Association Between Myocardial Infarction and the Mast Cells in the Adventitia of the Infarct-Related Coronary Artery

Petri Laine, MD; Maija Kaartinen, MD; Antti Penttilä, MD, PhD; Pertti Panula, MD, PhD; Timo Paavonen, MD, PhD; Petri T. Kovanen, MD, PhD

Background—Histamine, a product of mast cells, is an effective vasoconstrictor of atherosclerotic coronary arteries. Because it has been suggested that coronary spasm plays a role in acute coronary syndromes such as myocardial infarction (MI), we quantified and characterized the mast cells in the adventitia of infarct-related coronary arteries.

Methods and Results—In a series of 17 autopsied MI patients, we identified the segment of the left coronary artery with ruptured plaque responsible for the infarction. More distal segments from the infarct-related coronary artery, either with nonruptured plaques or with normal intima, were also studied. Corresponding segments taken from left coronary arteries obtained from 17 patients who had died of noncardiac causes served as controls. Adventitial mast cells in the infarct-related and the control coronary arteries were identified immunohistochemically by staining for tryptase. In the infarct-related coronary arteries, we also stained for chymase and histamine. Moreover, T lymphocytes and macrophages were identified immunohistochemically and counted. In the infarct-related coronary arteries, significantly larger numbers of mast cells were present in the adventitia backing ruptured plaques (98 ± 640 mast cells/mm², mean ± SD) than in the adventitia backing nonruptured plaques (41 ± 12 mast cells/mm²; P < 0.001) or backing normal intima (19 ± 8 mast cells/mm²; P < 0.001). No such difference was found among the 3 different segments in the control coronary arteries. The majority of mast cells contained not only tryptase but also chymase. Mast cells were the only cells in the coronary adventitia that contained histamine. The proportion of adventitial mast cells that were degranulated was highest in the segments with ruptured plaques. The numbers of adventitial macrophages and T lymphocytes were also increased in the segments with plaque rupture.

Conclusions—In infarct-related coronary arteries, the number of degranulated mast cells in the adventitia backing ruptured plaques is increased. Histamine released from the degranulated mast cells may reach the media, where it may locally provoke coronary spasm and thus contribute to the onset of MI. (Circulation. 1999;99:361-369.)

Key Words: atherosclerosis • mast cells • coronary disease • myocardial infarction • vasospasm

Myocardial infarction (MI) is usually the consequence of an eroded or ruptured coronary plaque which causes acute thrombotic occlusion of the involved vessel. Inflammation of the plaque appears to be an important step in the genesis of thrombotic coronary events. Rupture of a coronary plaque typically occurs at a site where inflammatory cells have accumulated. Mast cells, one type of inflammatory cell, were recently shown to have accumulated in coronary plaques at the site of rupture in MI. In the coronary artery, the majority of mast cells are found in the outer layer of the adventitia (10 times as many as in the intima). Interestingly, in a patient with variant angina who ultimately died of sudden cardiac death, the number of adventitial mast cells was highest in the spastic coronary segment. When stimulated, mast cells release histamine and other powerful vasoactive substances, such as prostaglandin D₂ and leukotriene C₄, which may have roles as mediators of coronary spasm in some patients. Indeed, in atherosclerotic coronary arteries, histamine is a powerful vasoconstrictor. The idea of a connection between mast cell histamine and coronary arterial spasm is supported by the recent finding that, in patients with variant angina, the concentration of histamine in the coronary circulation is elevated shortly before coronary spasms, with ensuing attacks of angina.

It has been postulated that coronary vasospasm plays a role in occlusive coronary thrombosis. In fact, in patients with acute MI who were treated with intracoronary streptokinase, vasospasm was found to be an important contributor to intermittent occlusion of the coronary arteries. Moreover, a vasoconstrictive response of coronary arteries to the ergonovine provocation test has been found to be strongly predictive.
of future MI. In the present study, we counted the mast cells, a source of histamine and other potential mediators of abnormal vasoconstriction, in the adventitia of the infarct-related left coronary arteries in a series of patients who had died of myocardial infarction (MI patients). Specifically, we compared the numbers of adventitial mast cells in affected and nonaffected segments of the infarct-related coronary artery.

### TABLE 1. Patients Who Died of Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age, y</th>
<th>Onset of Symptoms, h</th>
<th>Time After Death, h</th>
<th>Cause of Death</th>
<th>Clinical History</th>
<th>Medication</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>65</td>
<td>12</td>
<td>48</td>
<td>MI</td>
<td>Diabetes</td>
<td>Glibenclamide</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>78</td>
<td>24</td>
<td>48</td>
<td>MI</td>
<td>Diabetes</td>
<td>Metoprolol, aspirin, ISMN, enalapril, digoxin</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
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<td>4</td>
<td>48</td>
<td>MI</td>
<td>Diabetes</td>
<td>Glibenclamide, metformin</td>
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<tr>
<td>4</td>
<td>F</td>
<td>59</td>
<td>36</td>
<td>96</td>
<td>MI</td>
<td>Hypertension, diabetes, AP</td>
<td>Metoprolol, aspirin, ISMN, nifedipine, metformin, glibenclamide</td>
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<tr>
<td>5</td>
<td>M</td>
<td>61</td>
<td>1</td>
<td>72</td>
<td>MI</td>
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<td>...</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>64</td>
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<td>120</td>
<td>MI</td>
<td>Alcoholism</td>
<td>Fluoxetine</td>
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<tr>
<td>7</td>
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<td>144</td>
<td>MI</td>
<td>AP</td>
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<td>...</td>
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<tr>
<td>9</td>
<td>M</td>
<td>69</td>
<td>24</td>
<td>120</td>
<td>MI</td>
<td>Hypertension, previous MI, diabetes</td>
<td>Metoprolol, aspirin, ISMN, enalapril, digoxin, insulin</td>
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<td>60</td>
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<td>...</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>82</td>
<td>2</td>
<td>36</td>
<td>MI</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>72</td>
<td>36</td>
<td>72</td>
<td>MI</td>
<td>Diabetes, previous MI</td>
<td>Metoprolol, aspirin, ISMN, furosemide, metformin, glibenclamide</td>
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<td>15</td>
<td>F</td>
<td>81</td>
<td>72</td>
<td>72</td>
<td>MI</td>
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<td>67</td>
<td>48</td>
<td>72</td>
<td>MI</td>
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<td>Trimethoprim, aspirin, diltiazem</td>
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<tr>
<td>17</td>
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<td>12</td>
<td>72</td>
<td>MI</td>
<td>Esophageal carcinoma</td>
<td>Cisapride, ranitidine</td>
</tr>
</tbody>
</table>

Mean ± SD: 68 ± 8, 30 ± 24, 80 ± 29

AA indicates abdominal aneurysm; AP, angina pectoris; ISMN, isosorbide mononitrate; MI, myocardial infarction; and PE, pulmonary embolism.

### TABLE 2. Patients Who Died of Noncardiac Causes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age, y</th>
<th>Time After Death, h</th>
<th>Cause of Death</th>
<th>Clinical History</th>
<th>Medication</th>
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<tr>
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<td>M</td>
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<td>60</td>
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<td>COPD, pulmonary carcinoma</td>
<td>Budesonide, salbutamol</td>
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<tr>
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<td>96</td>
<td>Pneumonia</td>
<td>Alcoholism</td>
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<td>4</td>
<td>M</td>
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<td>20</td>
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<td>Morphine</td>
</tr>
<tr>
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<td>F</td>
<td>81</td>
<td>72</td>
<td>Dilated CMP</td>
<td>Dilated CMP</td>
<td>Carvedilol, enalapril, aspirin, furosemide</td>
</tr>
<tr>
<td>6</td>
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<td>Intoxication</td>
<td>Manic depressive disorder</td>
<td>Levopromazine</td>
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<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>60</td>
<td>Intoxication, pneumonia</td>
<td>Manic depressive disorder</td>
<td>Tioridazine</td>
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<td>8</td>
<td>M</td>
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<td>120</td>
<td>Gastric carcinoma</td>
<td>Gastric carcinoma</td>
<td>Morphine, ranitidine</td>
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<tr>
<td>9</td>
<td>F</td>
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<td>72</td>
<td>Pulmonary embolism</td>
<td>Pancreatic carcinoma</td>
<td>Buprenorphine</td>
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<td>Hepatic cirrhosis</td>
<td>Spirinolactone, furosemide</td>
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<tr>
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<td>F</td>
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<td>72</td>
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<td>Pulmonary carcinoma</td>
<td>Buprenorphine, ibuprofen</td>
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<tr>
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<td>F</td>
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<td>100</td>
<td>Mammary carcinoma</td>
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<td>84</td>
<td>48</td>
<td>Cerebral embolism</td>
<td>Atrial fibrillation</td>
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<tr>
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<td>120</td>
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<tr>
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<td>62</td>
<td>90</td>
<td>Suicide, shot in the head</td>
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</table>

Mean ± SD: 64 ± 11, 81 ± 29

CMP indicates cardiomyopathy; COPD, chronic obstructive pulmonary disease.
Methods

Patients
The autopsy series comprised coronary specimens from 17 MI patients. Four of the patients are part of a similar group in which we searched for the presence of mast cells in ruptured coronary plaques. A control group consisted of 17 patients who had a noncardiac death. Characteristics of the patients in both groups are shown in Tables 1 and 2.

Collection and Treatment of Tissue and Lesion Analysis
Infarcted myocardium was identified at autopsy with nitro blue tetrazolium enzyme staining and confirmed by histology. To obtain 3 segments (“segment with ruptured plaque,” “segment with nonruptured plaque,” and “segment with normal intima”) from the infarct-related coronary artery (all were left coronary arteries), the coronary arteries were cut into 3- to 5-mm segments, starting from the origin of the left coronary artery and moving distally until an occluded (thrombosed) lumen and a suspected ruptured plaque was found. Similar segments were then cut distally until a nonthrombosed (nonruptured) and a more distal segment without visible atherosclerotic changes plaque (normal intima) were found. The distances between these segments were 2 to 4 cm. The above-mentioned protocol for obtaining 3 segments was adapted for the left coronary arteries from control patients. The luminal surface in all the segments selected from the control coronary arteries was smooth and only occasionally slightly elevated without any yellow areas (“normal intima”).

The selected segments were fixed in Carnoy’s fluid for 24 hours and embedded in paraffin. Serial sections (2 to 4 μm) were cut and stained with hematoxylin-eosin and evaluated microscopically to verify the presence of a ruptured plaque, a nonruptured plaque, or normal intima. The following types of nonruptured lesions were found: 2 lesions of type III, 11 lesions of type IV, and 4 lesions of type Va. The normal intima in the segments without visible atherosclerotic changes exhibited variable thickness and moderate overall cellularity. In some cases, isolated foam cells could be identified, corresponding to an initial or type I lesion.

Immunohistochemistry
Sections were incubated with the following antibodies: alkaline phosphatase-conjugated anti-tryptase antibody G3 (0.7 μg/mL) and anti-chymase antibody B7 (4 μg/mL) for mast cells (Chemicon); polyclonal antibody against von Willebrand factor (1:2000) for endothelial cells, HAM 56 (1:100) for macrophages, and UCHL 1 (1:50) for T lymphocytes (Dakopatts); monoclonal peroxidase-conjugated anti-α-smooth muscle actin (1:12 000) for smooth muscle cells (Sigma), and a polyclonal antibody for histamine (1:10 000). The method used for immunocytochemical detection of histamine has been described previously. The antiserum stains histamine in mast cells, brain neurons, and gastric endocrine cells, but does not react with L-histidine or histidine-containing peptides. Preincubation of the antiserum with a histamine-protein conjugate (1 to 50 μg/mL) removed all staining from the mast cells. Single sections were stained for both tryptase and chymase by a sequential double-labeling method, as recently described. Other sections, in which both mast cells (tryptase) and endothelial cells (von Willebrand factor) were to be stained, were first incubated with the anti-tryptase antibody, then stained by the indirect immunoperoxidase method (with 3-amino-9-ethylcarbazole [AEC] as chromogen); they were then incubated overnight at 4°C with the anti-von Willebrand factor antibody, and finally stained by the avidin-biotin complex method (with 3,3′-diaminobenzidine [DAB] and ammonium nickel sulfate as chromogens). Histamine, macrophages, and T lymphocytes were stained with the avidin-biotin complex method with DAB and AEC. Smooth muscle cells were stained by the direct immunoperoxidase method with AEC. The sections were counterstained with Mayer’s hematoxylin.

Morphometric Analysis and Microscopy
The areas of the adventitia were measured by planimorphometry, using the Global Laboratory Image software program at the Department of Electron Microscopy, University of Helsinki, and the
immunopositive cells (mast cells, T lymphocytes, and macrophages were counted in the measured areas at ×400 magnification. Cell densities were expressed as numbers of cells per millimeter squared.

**Statistics**

Within-case comparisons were made of numbers of mast cells, macrophages, and T lymphocytes between the segments with ruptured plaque, nonruptured plaque, or normal intima. Poisson regression analysis was used to model the number of cells per unit of tissue area.

The mast cell counts were arranged as contingency tables. The location of the mast cells in the different coronary segments and the distance of the mast cells from the media or the degree of degranulation formed the marginals on the tables. The independence of marginals was tested with log-linear models. Differences were considered statistically significant when \( P < 0.05 \).

**Results**

Figure 1 shows sections of 3 segments of an infarct-related left coronary artery at low magnification (×10) to illustrate
the gross anatomy of the artery and the location of the typical thin adventitial layer present in the sections. A shows a proximal segment with a ruptured atheromatous plaque fissing into the plaque (arrow) and luminal thrombosis; B shows a middle segment with atheromatous changes (lipid accumulation) but no evidence of plaque rupture (type III lesion); and C shows a normal distal segment of the same coronary artery with no signs of lipid accumulation. The above-mentioned conclusions regarding the histological characteristics of the various segments were verified at microscopic examination at higher magnifications (×200 and ×400).

To better illustrate the cellular architecture of the coronary wall, sections of the above-mentioned 3 coronary segments are also shown at higher magnification (×100) (Figure 2). The mast cells appear to be more numerous in the adventitia backing the ruptured plaque (A) than in that backing the nonruptured plaque (B) or the normal intima (C). In Figure 2A, a cluster of inflammatory cells is visible in the adventitia. This infiltrate also contains mast cells. The inflammatory infiltrate is typically located at a greater distance from the media and is separated from the adventitial mast cells adjoining the medial boundary.
We next counted the mast cells in the adventitial layer of the coronary arteries of the 17 MI patients (Figure 3A) and the 17 control patients (Figure 3B). In the segments with plaque rupture, the numbers of adventitial mast cells were significantly higher (98 ± 40 mast cells/mm², mean ± SD; range, 33 to 215) than in the segments with nonruptured plaque (41 ± 12 mast cells/mm²; range, 24 to 72; P < 0.001). These latter values, again, were significantly higher than in the segments with normal intima (19 ± 8 mast cells/mm²; range, 7 to 33; P < 0.001). The above-mentioned trend was observed in every patient studied. Thus, in the segments containing the culprit lesion responsible for the infarction, the numbers of adventitial mast cells were, on average, 5-fold greater than in the normal segments of the same coronary artery. In contrast, no such trend was observed in the control coronary arteries (Figure 3B), the densities of the adventitial mast cells being roughly equal in all 3 segments: 9 ± 5 cells/mm² (range, 4 to 25) in the proximal segment (corresponding to the segment with plaque rupture), 8 ± 4 cells/mm² (range, 3 to 15) in the middle segment (corresponding to the segment with nonruptured plaque), and 10 ± 6 cells/mm² (range, 1 to 21) in the distal segment (corresponding to the segment with normal intima). Between the segments with plaque rupture and the corresponding proximal segments of the control coronary arteries, the densities of adventitial mast cells showed a 10-fold difference. Interestingly, even in the normal segments of the infarct-related artery, the mast cell densities were higher (by 2-fold) than in the corresponding segments of the control arteries, suggesting that the entire adventitial layer of the infarct-related coronary artery was affected by an inflammatory process.

Next, sections of the 3 segments of the infarct-related coronary arteries were immunostained for histamine. Figure 4 shows a histamine-stained mast cell (brown) next to a small adventitial vessel. In all the sections studied, only the mast cells stained positive for histamine.

In the intima of the coronary artery, a fraction of mast cells contain the neutral protease chymase, which is secreted on mast cell degranulation. Chymase is able to convert angiotensin I into angiotensin II, another potent vasoactive compound. The great majority of the adventitial mast cells contained chymase (in addition to tryptase). Interestingly, in the segments with plaque rupture, a larger proportion of mast cells contained chymase (88 ± 13%, mean ± SD; range, 38% to 94%) than in the segments with nonruptured plaque (80 ± 7%; range, 70% to 95%; P < 0.01), or in those with a normal intima (66 ± 17%; range, 17% to 91%; P < 0.001).

Mast cell degranulation, a sign of mast cell activation, is a prerequisite for their action on their environment. To estimate the degree of degranulation of the adventitial mast cells, we counted the numbers of extracellular granules in the vicinity of their parent mast cells in the various segments of the infarct-related coronary arteries. Figure 5 shows that the proportion of adventitial mast cells with extensive degranulation (> 5 extracellular granules) was significantly higher in the segments with plaque rupture (49 ± 18%, mean ± SD; range, 0% to 74%) than in those with nonruptured plaque (17 ± 9%; range, 0% to 34%; P < 0.001) or in those with normal intima (11 ± 11%; range, 0% to 33%; P < 0.001). In contrast, in the segments with plaque rupture, the proportion of resting adventitial mast cells (no extracellular granules) was significantly lower (6 ± 5%, mean ± SD; range, 0% to 20%) than in the segments with nonruptured plaque (26 ± 9%; range, 10% to 50%; P < 0.001) or in the normal segments (43 ± 21%; range, 20% to 100%; P < 0.001).

Significant proportions of the adventitial mast cells shown in Figure 2 were located close to the media. This observation was verified in every patient studied. Thus, on average, >40% of the adventitial mast cells were located in the immediate vicinity of the media (at distances < 30 μm; the diameter of one mast cell is 10 to 15 μm). Interestingly, the proportion of adventitial mast cells adjacent to the media (at distances < 30 μm) was higher in the segments with plaque rupture (48 ± 6%, mean ± SD; range, 40% to 64%) than those with a normal intima (33 ± 13%; range, 0% to 50%; P < 0.001). The corresponding values in the nonruptured plaque (39 ± 9%; range, 27% to 57%) were intermediate.

We next studied the relation between mast cells and adventitial vasa vasorum in the 3 segments of the infarct-related coronary arteries. In every segment, the majority (~70%) of the mast cells were found to be located in the close vicinity (at distances < 30 μm) of the vasa vasorum. A
close spatial relation between mast cells and the vasa vaso-
rum was observed in all the segments studied (Figure 6).

As shown above (Figure 2A), in addition to mast cells,
infiltrates of other inflammatory cells were visible in the
adventitia. To identify T lymphocytes and macrophages in the
adventitia of the various segments of the infarct-related
coronary arteries, the sections were stained with antibodies
against T lymphocytes and macrophages. Figure 7 shows an
adventitial inflammatory infiltrate in a coronary segment with
plaque rupture. On the left of an adventitial vessel with strong
positive staining for smooth muscle cells (brown) in the
vessel wall (A), lies the infiltration which contains both T
lymphocytes (B) and macrophages (C). Note that the macro-
phages stain brown and are scattered throughout the
adventitial layer (hematoxylin counterstaining, light
blue; magnification ×200).

Figure 7. Light microscopic views showing
smooth muscle cells (A), T lymphocytes (B), and
macrophages (C) in the adventitia of an infarct-
related coronary artery. The section was obtained
from a segment with ruptured plaque. A, Smooth
muscle cells stained brown. In each panel, the
border (arrows) between the media (M) and the
adventitia (A) can be clearly seen. The adventitial
vessels are surrounded by smooth muscle cells.
Next to the larger vessel is an inflammatory cell
infiltrate (left). B, T lymphocytes stain brown and
are mostly seen in the infiltrate. C, Macrophages
stain brown and are scattered throughout the
adventitial layer (hematoxylin counterstaining, light
blue; magnification ×200).
higher \((P\text{ range, } 115 \text{ to } 809, \text{ respectively})\), which again were significantly increased numbers of adventitial macrophages and T lymphocytes in the segments with plaque rupture. Thus, in the adventitia of the coronary segments with plaque rupture responsible for the infarction contained the greatest numbers of adventitial mast cells, which were significantly \((201 \pm 107/\text{mm}^2; \text{ mean } \pm \text{ SD; range, } 114 \text{ to } 569)\) and macrophages \((474 \pm 273/\text{mm}^2; \text{ range, } 164 \text{ to } 972)\) were both significantly \((P<0.001)\) higher than in the segments with nonruptured plaque \((126 \pm 71/\text{mm}^2; \text{ range, } 56 \text{ to } 361; \text{ and } 308 \pm 223/\text{mm}^2; \text{ range, } 115 \text{ to } 809, \text{ respectively})\), which again were significantly higher \((P<0.001)\) than the corresponding values in the segments with a normal intima \((65 \pm 36/\text{mm}^2; \text{ range, } 35 \text{ to } 175; \text{ and } 152 \pm 79/\text{mm}^2; \text{ range, } 82 \text{ to } 377)\). Thus, the differences in the density between these 2 types of inflammatory cell paralleled those of mast cells.

**Discussion**

In the infarct-related coronary arteries of MI patients, the segments including the plaque rupture responsible for the infarction contained the greatest numbers of adventitial mast cells. Of special interest is the finding that even in the normal segments of the infarct-related artery, the mast cell densities were higher \((2\text{-fold})\) than in the corresponding (distal) segments of the control arteries. This finding suggests that the entire adventitial layer of the infarct-related coronary artery was affected by an inflammatory process.

Inflammatory infiltrates consisting mainly of lymphocytes and plasma cells were previously observed in the coronary adventitia of patients with unstable angina who had sudden cardiac death or acute MI. We also found significantly increased numbers of adventitial macrophages and T lymphocytes in the segments with plaque rupture. Thus, in the adventitia of the coronary segments with plaque rupture, the mast cells resided in areas where other inflammatory cells were also present.

We found that in the adventitia the mast cells were the only cells that contained histamine. The close relation between the adventitial mast cells and the media, the layer responsible for the regulation of coronary artery tone, suggests that part of the histamine released from the stimulated adventitial mast cells could diffuse directly into the media. The close relation between the histamine-containing mast cells and the vasa vasorum provides another possible route for released histamine to reach the medial layer. Interestingly, in the denseplexuses of microvessels characteristic of atherosclerotic coronary segments, the direction of flow is inward from the adventitial vasa vasorum and is strongly \((5\text{-fold})\) increased.

Small numbers of mast cells were also present in the medial layer. There, as in the adventitia, the numbers of mast cells were significantly greater in the segments with plaque rupture \((\text{on average, } 5.5 \text{ mast cells/\text{mm}^2}; \text{ range, } 0 \text{ to } 10)\) than in the segments with nonruptured plaque \((\text{on average, } 1.4 \text{ mast cells/\text{mm}^2}; \text{ range, } 0 \text{ to } 5)\). In the segments without atherosclerotic changes, virtually no mast cells were observed. Thus, the mast cells in the media backing the ruptured and intact plaques form a small local source of histamine.

In the medial layer, the vasoactive histamine, if bound to histamine-1–receptors on smooth muscle cells, will cause these to contract. In atherosclerotic coronary segments, smooth muscle contraction in response to histamine is likely to be vigorous, the damaged endothelium having lost its opposing vasodilatory capacity. Indeed, after intracoronary injection of histamine, contraction of the coronary arteries was observed in atherosclerotic segments but not in the normal areas of these arteries. The hypothesis that, in MI, coronary spasm at sites of plaque rupture is caused \((\text{at least partly})\) by coronary adventitial mast cells is supported by the clinicopathological observation of Forman et al. In a patient who had sudden cardiac death after follow-up for several years, the angiographically detected spastic segment of the left descending coronary artery contained increased numbers of adventitial mast cells. It should be borne in mind, however, that an abnormal coronary vasoconstriction associated with mast cell activation and ensuing histamine release would be only one of many factors involved in unstable coronary artery syndromes, which is the outcome of many complex mechanisms, notably the release of specific platelet mediators (eg, thromboxane A\(_2\) and serotonin).

The present study shows that most of the mast cells in the human coronary adventitia contain not only tryptase but also chymase. Interestingly, in the segments with plaque rupture, most of the adventitial mast cells contained chymase \((88\%)\), the proportion being significantly higher than in the mast cells within the ruptured plaques \((37\%)\). In vitro, chymase effectively converts angiotensin I into angiotensin II, and angiotensin II receptors are present in the medial smooth muscle cells of human coronary arteries. Thus, the angiotensin II generated by the chymase released from mast cells could act synergistically with histamine and aggravate the local constriction of the infarct-related coronary artery.
Coronary plaques usually rupture at sites where the circumferential stress is high and where the plaque has been weakened as a result of a local inflammatory reaction. Interestingly, the rupture sites contain large numbers of tryptase- and chymase-secreting mast cells, suggesting that mast cells also play a role in plaque rupture by contributing to matrix degradation in the plaque. The present finding of degranulated mast cells in even larger numbers (10-fold) in the adventitial layer backing the ruptured plaques suggests that mast cells contribute to the development of thrombotic coronary artery occlusion by multiple mechanisms.

Limitations of the Study
Determination of the degree of mast cell degranulation after death is suboptimal. Degranulation may occur shortly after death from anoxia. Alternatively, degranulation may have been secondary to the handling of the coronary arteries during dissection or resulting from the manipulations used for procurement of tissue samples and histological processing. Therefore, all specimens included a thick layer of surrounding tissue. However, this may have delayed fixation of the adventitial mast cells. Despite these possibilities, comparison between the different types of coronary segment revealed that the extent of mast cell degranulation was highest in the adventitial areas backing ruptures, where a strong inflammatory component was also present.

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Association Between Myocardial Infarction and the Mast Cells in the Adventitia of the Infarct-Related Coronary Artery

Petri Laine, Maija Kaartinen, Antti Penttilä, Pertti Panula, Timo Paavonen and Petri T. Kovanen

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