MORPHOLOGIC STUDIES

Increase in Atherosclerosis and Adventitial Mast Cells in Cocaine Abusers: An Alternative Mechanism of Cocaine-Associated Coronary Vasospasm and Thrombosis*

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Coronary vasospasm has been implicated as a cause of myocardial ischemia and sudden cardiac death in cocaine abusers. However, the mechanism or mechanisms remain unknown. Autopsy records \( n = 5,871 \) from the medical examiner's files at Baltimore, Maryland and northern Virginia were examined and 495 persons (8.4%) were identified with positive toxicologic findings for cocaine. Of these, six subjects (1.2%) had total thrombotic occlusion, involving primarily the left anterior descending coronary artery. The mean number of adventitial mast cells per coronary segment and the degree of atherosclerosis were determined. These observations were compared with findings in age- and gender-matched subjects who died from cocaine overdose and in patients who had sudden cardiac death (acute thrombosis) without a history of illicit drug abuse.

Cocaine-associated thrombosis has been well described (1–22); however, the underlying mechanism or mechanisms have not been defined. Previous clinical studies (2,5,7,9,10,12,14,15,17,19–21) suggested that coronary spasm in the setting of cocaine abuse occurs predominantly in patients with either normal coronary arteries or vessels with mild atherosclerosis. Cocaine-associated thrombosis and vasospasm have been suggested to result from direct aggregation of platelets and subsequent release of vasoactive mediators or from indirect mechanisms involving blockade of reuptake of released norepinephrine at the presynaptic nerve terminals. Coronary spasm in the absence of cocaine abuse has been shown angiographically to be localized to sites of organic disease (23). Numerous mechanisms have been proposed.

There were significantly more mast cells in subjects with cocaine-associated thrombosis than in the other groups. The number of mast cells showed a significant correlation with the degree of cross-sectional luminal narrowing \( r = 0.68 \) in subjects with cocaine-associated thrombosis but not in subjects with sudden death due to thrombosis \( r = 0.34, p < 0.03 \). Subjects with cocaine-associated thrombosis also had significant coronary atherosclerosis without plaque hemorrhage (five had one or more vessels with >75% cross-sectional area luminal narrowing) despite a mean age of 29 ± 2 years.

These findings suggest that adventitial mast cells may potentiate atherosclerosis and vasospasm, thrombosis and premature sudden death in long-term cocaine abusers.

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Data collection. We reviewed files from the Office of the Chief Medical Examiner of the State of Maryland and northern Virginia and identified all deaths associated with cocaine abuse from June 1987 through November 1988. Medical records were reviewed for age, gender, race, clinical history of habitual cocaine abuse, route of cocaine administration, cocaine toxicology, symptoms and mode of
death. A total of 5,871 records were reviewed and 495 subjects (8.4%) had a positive cocaine toxicology screen or recent history of cocaine abuse, or both. Six patients died of cocaine abuse associated with acute coronary thrombosis and constitute the basis for this study.

These patients were compared with six randomly selected age- and gender-matched subjects who died from cocaine overdose and six patients selected from the files in the Armed Forces Institute of Pathology who died suddenly and had severe coronary atherosclerosis and thrombosis with a negative toxicology screen for drug abuse.

Gross morphologic examination. All hearts of subjects with cocaine-associated death were examined at our institute for weight, right and left ventricular thickness and valvular abnormalities. The right, left main, left anterior descending, left circumflex, left diagonal and left obtuse marginal coronary arteries were examined for the presence of atherosclerosis and thrombosis by transverse cuts at 3 to 5 mm intervals. The presence of acute or healed myocardial infarction was also noted. Multiple sections of the heart (minimum of three sections) from the right and left ventricles or sections from areas with grossly suspected pathologic change, or both, were examined by light microscopy.

Histologic assessment of coronary arteries. Histologic sections of the 1st 3 cm of the three major coronary arteries (right, left anterior descending and left circumflex) and branches when involved by thrombosis were examined by light microscopy. Myocardial and coronary sections were processed routinely through a graded series of alcohol and xylene and embedded in paraffin, cut at 6 μm and stained with hematoxylin-eosin, Movat pentachrome stain and toluidine blue stains. On average, eight sections per artery were evaluated for the extent of cross-sectional area luminal narrowing by atherosclerotic plaque and presence of thrombosis. The type of atherosclerotic plaque and the presence or absence of hemorrhage and inflammation in the arterial wall were also noted. Severe coronary atherosclerosis was defined as >75% cross-sectional area luminal narrowing. The number of medial and adventitial mast cells was counted at ×400 magnification. The number of mast cells from each section was pooled and the average number of mast cells per section calculated (26). The percent of mast cells that were degranulated was not estimated because mast cell degranulation can occur through rough handling of the specimen (26).

Statistical analysis. All values are expressed as mean values ± SEM. Study groups were compared with the unpaired two-tailed t test. The number of mast cells per histologic section was compared with percent cross-sectional luminal narrowing in arteries with thrombosis by using linear regression analysis.

Results

Clinical characteristics. The clinical characteristics of the 12 autopsy study subjects who abused cocaine are summarized in Table 1. Their ages ranged from 21 to 38 years. In 6 (1.2%) of the 495 autopsy cases with positive findings for cocaine abuse, the subject had coronary thrombosis with underlying atherosclerosis. These six subjects had a mean age ± SD of 29 ± 2 years. Data from Subject 2 were previously reported (27). All six subjects had a history of taking cocaine hours before death. Five of the six had a history of habitual cocaine abuse; in the sixth subject the long-term history of cocaine abuse was unknown. Toxicology screen for cocaine was performed in five subjects and

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Age/yr</th>
<th>Gender</th>
<th>Race</th>
<th>Route of Admin</th>
<th>Benzyll Benoyl Level</th>
<th>Cocaine Abuse</th>
<th>Symptoms of Death</th>
<th>Mode of Death</th>
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<tbody>
<tr>
<td>1</td>
<td>21/M</td>
<td>W</td>
<td>—</td>
<td>—</td>
<td>0 ± 0.2</td>
<td>—</td>
<td>Back pain</td>
<td>SCD</td>
</tr>
<tr>
<td>2</td>
<td>23/F</td>
<td>B</td>
<td>SM</td>
<td>0.2± Perspectives</td>
<td>0 ± 0.2</td>
<td>+</td>
<td>CP</td>
<td>SCD</td>
</tr>
<tr>
<td>3</td>
<td>26/M</td>
<td>B</td>
<td>—</td>
<td>0 ± 0.2</td>
<td>0 ± 0.2</td>
<td>+</td>
<td>CP, N, V</td>
<td>SCD</td>
</tr>
<tr>
<td>4</td>
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<td>IV</td>
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<td>+</td>
<td>None</td>
<td>SCD</td>
</tr>
<tr>
<td>5</td>
<td>34/M</td>
<td>W</td>
<td>IN</td>
<td>1.00±0.42</td>
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<td>+</td>
<td>CP</td>
<td>AMI</td>
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<tr>
<td>6</td>
<td>36/M</td>
<td>B</td>
<td>IN</td>
<td>0 ± 0.2</td>
<td>0 ± 0.2</td>
<td>+</td>
<td>CP</td>
<td>SCD</td>
</tr>
<tr>
<td>CO</td>
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<tr>
<td>7</td>
<td>22/F</td>
<td>W</td>
<td>IV</td>
<td>5 ± 0.2</td>
<td>5 ± 0.2</td>
<td>+</td>
<td>None</td>
<td>SD</td>
</tr>
<tr>
<td>8</td>
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<td>B</td>
<td>IN</td>
<td>9 ± 0.2</td>
<td>9 ± 0.2</td>
<td>+</td>
<td>Convulsions</td>
<td>SD</td>
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<tr>
<td>9</td>
<td>26/M</td>
<td>B</td>
<td>SM, IN</td>
<td>0 ± 0.2</td>
<td>0 ± 0.2</td>
<td>+</td>
<td>Halluc, arrhy</td>
<td>SD</td>
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<tr>
<td>10</td>
<td>26/M</td>
<td>W</td>
<td>—</td>
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<td>+</td>
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<tr>
<td>11</td>
<td>33/M</td>
<td>W</td>
<td>—</td>
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<td>+</td>
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<td>SD</td>
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<tr>
<td>12</td>
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<td>W</td>
<td>—</td>
<td>1.3±0.2</td>
<td>1.3±0.2</td>
<td>+</td>
<td>None</td>
<td>SD</td>
</tr>
</tbody>
</table>

*Found dead in bathtub with vomitus; †recent use; ‡history of cocaine use verified by family; §cocaine metabolites were not tested—sister gave history of patient having used cocaine the previous night, premortem cholesterol 126 mg/dl; ‡thrombosis levels drawn after 20 h; ‡phencyclidine. Admin = administration; AMI = acute myocardial infarction; arrhy = cardiac arrhythmias; B = black; Benzyll = benzoylcgonine; CO = patients who died of cocaine overdose; CP = chest pain; CSD-T = patients with cocaine-related sudden death and thrombosis; F = female; Halluc = hallucinations; IN = intranasal; IV = intravenous; M = male; N = nausea; SCD = sudden cardiac death; SD = sudden death; SM = smoking; V = vomiting; W = white.
was positive for cocaine or one of its major metabolites, or both, in three subjects. One patient died 20 h after cocaine ingestion and had a negative cocaine screen. Three subjects developed symptoms of chest pain. Five subjects had a sudden cardiac death and one subject died after acute myocardial infarction.

The six age- and gender-matched subjects who died of cocaine overdose had a mean age ± SD of 29 ± 2 years. Five of the six had a history of long-term cocaine abuse: the cocaine history of one subject was unknown. All six subjects had a positive toxicology screen for blood cocaine at the time of death. One patient’s blood also tested positive for phencyclidine at the time of death.

### Morphologic Assessment of Coronary Arteries

**Gross examination.** All subjects with cocaine-associated thrombosis had an occlusive platelet-rich thrombus, with a few acute inflammatory cells primarily involving the left anterior descending coronary artery. Two subjects had additional thrombi in the left circumflex and left diagonal coronary arteries. Three subjects had gross evidence of myocardial infarction; two subjects had a subendocardial and one had a healed transmural myocardial infarction of the left ventricle. The degree of coronary atherosclerosis was severe in the six subjects with cocaine-associated thrombosis (Table 2). Of these, one subject had triple vessel disease (>75% cross-sectional luminal narrowing), one had double vessel disease (Fig. 1), two subjects had single vessel disease and two had noncritical atherosclerosis in major coronary arteries. However, one subject had 95% luminal narrowing of the first left diagonal coronary artery.

**Subjects who died suddenly with coronary thrombosis and no history of drug abuse had severe coronary atherosclerosis:** three subjects had triple vessel disease, one subject had double vessel disease and one had single vessel disease. All had thrombosis involving one or more coronary arteries (Table 2).

### Table 2. Morphologic Assessment of the 1st 3 cm of the Left Anterior Descending (LAD), Left Circumflex (LCx) and Right Coronary (RCA) Arteries in 18 Subjects*

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Heart Weight (g)</th>
<th>No. of Cor Art</th>
<th>No. of MCCorr Art</th>
<th>Max Ath (75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gender</td>
<td>No. of Art</td>
<td>No. of Art</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;75% Ath*</td>
<td>With Occ Thr</td>
<td>LAD</td>
<td>LCx</td>
</tr>
<tr>
<td>CSD-T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21/M</td>
<td>400</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>23/F</td>
<td>215</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>26/M</td>
<td>410</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>31/M</td>
<td>480</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>34/M</td>
<td>465</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>36/M</td>
<td>386</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>35</td>
<td>44±0.2</td>
<td>125±11</td>
<td>65±8</td>
</tr>
<tr>
<td>SD-T</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>45/M</td>
<td>406</td>
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<td>1</td>
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<td>8</td>
<td>38/M</td>
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<td>1</td>
</tr>
<tr>
<td>9</td>
<td>33/M</td>
<td>455</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>24/M</td>
<td>450</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>36/M</td>
<td>400</td>
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<td>2</td>
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<td>12</td>
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</tr>
<tr>
<td>Mean</td>
<td>34</td>
<td>56±0.4</td>
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<td>CO</td>
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</tr>
<tr>
<td>13</td>
<td>22/F</td>
<td>260</td>
<td>0</td>
<td>0</td>
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<tr>
<td>14</td>
<td>23/M</td>
<td>455</td>
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<td>0</td>
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<tr>
<td>15</td>
<td>26/M</td>
<td>375</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>26/M</td>
<td>450</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>33/M</td>
<td>570</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>36/M</td>
<td>370</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>28</td>
<td>46±0.5</td>
<td>20±5</td>
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</table>

*The 18 subjects included 6 with a history of cocaine abuse who died suddenly with acute coronary thrombosis (CSD-T), 6 without a history of cocaine abuse who died suddenly with acute coronary thrombosis (SD-T) and 6 who died after a cocaine overdose (CO). *Refers to percent cross-sectional area luminal narrowing. 1The left first diagonal coronary artery had 95% luminal narrowing by atherosclerotic plaque with superimposed occlusive thrombus (Fig. 2). *p = 0.0002 for patients with a history of cocaine abuse who died suddenly with acute coronary thrombosis versus patients without a history of cocaine abuse who died suddenly with acute coronary thrombosis. *p = 0.0004 for patients with a history of cocaine abuse who died suddenly with acute coronary thrombosis versus patients who died after cocaine overdose. *p = 0.0019 for patients without a history of cocaine abuse who died suddenly with acute coronary thrombosis versus patients who died after cocaine overdose. Values are expressed as mean values ± SD. Ath = atherosclerosis; Cor Art = coronary arteries; Max = maximal; MC = mast cells; Occ = occlusive; RCA = right coronary artery; Thr = thrombus; other abbreviations as in Table 1.
Figure 1. Patient I. A and B. Sections from the left circumflex (LC) coronary artery, with B showing 90% luminal narrowing. Note the absence of a thrombus. C, D, and E. Consecutive sections of the left anterior descending (LAD) coronary artery with 90% to 95% cross-sectional area luminal narrowing by atherosclerotic plaque with superimposed total obstruction by platelet thrombus. F. Close-up view of the area of intima in C in contact with the platelet thrombus, which contains a few entrapped inflammatory cells. G. Toluidine blue stain demonstrating the presence of a large number of mast cells (arrowheads) in the adventitia of the left anterior descending coronary artery. (Movat stain, A and B magnification × 20; hematoxylin and eosin, C, D, and E magnification × 15, F magnification × 150; toluidine blue, G, magnification × 300.)

Light microscopy. Histologic examination of coronary arteries in patients with acute coronary thrombosis associated with cocaine abuse revealed smooth muscle cell-rich fibrous plaques containing foam cells. Medial or intimal inflammation, or both, consisting primarily of lymphocytes and plasma cells was seen in four of the six subjects. No complicated lesions (that is, hemorrhage into the plaque, calcification or plaque rupture) were noted in any of these cases. Subjects who died of cocaine overdose had noncritical coronary atherosclerosis (Table 2).

Atherosclerotic plaques in five of the six patients with
thrombosis and with no history of cocaine abuse consisted of large areas of pustular debris with plaque hemorrhage. The subject without plaque hemorrhage had underlying organizing fibrin deposition. None of these subjects had inflammation of the arterial wall, although focal lymphocytic infiltrate was occasionally seen in the atherosclerotic intima and adventitia.

Adventitial mast cells. The number of adventitial mast cells was significantly greater in the left anterior descending coronary artery in subjects with cocaine-associated thrombosis than in subjects in the other groups (Table 2, Fig. 1). Statistical comparisons of mast cell numbers in subjects with acute platelet thrombosis involving the left circumflex coronary artery were not performed because there were only two subjects in each group. When the maximal number of mast cells per histologic section in coronary segments with atherosclerosis and thrombosis was plotted against percent cross-sectional area luminal narrowing, arteries from cocaine abusers showed a significant correlation ($r = 0.68$) whereas those of nonabusers did not $(r = 0.34)$; this difference was significant ($p < 0.03$; Fig. 2).

**Figure 2.** Number of mast cells in coronary artery sections with thrombosis plotted against the degree of cross-sectional area luminal narrowing. Results show a positive correlation in patients with cocaine-related sudden death and thrombosis in contrast to the findings in patients with sudden death and thrombosis (SDT) without a history of cocaine abuse. Correlation coefficients were significant at the level of $p < 0.03$.

**Discussion**

In the present study, coronary platelet thrombosis was associated with cocaine abuse in young individuals with moderate to severe atherosclerotic plaques primarily involving the left anterior descending coronary artery; the plaques were rich in smooth muscle and foam cells, with the media frequently infiltrated by chronic inflammatory cells. No plaque hemorrhage, rupture or calcification was noted in any of these cases even though three subjects had either acute or healed myocardial infarction. Therefore, these observations suggest that the atherosclerotic lesions of habitual cocaine abusers are dissimilar to those of patients presenting with a typical coronary ischemic syndrome. In contrast, five of the six subjects with thrombosis and sudden coronary death in the absence of cocaine abuse had hemorrhage into a plaque and the remaining patient had underlying fibrin deposition. Davies et al. (28,29) determined that “acute evolving coronary arterial lesions” (that is, atheromatous plaques undergoing fissuring or rupture) are the underlying mechanism in 95% of patients with coronary atherosclerosis and thrombosis.

Mast cells and atherosclerosis. The number of mast cells in the adventitia has been shown (30) to increase with the progression of atherosclerosis and mast cells are more commonly observed (26) in fresh thrombi and hemorrhage into a plaque than in fully organized thrombi. In the present study, subjects with cocaine-associated thrombosis had more mast cells than did subjects in the noncocaine thrombosis or cocaine overdose groups. Furthermore, linear regression analysis revealed a positive correlation $(r = 0.68)$ between the number of mast cells and the degree of cross-sectional area luminal narrowing in sections with thrombosis in cocaine abusers, whereas there was no correlation $(r =$
0.34) in the subjects with thrombosis who had no history of drug abuse. Also, mast cells were increased in the coronary arteries of cocaine abusers, regardless of thrombosis, and were similar in number to those in patients with sudden death and severe atherosclerosis and thrombosis. Therefore, it appears that the mechanism of thrombosis in cocaine abuse may be dissimilar to that of the typical coronary ischemic syndrome or acute myocardial infarction.

Recent evidence (31,32) suggests that human arterial mast cells may be involved in lipid uptake, thereby promoting atherogenesis. The increased numbers of lymphocytes and plasma cells have been found in the adventitia of atherosclerotic vessels (33). It has been shown that lymphokines from inducer T lymphocytes stimulate mast cell proliferation (34). Activated mast cells may involve the atherogenic properties of histamine, namely, increasing endothelial cell permeability, which may indirectly facilitate lipoprotein uptake (35).

Mast cell recruitment and degranulation. The mechanism or mechanisms that lead to mast cell recruitment and proliferation in the vessel wall are unknown. Blood basophils migrate to areas of delayed-type allergic reactions (34). Inflammatory cells, predominantly lymphocytes, admixed with plasma cells have been found in the adventitia of atherosclerotic vessels (35). It has been shown that lymphokines from inducer T lymphocytes stimulate mast cell proliferation (36). Histamine, through its action on endogenous catecholamines, may affect lymphocyte activity (37) and mast cell proliferation. Stimulated mast cells release peroxidase enzymes, which have been associated with tissue injury (38). In addition, degranulation of human mast cells induces an endothelial antigen that promotes leukocyte adhesions (39).

Mast cells express membrane receptors that bind immunoglobulin E antibody with high affinity, which results in the rapid release of histamine on stimulation (40,41). Other mediators of mast cell degranulation are complement fragments (C5a), basic peptides and certain drugs (42). Illicit cocaine is often contaminated with undefined chemicals and other drugs that may be immunogenic and these may cause degranulation through unknown mechanisms (43). One common drug used in conjunction with cocaine is morphine sulfate, a known secretagogue of human mast cells (39). Very low density lipoprotein cholesterol at physiologic concentrations has been shown to trigger the release of histamine from human basophils (44).

Role of mast cell products in coronary vasospasm. Observations in both animals (45) and humans (25) suggest that mast cells with rich stores of histamine may play an important role in the pathogenesis of coronary vasospasm and thrombosis. We (26) previously reported a statistically significant increase in adventitial mast cells in a patient with clinically documented vasospasm and nonsignificant coronary atherosclerosis. We (46) and others (47) demonstrated an increased sensitivity to histamine in isolated atherosclerotic vessels of Watanabe heritable hyperlipidemic rabbits and human coronary arteries. In cholesterol-fed miniature swine, histamine-induced focal spasm in areas of underlying atherosclerosis in vivo (48); in addition, it was used successfully as a provocative test to induce spasm in patients with suspected variant angina (25). Atherosclerotic arteries in humans were shown (24) to contain more histamine than normal vessels. Other mast cell products, such as prostaglandin D2 and leukotrienes C4 and D4, are also important modulators of smooth muscle tone. In vitro, prostaglandin D2 contracts canine and human epicardial coronary arteries and human vessels constrict to levels ranging from 0.5% to 800% above the maximal norepinephrine response (49–52).

**Cocaine-associated thrombosis.** During the past 5 years, approximately 58 clinical cases of cocaine-associated myocardial infarction have been reported. It is important to note that the occurrence of myocardial infarction after cocaine use does not appear to be related to dose, route of administration or the time of symptom onset. It is speculated (33) that myocardial ischemia induced by cocaine may be related to focal vasospastic constriction or spasm.

A large number of case reports (1–10,12–15,17–21) of young cocaine abusers have demonstrated the presence of thrombosis by coronary angiography. The majority of these patients have angiographically normal vessels or only mild atherosclerotic disease. However, we and others (15,16,54,55) demonstrated at autopsy the presence of moderate to severe coronary atherosclerosis in the areas of thrombosis. Mittleman and Werli (16) reviewed 34 autopsy cases of cocaine abusers (mean age 32 years, range 23 to 71); in 15, death was attributed to severe coronary atherosclerosis (90% stenosis). Dressler et al. (55) studied the hearts of 22 cocaine abusers (mean age 32 years) at necropsy and observed that 8 patients (36%) had one or more major coronary arteries narrowed >75% in cross-sectional area by atherosclerotic plaque. The increased incidence of atherosclerosis in cocaine abusers observed at necropsy may result from angiographic underestimation of the degree of coronary luminal narrowing compared with that estimated by histologic examination (56,57).

**Mechanisms of cocaine-associated thrombosis.** Most coronary thrombi reported at autopsy in cocaine abusers have consisted of platelets (3,11,15,16). Direct platelet aggregation may occur through alpha-adrenergic properties of cocaine, thereby causing serotonin-induced vasospasm and coronary thrombosis, particularly in areas of fixed stenosis. However, little is known about the in vivo effects of cocaine on platelet function. An in vitro study (22) of rabbit platelet-rich plasma showed that cocaine in low concentrations increased platelet aggregability and thromboxane production and decreased prostacyclin production, whereas high doses elicited opposite effects. This potential predisposition to clotting could explain the in situ formation of coronary thrombosis in the absence of plaque hemorrhage and rupture.

Coronary spasm may be an alternative explanation for thrombosis associated with cocaine abuse; however, direct evidence of cocaine-induced vasospasm in humans is lack-
Two separate reports (19, 58) documented ergonovine maleate-induced vasospasm only in those cocaine abusers who had severe coronary stenosis (three of seven patients studied). These data suggest that a subgroup of cocaine abusers may be predisposed to coronary spasm through mechanisms independent of a direct effect of cocaine.

In vivo experiments (59, 60) in animal models with normal coronary arteries support the view that cocaine causes vasoconstriction. However, these studies disclosed a diffuse diminution in coronary artery caliber after cocaine as opposed to severe focal vasoconstriction associated with vasospasm in humans. Hale et al. (60) demonstrated that cocaine decreased myocardial blood flow by 20% to 30%. This degree of flow reduction is not sufficient to explain the occurrence of infarction in humans with normal coronary arteries as determined by angiography.

Lange et al. (61) reported the effects of intranasal cocaine during cardiac catheterization in patients undergoing coronary angiography for the evaluation of chest pain. Myocardial blood flow decreased by 17 ± 12%, whereas vascular resistance increased by 33 ± 29%; however, no ischemic events were observed. A minimal reduction in extramural vessel diameter was noted and the authors (61) presumed that the increase in vascular resistance was secondary to vasoconstriction of the intramural coronary vessels. Observations (62) supporting this notion have been demonstrated in vitro after cocaine administration. It is therefore conceivable that an alternative mechanism of coronary vasospasm in large caliber vessels unrelated to the direct effects of cocaine may be involved in patients with cocaine-associated myocardial ischemia.

Risk factors and atherosclerosis. Risk factors such as cigarette smoking, total serum cholesterol and lipoproteins are predictive of coronary and aortic atherosclerosis in old as well as young individuals (63). Although clinical information is not uniformly available in patients with cocaine-related death, the predominant risk factor in this relatively young group of patients appears to be smoking. Overall, the incidence of severe coronary artery stenosis in young subjects at autopsy appears to be extremely low. Roberts (64) studied epicardial coronary arteries in 40 patients (mean age 52 years), most of whom died of leukemia and had no past clinical history of cardiovascular disease. Only 3% of the histologic sections showed >75% cross-sectional area luminal narrowing by atherosclerotic plaque. Of the 162 men (21 to 34 years of age, average total cholesterol value 184 ± 55 mg/dl) from a study on the pathobiologic determinants of atherosclerosis in youth who died of unnatural causes, none showed severe (≥75% cross-sectional area luminal narrowing) coronary atherosclerosis (Cornhill, personal communication).

Because heritable disorders of elevated serum cholesterol such as familial hypercholesterolemia are infrequent, excessive serum lipoproteins as a mechanism of cocaine-accelerated atherosclerosis is probably unlikely. Homozygous individuals (estimated incidence 1 in 1 million) usually develop xanthomas and manifest coronary heart disease during childhood (65). Heterozygous patients (estimated incidence 1 in 500) usually develop xanthomas by 20 years of age and symptomatic coronary artery disease occurs on average by 40 years of age (65). None of the patients in the present study had xanthomas and the total cholesterol level determined before death in one patient with cocaine-associated thrombosis was <200 mg/dl.

Conclusions. This study demonstrates that cocaine abusers who died of acute coronary thrombosis had moderate to severe coronary atherosclerosis and an increased number of adventitial mast cells. The degree of cross-sectional luminal narrowing of coronary arteries in these patients was higher than expected for individuals whose average age is only 29 years. Although the mechanism of cocaine-associated thrombosis is unknown, adventitial mast cells may initiate a deleterious cascade of events leading to premature atherosclerosis, vasospasm, thrombosis and sudden death in selected individuals who habitually use cocaine.

References


