Left Ventricular Muscle Mass and Elevated Heart Rate Are Associated With Coronary Plaque Disruption

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Background—Plaque disruption is the central pathophysiological mechanism underlying acute coronary syndromes and the progression of coronary atherosclerosis. There exists only scant information about the factors that are associated with its development. The aim of the current study was to analyze the contribution of hemodynamic forces in the pathogenesis of plaque disruption. Plaque disruption was diagnosed by coronary angiography of stenosed but not completely occluded coronary arteries.

Methods and Results—This study retrospectively analyzed 106 patients who underwent 2 coronary angiography procedures within 6 months. We investigated 53 patients with initially smooth stenoses who developed plaque disruption by the time of the second coronary angiogram and compared these patients with 53 age- and sex-matched individuals with smooth stenoses without angiographic signs of plaque disruption. The 2 groups were compared by analyzing central hemodynamics, echocardiographic measurements, and cardiovascular medication use. Logistic regression analysis identified positive associations between plaque disruption, left ventricular muscle mass \(270 \text{ g}\), and a mean heart rate \(80 \text{ bpm}\) and a negative association with the use of \(\beta\)-blockers.

Conclusions—The associations documented by our investigation indicate that hemodynamic forces may play a crucial role in the pathogenesis of plaque disruption. These findings may help to identify patients who are at an increased risk of plaque disruption and who might gain benefit from pharmacological interventions aimed at reducing heart rate, for example, by the use of \(\beta\)-blockers, or a reduction of left ventricular hypertrophy. (Circulation. 2001;104:1477-1482.)

Key Words: plaque ■ heart rate ■ hypertrophy ■ receptors, adrenergic, \(\beta\) ■ coronary disease

For a long time, the progression of coronary artery disease leading to acute coronary syndromes was believed to be due to the continuous progression of coronary atherosclerosis. However, serial coronary angiography has shown that the progression of coronary artery disease occurs irregularly rather than linearly with time.\(^1\) Rapid progression of coronary atherosclerosis leading to complex coronary stenosis with consecutive acute coronary syndromes often is due to plaque disruption.\(^2\) Plaques that are prone to disruption are characterized by a thin, fibrous cap with a reduced collagen content covering a large lipid pool.\(^3,4\) Acute coronary syndromes will occur when thrombus formation leads to a severe reduction of coronary blood flow.

Little is known about the duration from the onset of plaque disruption to the onset of acute coronary syndromes.\(^5\) A less severe reduction of coronary blood flow resulting from mural thrombosis will result in the consecutive evolution of more stenotic lesions.\(^6,7\) Cardiovascular science focuses on the identification of potential strategies to achieve plaque stabilization,\(^8,9\) but little is known about the determinants that contribute to the development of plaque disruption.\(^10\) Apart from local inflammation\(^11\) and the fundamental role of hypercholesterolemia,\(^12\) hemodynamic stress, including shear stress, flexion stress, and circumferential stress, may precipitate plaque disruption.\(^13\) Specific situations, including cold weather, emotional stress, arousal,\(^14\) and physical activity,\(^15\) have been shown to be associated with acute coronary syndromes, indicating that sympathetic overstimulation may be an important trigger of plaque disruption.\(^16\) The Framingham Study identified arterial hypertension as the most important predictor of congestive heart failure, mainly due to the development of left ventricular hypertrophy and coronary artery disease. Development of left ventricular hypertrophy strongly predicts myocardial infarction and cardiovascular death in patients with hypertension. In addition, an elevated heart rate\(^17\) was found to be associated with increased cardiovascular mortality rates in experimental studies\(^18\) and in hypertensive patients.\(^19,20\) The aim of the current study was to analyze the contribution of hemodynamic forces in the pathogenesis of plaque disruption.

Methods

Patients

The postulated hypothesis focused on the significant contribution of fast heart rate and hypertensive left ventricular hypertrophy to plaque disruption. This study comprised a single-center, retrospective analy-
Coronary Arteriography and Quantitative Angiographic Analysis

Angiography of the right and left coronary arteries was performed in at least 3 and 6 projections by using identical projections for both investigations. In cases of insufficient quality or different projections, the patients were not included in the study. Quantitative coronary angiography of the target lesion was performed with the help of an automatic edge-detection system that refers to the known diameter of the guiding catheter (Cardio 500, Fa Kontron). Assessment of the degree of stenosis was performed in the angiographic view displaying the most severe stenosis degree. Quantitative coronary angiography analyzed stenosis degree (%), minimal lumen diameter (mm), vessel diameter (mm), and stenosis length (mm) after intracoronary application of isosorbide dinitrate (0.3 to 0.6 mg). Multivessel disease was defined when at least 2 major coronary arteries had >50% stenosis.

Hemodynamic Measurements

Hemodynamic measurements were obtained during the hospital stay for the first coronary angiography. Heart rate was analyzed by using 24-hour registration of the ECG that analyzed maximum heart rate, minimum heart rate, and mean heart rate. Aortic pressures were measured by fluid-filled catheter systems (5F or 7F pigtail catheter) that analyzed systolic pressure, diastolic pressure, pulse pressure, and the maximal rate of increase of aortic pressure (dP/dtmax). Fractional pulse pressure was defined as the ratio of pulse pressure to mean pressure. Cardiac index was measured by the Fick oxygen method.

Echocardiographic Measurements

Quantitative echocardiography was performed before the first angiography (Toshiba SSH-160 A). Echocardiography of the left ventricle was performed with the transducer in the conventional position for both long- and short-axis and 2- and 4-chamber views. M-mode scans were obtained by the 2-dimensional technique that analyzed intraventricular septal thickness, posterior wall thickness at the end of diastole, and left ventricular end-diastolic and end-systolic internal diameters. End-diastolic dimensions were used to calculate left ventricular muscle mass21 and peak systolic meridional stress.22

Medication Use

The effect of the following drugs was assessed: angiotensin-converting enzyme inhibitors, β-blockers, digitalis, calcium antagonists, antiarrhythmics not belonging to the groups of β-blockers or calcium antagonists, and statins. None of the patients was on continuous β-blocker medication at the time of the initial angiogram. However, at that time, 13 patients who developed plaque disruption and 19 patients without progression of coronary artery disease were already receiving statins. Patients were classified as taking the medication only if it had been used continuously over the complete time span. Data regarding medication usage were excluded in patients who took the medication only for a portion of the period.

Statistical Analysis

All data are presented as mean±SD. Statistical significance was accepted when P<0.05. Discrete variables were compared as rates, and comparisons were made by χ² analysis. However, when the expected value of a cell was <5, Fisher’s exact test was used. Continuous variables were analyzed with the help of 2-tailed t tests.
for independent samples. Logistic regression analysis was performed to determine associations between hemodynamics, echocardiography, medications, and plaque disruption. Statistical tests were adjusted for multiple comparisons. Continuous variables were dichotomized by cut points derived by dividing the data into 2 groups, each containing ~50% of the population. Only those variables that reached $P<0.10$ in the univariate analysis were included in the multivariate analysis. The data are presented as odds ratio (ORs) and 95% confidence intervals (CIs). Statistical analysis was performed with PC SAS software version 6.10 (SAS).

**Results**

**Demographic Data**

The patients’ baseline clinical characteristics are listed in Table 1. Apart from a significantly increased incidence of arterial hypertension in the group of patients with plaque disruption, cardiovascular risk factors were not different. Quantification of LDL and HDL cholesterol levels showed significantly higher values for LDL ($141 \pm 68$ vs $123 \pm 19$ mg/dL, $P<0.01$), and a trend toward lower values for HDL ($49 \pm 8$ vs $52 \pm 6$ mg/dL, $P=0.08$) in patients who developed plaque disruption. Cardiovascular risk factors were not included in the multivariate analysis for 2 reasons. First, adequate therapy (eg, antihypertensive therapy, statins) is likely to reduce the impact of risk factors in the pathogenesis of plaque disruption. Second, the integration of additional variables into the multivariate analysis would have resulted in different values of significance, requiring a larger number of patients than was included in our database. After plaque disruption, clinical presentation before the second coronary angiography was different between the 2 groups. In the group of patients with plaque disruption, 48 patients presented with an acute coronary syndrome (unstable angina pectoris class III, class B and C according to Braunwald, n=39; acute myocardial infarction, n=9) with elevated cardiac enzymes (creatine kinase-MB and/or troponin I). All patients received percutaneous transluminal revascularization of the target vessel (stent implantation in 51 patients; percutaneous transluminal coronary angioplasty in 2 patients). In the group of patients without progression of coronary artery disease, 51 patients presented with stable angina pectoris; 2 patients were admitted with unstable angina pectoris. None of the patients showed any elevation of cardiac enzymes, and none of the patients received percutaneous transluminal revascularization of the target vessel. Blood pressure obtained during the second coronary angiography was significantly different between the 2 groups. At this time, systolic pressure ($164 \pm 29$ vs $123 \pm 19$ mm Hg, $P<0.01$), diastolic pressure ($81 \pm 13$ vs $74 \pm 11$ mm Hg, $P=0.01$), and mean heart rate ($84 \pm 11$ vs $68 \pm 9$ bpm, $P<0.01$) were significantly higher in patients with plaque disruption. Table 2 summarizes the data on quantitative and qualitative coronary angiography of the 2 coronary angiography sessions.

**Hemodynamic Determinants**

Data on central hemodynamics as obtained during the hospital stay for the first coronary angiogram are summarized in Table 3. Univariate analysis showed a trend toward higher systolic blood pressure and a higher fractional pulse pressure in those patients who developed plaque disruption. Maximum heart rate, minimum heart rate, maximal increase in aortic pressure ($dp/dt_{max}$), and cardiac index all showed higher values in patients with plaque disruption on the second angiogram, without statistically significant differences. However, mean heart rate and the number of patients with a mean heart rate $>80$ bpm were significantly higher in the group of patients with plaque disruption.

**Echocardiographic Measurements**

Echocardiography revealed no significant differences in left ventricular diameter at the end of diastole (Table 4). There was an insigificant trend toward a larger thickness of the interventricular septum and the left ventricular posterior wall.
Left ventricular mass showed significantly higher values in the group of patients with plaque disruption.

Medication Use
There was a trend toward less frequent use of angiotensin-converting enzyme inhibitors, calcium antagonists, and statins in the group of patients with plaque disruption (Table 5). In patients with smooth stenosis, continuous β-blocker medication use was significantly more frequent compared with that in patients with plaque disruption.

Independent Predictors of Plaque Disruption
Multivariate analysis (Table 6) identified significant associations between left ventricular mass >270 g, mean heart rate >80 bpm, and the future development of plaque disruption, whereas continuous medication with β-blockers prevented plaque disruption. Further investigation analyzing the correct adjustment for covariates showed no associations between increased heart rate at the first angiogram and the continuous intake of β-blockers and demonstrated that patients with a mean heart rate >80 bpm at the time of the first angiography were more likely to develop plaque disruption, despite introduction of a β-blocker medication. Continuous β-blocker medication use was initiated in 58 patients (23 patients in the group with plaque disruption and 35 patients in the control group). Of these patients, a higher proportion showed a mean heart rate >80 bpm in the group with plaque disruption (57%) compared with the control group (29%, P=0.03).

Further analysis of our data showed that 93% of patients with plaque disruption and left ventricular muscle mass >270 g were hypertensive. No association between left ventricular mass >270 g and β-blocker medication use was observed. Of the patients who were treated with continuous β-blocker therapy, a left ventricular mass >270 g was more frequent in patients with plaque disruption (61%) compared with the control group (31%, P=0.02). Despite analysis of various thresholds, elevated LDL cholesterol was not identified as an independent predictor of plaque disruption.

Discussion
These data indicate that hemodynamic forces are associated with the future development of plaque disruption. Left ventricular muscle mass and elevated heart rate were significantly associated with an increased incidence of plaque disruption, whereas medication with β-adrenergic blockers was associated with a reduced incidence of disruption of vulnerable plaques.

Pathophysiological Mechanisms and Clinical Implications
This is the first investigation that analyzed the relationship between hemodynamic forces and plaque disruption. Plaque disruption is a central mechanism in the natural history of coronary artery disease. Numerous studies have clearly shown that hemodynamic forces are associated with plaque disruption.

### Table 3. Central Hemodynamics Obtained During the First Hospital Stay

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plaque Disruption (n=53)</th>
<th>Smooth Stenosis (n=53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;sub&gt;d&lt;/sub&gt;, mm Hg</td>
<td>148±32</td>
<td>143±26</td>
<td>0.17</td>
</tr>
<tr>
<td>P&lt;sub&gt;d&lt;/sub&gt;, mm Hg</td>
<td>78±14</td>
<td>79±13</td>
<td>0.39</td>
</tr>
<tr>
<td>PPF</td>
<td>0.62±0.12</td>
<td>0.58±0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>HR mean, 1/min</td>
<td>80±13</td>
<td>75±9</td>
<td>0.04</td>
</tr>
<tr>
<td>HR mean &gt;80/min</td>
<td>27 (51%)</td>
<td>15 (28%)</td>
<td>0.02</td>
</tr>
<tr>
<td>HR max, 1/min</td>
<td>122±14</td>
<td>119±12</td>
<td>0.18</td>
</tr>
<tr>
<td>HR min, 1/min</td>
<td>49±8</td>
<td>46±12</td>
<td>0.28</td>
</tr>
<tr>
<td>dP/dtmax, mm Hg/s</td>
<td>998±429</td>
<td>900±399</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiac index, L·min&lt;sup&gt;-1&lt;/sup&gt;·m&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>3.4±1.2</td>
<td>3.1±0.8</td>
<td>0.20</td>
</tr>
</tbody>
</table>

P<sub>d</sub> indicates systolic blood pressure; P<sub>d</sub> indicates diastolic blood pressure; PPF, fractional pulse pressure; HR, heart rate; and dP/dt<sub>max</sub>, maximal rate of increase of aortic pressure.

### Table 4. Left Ventricular Geometry, Mass, and Stress

<table>
<thead>
<tr>
<th>Left Ventricular Echogram</th>
<th>Plaque Disruption (n=53)</th>
<th>Smooth Stenosis (n=53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter at end of diastole, mm</td>
<td>52±4</td>
<td>50±3</td>
<td>0.23</td>
</tr>
<tr>
<td>Wall thickness IVS, mm</td>
<td>11.8±1.1</td>
<td>11.4±1.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Wall thickness LV PW, mm</td>
<td>11.1±0.9</td>
<td>10.9±1.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>282±48</td>
<td>261±44</td>
<td>0.02</td>
</tr>
<tr>
<td>Left ventricular mass &gt;270 g</td>
<td>31 (58%)</td>
<td>18 (34%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak systolic stress, kdyn/cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>200±45</td>
<td>192±42</td>
<td>0.18</td>
</tr>
</tbody>
</table>

IVS indicates interventricular septum; LV PW, left ventricular posterior wall.

### Table 5. Medication Use by Group

<table>
<thead>
<tr>
<th>Medication</th>
<th>Plaque Disruption (n=53)</th>
<th>Smooth Stenosis (n=53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>13 (25%)</td>
<td>22 (42%)</td>
<td>0.06</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>23 (43%)</td>
<td>35 (66%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Digitalis</td>
<td>10 (19%)</td>
<td>7 (13%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>17 (32%)</td>
<td>24 (45%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Statins</td>
<td>27 (51%)</td>
<td>37 (70%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

### Table 6. Multivariate Analysis on Associations With Coronary Plaque Disruption

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass &gt;270 g</td>
<td>4.92 (1.83–13.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>HR mean &gt;80 bpm</td>
<td>3.19 (1.15–8.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>β-Blocker use</td>
<td>0.32 (0.13–0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Wall thickness IVS</td>
<td>1.68 (0.57–9.91)</td>
<td>0.06</td>
</tr>
<tr>
<td>PPF</td>
<td>1.81 (0.67–4.90)</td>
<td>0.07</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.51 (0.19–1.34)</td>
<td>0.06</td>
</tr>
<tr>
<td>Statins</td>
<td>0.42 (0.16–1.22)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

HR indicates heart rate; IVS, interventricular septum; PPF, fractional pulse pressure; and ACE, angiotensin-converting enzyme.
demonstrated a close association between heart rate and increased cardiovascular mortality. Rapid heart rate is positively correlated with the risk for future hypertension and cardiovascular events in normotensive and hypertensive patients. A meta-analysis of secondary prevention trials reported a reduction in cardiac mortality, incidence of reinfection, and sudden death of 20% to 30%, probably due to the plaque-stabilizing properties of β-adrenergic blockers.

Left ventricular muscle mass was also markedly associated with the development of plaque disruption. Left ventricular hypertrophy represents a manifestation of preclinical cardiovascular disease and favors the occurrence of myocardial infarction and cardiovascular death. Systemic arterial hypertension is one of the major risk factors of coronary artery disease and left ventricular hypertrophy. Regression of left ventricular hypertrophy has been associated with an improvement of coronary flow reserve and significantly lower rates of consequent morbidity and mortality. One hypothesis refers to a potential association between increased left ventricular muscle mass and coronary atherosclerosis, probably due to an increase in arterial wall thickness. In addition, the presence of increased left ventricular muscle mass in patients with plaque disruption precludes the existence of increased blood pressure values, despite the lack of significant differences in blood pressure between the 2 groups at the time of the first coronary angiography.

Limitations of the Study
The main limitation refers to the angiographic identification of plaque disruption. In an individual case, coronary angiography may not be sufficiently sensitive, especially for the identification of plaque disruption and small thrombi. Intra-vascular ultrasound was not performed in the setting of acute coronary syndromes so as to avoid jeopardizing the well-being of the patients.

A second limitation refers to the question of whether in a subset of patients, an increased heart rate before the initiation of β-blockade may constitute a marker of plaque disruption. In our investigation, 43% of patients developed plaque disruption despite β-blocker intake. Our investigation analyzed heart rate as assessed by 24-hour ECG registration at the time of the first coronary angiography. However, episodes of critical tachycardia that occurred in the interval between the 2 coronary angiographies, despite the intake of β-blockers, were not analyzed by this investigation. We can only speculate that in these patients, β-blockade alone was not sufficient to adequately control heart rate over the complete period between the initiation of medication use and plaque destabilization, indicating that a more aggressive control of heart rate (eg, by the use of more intensive β-blockade) would have been beneficial.

Finally, comparable to the association shown between cardiovascular risk factors and the future development of coronary artery disease, our study showed associations between determinants and plaque disruption but was unable to demonstrate clear causality, thus only allowing speculation about the reasons why these associations were found. Furthermore, despite the fact that our study failed to demonstrate associations between plaque destabilization and cholesterol, plaque disruption certainly constitutes a multifactorial process involving hemodynamic stress, local inflammation, and hypercholesterolemia.

Conclusions
This study found independent associations between left ventricular muscle mass, increased heart rate, the absence of continuous medication with β-adrenergic blockers, and plaque disruption. These findings may help to identify patients who are at an increased risk of plaque disruption and who might gain benefit from pharmacological interventions aimed at reducing heart rate, for example, by the use of β-adrenergic blockers, or a regression of left ventricular hypertrophy.

References


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