; \texttimes 6100.)
resistance vessels could be responsible for the decreased coronary reserve in group B patients. Whether this would contribute to overall enhancement of coronary resistance cannot be determined from the available data.

It may be questioned whether dipyridamole in the selected dose produced maximal coronary vasodilation. Minimal coronary resistance of the normal canine heart has been found to be approximately 0.15 to 0.20 mm Hg/ml/100 g/min.\(^{11, 38, 29}\) Comparable values can be obtained in control subjects after intravenous administration of 0.5 mg/kg dipyridamole.\(^ {5, 18, 30}\) In group B patients, reduction of coronary reserve could conceivably represent a shift in the dose-response curve of dipyridamole. Observations in patients with idiopathic dilated cardiomyopathy\(^ {40}\) do not support this hypothesis because in this study a single dose of 0.5 mg/kg dipyridamole was sufficient to achieve exhaustion of coronary vascular reserve.

Another crucial point of this study may be the evaluation of the microvascular system. It must be taken into account that the range of vessels that could be analyzed is limited by technical and statistical difficulties, and vessels between 50 to 200 \(\mu m\) are neither accessible to light and electron microscopic examination nor to study by angiographic techniques.

The main variability of the morphometric measurements results from the small dimensions of the endomyocardial biopsy samples. Furthermore, artifacts caused by the biopsy procedure and the immersion fixation technique limit the reliability of microscopic analysis.

The results of the present study demonstrate that coronary reserve is markedly reduced in patients with left ventricular hypertrophy secondary to arterial hypertension, which could explain the frequent observation of stress-induced angina. During exertion an imbalance between myocardial oxygen supply and oxygen demand occurs, which can result in reversible subendocardial ischemia.

References

15. Romhilt DW, Estes EH: A point score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 75: 752, 1968


Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries.
D Opherk, G Mall, H Zebe, F Schwarz, E Weihe, J Manthey and W Kübler

Circulation. 1984;69:1-7
doi: 10.1161/01.CIR.69.1.1

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/69/1/1