Serotonin Is Associated with Coronary Artery Disease and Cardiac Events

Kjell Vikenes, MD; Mikael Farstad, MD, PhD; Jan Erik Nordrehaug, MD, PhD

Background—Blood platelets are related to coronary atherogenesis. Platelets secrete serotonin (5-hydroxytryptamine) which has several effects on the vascular wall and promotes thrombogenesis, mitogenesis, and proliferation of smooth muscle cells. Serotonin may therefore be one of the factors involved in the development of coronary artery disease (CAD). We have assessed serotonin among conventional predictors for CAD in patients undergoing coronary angiography for chest pain or clinically suspected angina pectoris.

Methods and Results—Of 121 consecutive male patients (mean age 65, range 41 to 90 years) undergoing angiography, 96 had coronary artery stenosis and 25 had normal angiograms. Serotonin, blood platelet count, and conventional biochemical risk factors for CAD were determined in the morning the day before the angiography. High serotonin (cut-point 1000 nmol/L) was significantly associated with CAD with an odds ratio (OR) of 3.4 (95% confidence interval 1.2 to 9.8). The corresponding OR for smokers was 4.8 (1.9 to 12.2); hypercholesterolemia (>7 mmol/L), 2.9 (1.1 to 7.6); high platelet count (cut-point 325 10^9 /L), 3.0 (1.0 to 9.5); and family history of heart disease, 2.3 (1.0 to 5.2). After adjustment with conventional risk factors, the OR for CAD was 3.8 (1.1 to 13.1), comparing high and low values of serotonin. The relation between serotonin and CAD was strengthened only when patients >70 years (n=82) were included in the analysis. In this age group, the occurrence of cardiac events during a mean of 3.7 years of follow-up was significantly associated with high serotonin values.

Conclusions—The study suggests that serotonin is associated with coronary artery disease and occurrence of cardiac events, particularly in younger age groups. This association seems to persist after adjustment for conventional risk factors. (Circulation. 1999;100:483-489.)

Key Words: risk factors ■ atherosclerosis ■ ischemia ■ coronary disease ■ platelets

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Experimental studies indicate that blood platelets are involved in the development of atherosclerosis.1–5 The pathophysiological mechanisms by which platelets contribute to this process are not fully understood. Experimental animal studies have demonstrated that platelets are activated and aggregate at the sites of coronary artery stenosis and endothelial injury.6–8 Activated platelets release serotonin in substantial quantities causing vasoconstriction7,9 and recurrent aggregation of platelets with cyclic flow reductions.7 Serotonin also acts as a growth factor stimulating mitogenesis and migration of arterial smooth muscle cells.10,11 These effects are blocked by the specific serotonin receptor antagonist ketanserin10,12 whereas thromboxane A₂, released from platelets, acts synergistically with serotonin.13,14 Furthermore, serotonin has been shown to promote proliferation of vascular endothelial cells,15,16 and direct endothelial injury in cell culture has been suggested by the release of lactate dehydrogenase and preloaded (14C)-adenine when exposed to serotonin.17

Serotonin release during coronary angioplasty and infusion of serotonin at coronary angiography have both contributed to clinically relevant vasoconstriction in patients with coronary artery disease.18,19 The effects were seen with plasma levels of serotonin equivalent to those resulting from local platelet activation and were attenuated by ketanserin. Until this study, cardiovascular complications have not been convincingly reduced by ketanserin in patients with various manifestations of arteriosclerotic disease, but a reduction of mortality has been suggested in nonrandomized studies.20,21 Although an effect on restenosis after coronary angioplasty has been shown,22 a larger study failed to confirm this.23 Ketanserin reduces the number of cases of preeclampsia and severe hypertension.24

Thus, serotonin clearly has important vascular actions and may also be involved in atherogenesis. In this study, we assessed serotonin as a clinical marker of coronary artery disease in patients with stable symptoms admitted to elective coronary angiography for chest pain.

Methods

Patient Population
A total of 122 consecutive male patients >20 years of age undergoing coronary angiography were included in the study. One patient...
was excluded due to failure of the determination of serotonin. On the basis of angiography, 96 of the remaining 121 patients had significant coronary artery disease, and 25 were classified as having normal angiograms. Reasons for referral to angiography included one or more of the following: medical history with suspicion of angina pectoris, the detection of a previous infarction in the resting ECG or by echocardiography, or ST depression >1 mm in the exercise ECG. None of the patients had suffered acute cardiac illness for the previous 3 months.

Hypercholesterolemia was classified according to pretreatment values (26% of the study population were on cholesterol lowering medication), or cholesterol values >7.0 mmol/L in untreated patients. Hypertension was classified according to previously diagnosed hypertension and use of current antihypertensive medication.

Biochemical Measurements
Blood samples were drawn in the morning between 8 AM and noon the day before angiography. Venous blood was collected in Vacutainer tubes with ACD solution (22g Na citrate, 8 g citrate, and 24.5 g dextrose per liter) 9:15 vol/ vol. The samples were centrifuged at 450g for 5 minutes and platelet rich plasma (PRP) was pipetted off the supernatant. Platelets were counted with a Coulter Counter, Model S-Plus III (Coulter Electronics). Because all patients had a hematocrit within reference values, no correction for hematocrit was done.

Total serotonin in PRP and serotonin content in platelets were measured. Four hundred fifty microliers of PRP were mixed with 150 lL of 2.8 mol/L per chloric acid, and serotonin was measured by a HPLC method with a Zipax SCX column (DuPont) eluted with a 150 mmol/L sodium acetate (pH 5.2), 10 mL n-propanol/L, and fluorometry with excitation at 304 nm and detection at 340 nm as previously described.25

Precision for the serotonin determination was better than ±5% both within and between runs. Serotonin (5-hydroxytryptamine) was also assayed directly in serum prepared from whole blood using thrombin-coated vacuum tubes. Serotonin recovered from serum amounted to only 465±53 mmol/L compared with 901±113 mmol/L in PRP, and the correlation coefficient was only 0.586. Because serotonin binds to proteins during the coagulation process and reduces the amount of measurable serotonin in serum,25 we used platelet rich plasma throughout the experiment.

Cholesterol was determined in the hospital routine laboratory by a Technicon Chem 1 (Technicon Instruments) according to the instrument manual. 5-hydroxytryptamine (serotonin)-creatinine sulfate complex was purchased from Sigma Chemical Co (St. Louis, Mo). All other reagents were of the highest purity commercially available.

Angiography
Left ventricular angiography and selective coronary angiography from the groin were performed according to standard techniques in our laboratory.26 The angiograms were assessed by 2 cardiologists who had no knowledge of the serotonin values. Coronary artery stenosis was confirmed in orthogonal views and a luminal reduction of 50% in any of the main coronary arteries or major side branches was considered significant. A few patients with minimal coronary artery disease were included in the group with normal angiograms, but in general the angiographic distinction between the 2 groups was definite and without disagreement between the 2 observers. The extent of cardiac disease was determined according to the number of main vessels or major side branches with stenoses.

Long-Term Follow-Up
End points were cardiac events, defined as reoccurrence of nonfatal myocardial infarction (ICD9, Code 410), cardiac death and readmission for unstable angina (ICD9, Code 411), and based on a systematic and detailed review of the hospital charts on deaths (via the National Death Registry) and readmissions. All the patients were living in the catchment area of our hospital, and follow-up was complete for the whole study population.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 121)</th>
<th>NonCAD Patients (n = 25)</th>
<th>CAD Patients (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>65 (41–90)</td>
<td>66 (42–90)</td>
<td>64 (41–88)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>38 (31)</td>
<td>9 (36)</td>
<td>29 (30)</td>
</tr>
<tr>
<td>60–70</td>
<td>47 (39)</td>
<td>7 (28)</td>
<td>40 (42)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>36 (30)</td>
<td>9 (36)</td>
<td>27 (28)</td>
</tr>
<tr>
<td>Body mass index, weight/height</td>
<td>26.0±0.3</td>
<td>26.0±0.3</td>
<td>26.0±0.3</td>
</tr>
<tr>
<td>Never smokers</td>
<td>42 (35)</td>
<td>16 (64)</td>
<td>26 (27)</td>
</tr>
<tr>
<td>Smokers</td>
<td>79 (65)</td>
<td>9 (36)</td>
<td>70 (73)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>22 (18)</td>
<td>3 (12)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>57 (47)</td>
<td>6 (24)</td>
<td>51 (53)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>49 (40)</td>
<td>7 (28)</td>
<td>42 (44)</td>
</tr>
<tr>
<td>Treated hypercholesterolemia</td>
<td>31 (26)</td>
<td>2 (8)</td>
<td>29 (30)</td>
</tr>
<tr>
<td>Cholesterol &gt;7 mmol/L (untreated patients)</td>
<td>18 (15)</td>
<td>5 (20)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (9)</td>
<td>3 (12)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (26)</td>
<td>6 (24)</td>
<td>26 (27)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>57 (47)</td>
<td>8 (32)</td>
<td>49 (51)</td>
</tr>
<tr>
<td>Current use of acetylsalicylic acid</td>
<td>92 (76)</td>
<td>14 (56)</td>
<td>78 (81)</td>
</tr>
<tr>
<td>Use of dicoumarol</td>
<td>11 (9)</td>
<td>1 (4)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>56 (46)</td>
<td>0</td>
<td>56 (58)</td>
</tr>
<tr>
<td>Prior bypass surgery</td>
<td>24 (20)</td>
<td>0</td>
<td>24 (25)</td>
</tr>
<tr>
<td>Prior coronary angioplasty</td>
<td>19 (16)</td>
<td>0</td>
<td>19 (20)</td>
</tr>
</tbody>
</table>

Percentages in parenthesis if not otherwise stated. CAD indicates coronary artery disease. For statistical analysis, see Results and Tables 3 and 4.

### Statistical Analysis

Data are presented as mean±SEM. Student’s t test was used when comparing means, and Yates corrected χ² or Fisher’s exact test for analysis of 2×2 tables. Univariate and multivariate logistic regression analysis (SPSS version 6.1 for Windows) were performed to assess the influence of various variables on coronary artery disease (normal/abnormal). Change in estimate method was used to assess possible confounders. If OR of serotonin for CAD was reduced by <10%, the variable was not included as a confounder. However, age, smoking, hypertension, history of CAD, hypercholesterolemia, and current use of acetylsalicylic acid were always included. A multivariate analysis with the Cox proportional hazards model (SPSS version 6.1 for Windows) was performed to assess the association of serotonin with cardiac events during follow-up period. Inclusion of possible confounders was performed according to the same principles as in the logistic regression analysis. Kaplan-Meier method was used to evaluate differences in event-free survival between patients with high/low values around the mean (cut-point 1000 nmol/l) of serotonin. Differences were considered significant with 2-sided values of P<0.05.

### Results

Patient Characteristics
Table 1 shows the demographic and clinical variables for the 121 patients. There were significantly more ex-smokers among patients with coronary artery disease (P<0.01), and more patients were taking medication for hypercholesterolemia (P<0.05) compared with patients without coronary
stenosis. None of the patients with normal angiograms had a history of myocardial infarction or coronary invasive cardiological or surgical procedures.

Serotonin and Platelets
Total serotonin levels and the number of platelets were significantly higher among patients who had coronary artery disease compared with those with normal angiograms (Table 2). The subgroup with previous myocardial infarction did not have higher serotonin levels or platelet counts than patients with coronary stenosis alone. The univariate relation between total serotonin and platelet count is shown in Figure 1, r=0.55, P<0.001.

Figure 2 shows mean values and 95% CI for serotonin in patients with and without coronary artery disease according to 3 age groups. The difference in serotonin level was most striking <60 years of age (P<0.001); in the groups 60 to 70 years and >70 years the difference was steadily reduced and became nonsignificant.

In the lowest to highest age groups of patients with coronary artery disease, the platelet counts (10^9/L PRP) were 351±58 (P=0.008 versus nonCAD group), 296±11, and 273±18, respectively. In nonCAD patients, there was no significant difference in total serotonin and platelet count among the age groups.

Table 2. Total Serotonin and Platelet Count in Subgroups of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Serotonin (nmol/L PRP)</th>
<th>Platelet Count (10^9/L PRP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonCAD</td>
<td>842±58</td>
<td>256±14</td>
</tr>
<tr>
<td>(n=25)</td>
<td>(726–958)</td>
<td>(228–284)</td>
</tr>
<tr>
<td>CAD all</td>
<td>1054±51*</td>
<td>308±9*</td>
</tr>
<tr>
<td>(n=96)</td>
<td>(952–1156)</td>
<td>(290–326)</td>
</tr>
<tr>
<td>CAD AP</td>
<td>1048±71*</td>
<td>306±13*</td>
</tr>
<tr>
<td>(n=40)</td>
<td>(883–1139)</td>
<td>(280–332)</td>
</tr>
<tr>
<td>CAD MI</td>
<td>1058±72*</td>
<td>310±13*</td>
</tr>
<tr>
<td>(n=56)</td>
<td>(914–1202)</td>
<td>(284–336)</td>
</tr>
</tbody>
</table>

Values given are mean±SEM. Numbers in parentheses are 95% confidence limits.

*Significance versus nonCAD group (P<0.01).

MI indicates myocardial infarction; AP, angina pectoris; and PRP, platelet rich plasma.

Serotonin and Conventional Risk Factors
Table 3 shows the unadjusted and adjusted OR for CAD comparing individuals with serotonin ≥1000 nmol/L PRP with individuals with lower serotonin values.

Serotonin remained significantly associated with CAD after adjustment for the conventional risk factors age, hypertension, diabetes, hypercholesterolemia, smoking, and family history of cardiac disease. When platelet count (cut-point 325 10^9 /L PRP) was included in the multivariate analysis, high serotonin was associated with a 3.7-fold (1.0 to 15.1, P=0.054) risk for CAD. The univariate OR of platelet count was 3.0 (1.0 to 9.5), P=0.059, and adjusted OR 1.0 (0.02 to 4.2), P=1.00, increasing to 2.0 (0.6 to 7.0, P=0.296) when serotonin was excluded from the multivariate analysis.

In patients <70 years (n=82), the association between serotonin and coronary artery disease was strengthened (Table 4). If platelet count was included in the multivariate analysis, OR of serotonin for CAD rose from 15.3 (1.6 to 147.6) to 20.3 (1.6 to 249.8). There was no association between platelet count and coronary artery disease in this subgroup.

Serotonin and Extent of Coronary Artery Disease
In Table 5 the CAD group is divided according to single (26%) or multivessel disease (74%). Among the patients in the lower quartile of serotonin values, the highest percentage of patients were found in the group with no coronary artery disease. In the same quartile, there was a steady decreasing percentage of patients with single vessel disease compared with patients with multivessel disease.

Long-Term Follow-Up
During the mean follow-up period of 44±15 (SD) months, 11 cardiac events occurred and all events were in patients with CAD. Four patients suffered a nonfatal acute myocardial infarction, 2 suffered cardiac deaths, and 6 were admitted for unstable angina. Mean time for an event to happen was 24 months, range 1 to 45 months.

In a multivariate Cox regression analysis, adjusting for conventional risk factors and use of acetylsalicylic acid, hazard ratio of serotonin (high/low values, cut-point 1000

Figure 2. Mean serotonin in CAD patients in various age groups compared with patients with normal angiograms (nonCAD). Age group <60 years comprises 38 patients; the group 60 to 70 years,47; and the group >70 years, 36.

Serotonin and Coronary Artery Disease
nmol/L) was 2.6 (0.7 to 9.6), \( P = 0.14 \). Age was significantly associated with occurrence of cardiac events \( (P = 0.04) \), and hazard ratio of current smoker was 5.7 (1.3 to 26.2), \( P = 0.02 \). In patients <70 years \( (n = 82) \), hazard ratio of serotonin increased to 12.3 (1.2 to 122.4), \( P = 0.03 \).

Figure 3 shows a Kaplan-Meier plot with event-free curves for CAD-patients <70 years, \( n = 82 \), suggesting a better prognosis with regard to cardiac events for patients with low serotonin (log rank test, \( P = 0.046 \)) during a mean of 3.7 years of follow-up.

**Discussion**

This study suggests that serotonin is associated with coronary artery disease. The association between serotonin and coronary stenosis remained significant after adjustment for confounders and seemed to be more important in the younger age groups. Our patients had stable symptoms allowing serotonin determination under basal conditions. The result was further strengthened by the finding that serotonin was related not only to the presence but also to the extent of coronary artery disease and with cardiac events during follow-up.

Clinical studies have shown that blood platelet count and function are related to total and cardiovascular death during long-term follow-up. A significant correlation between blood platelets and total serotonin levels. When blood platelets were adjusted for in our statistical analysis, the relationship between serotonin and coronary artery disease was somewhat attenuated. In contrast, the relationship between platelets and coronary artery stenosis demonstrated in the univariate analysis disappeared completely after adjustment with serotonin in the multivariate analysis. Current use of acetylsalicylic acid, which has important effects on platelet function and serotonin secretion, was also adjusted for but did not weaken the association of serotonin with coronary disease.

The important role that serotonin plays in initiating thrombosis and vasoconstriction has been extensively studied in an animal model. In the early experiments, it was shown that the specific serotonin inhibitor ketanserin protected against the cyclic flow variations at the site of coronary stenosis. The serotonin concentration at the stenosis site is elevated and causes platelet aggregation and vasospasm which are the main mediators of the reduced flow. Thromboxane A\(_2\) has been shown to act synergistically with serotonin to cause vasoconstriction, platelet aggregation, and reduction in blood flow. In the animal models, endothelial injury was created to induce cyclic flow variations. However, serotonin itself

**TABLE 3. Logistic Regression Analysis With Normal/Abnormal Coronary Arteries as Dependent Variable**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients 0/1</th>
<th>Univariate OR (95% CI) P</th>
<th>Adjusted OR (95% CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (=1000 vs &lt;1000)</td>
<td>72/49</td>
<td>3.38 (1.17–9.76) 0.024</td>
<td>3.84 (1.12–13.11) 0.032</td>
</tr>
<tr>
<td>Age, y</td>
<td>72/49</td>
<td>0.98 (0.94–1.02) 0.370</td>
<td>1.03 (0.98–1.09) 0.231</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>72/49</td>
<td>2.91 (1.11–7.61) 0.029</td>
<td>2.41 (0.77–7.57) 0.131</td>
</tr>
<tr>
<td>Smoker</td>
<td>42/79</td>
<td>4.79 (1.88–12.16) 0.001</td>
<td>3.78 (1.34–10.68) 0.012</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>32/89</td>
<td>1.18 (0.42–3.30) 0.756</td>
<td>0.92 (0.27–3.07) 0.889</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>110/11</td>
<td>0.67 (0.16–2.72) 0.572</td>
<td>1.23 (0.22–6.88) 0.812</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>64/57</td>
<td>2.32 (1.03–5.23) 0.043</td>
<td>2.61 (0.97–7.05) 0.058</td>
</tr>
<tr>
<td>Current use of acetylsalicylic acid</td>
<td>29/92</td>
<td>3.40 (1.33–8.73) 0.011</td>
<td>4.30 (1.37–13.53) 0.013</td>
</tr>
</tbody>
</table>

All variables except age (continuous) are binary variables. *See Methods for classification. \( n = 121 \).

**TABLE 4. Logistic Regression Analysis in Patients <70 Years With Normal/Abnormal Coronary Arteries as Dependent Variable**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients 0/1</th>
<th>Univariate OR (95% CI) P</th>
<th>Adjusted OR (95% CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (=1000 vs &lt;1000)</td>
<td>46/36</td>
<td>13.79 (1.71–111.30) 0.014</td>
<td>15.29 (1.58–147.60) 0.018</td>
</tr>
<tr>
<td>Age, y</td>
<td>34/48</td>
<td>1.04 (0.96–1.13) 0.316</td>
<td>1.08 (0.97–1.19) 0.169</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>34/48</td>
<td>3.10 (0.93–10.27) 0.065</td>
<td>2.15 (0.44–10.59) 0.347</td>
</tr>
<tr>
<td>Smoker</td>
<td>23/59</td>
<td>4.71 (1.41–15.70) 0.012</td>
<td>3.59 (0.78–16.45) 0.102</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>60/22</td>
<td>0.90 (0.25–3.23) 0.872</td>
<td>0.61 (0.11–3.40) 0.577</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>38/44</td>
<td>1.55 (0.62–3.84) 0.345</td>
<td>2.13 (0.64–7.12) 0.219</td>
</tr>
<tr>
<td>Current use of acetylsalicylic acid</td>
<td>14/68</td>
<td>3.64 (0.99–13.35) 0.051</td>
<td>4.99 (0.92–27.14) 0.063</td>
</tr>
</tbody>
</table>

All variables except age (continuous) are binary variables. *See Methods for classification. \( n = 82 \).
TABLE 5. Number of Patients According to Different Values of Serotonin (nmol/L PRP) Related to Number of Stenosed Coronary Arteries

<table>
<thead>
<tr>
<th>Serotonin Values</th>
<th>Degree of CAD</th>
<th>NonCAD (n=25)</th>
<th>1-vessel CAD (n=25)</th>
<th>Multivessel CAD (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower quartile</td>
<td>(&lt;800)</td>
<td>14 (56)</td>
<td>10 (40)</td>
<td>24 (34)*</td>
</tr>
<tr>
<td>Upper 3 quartiles</td>
<td></td>
<td>11 (44)</td>
<td>15 (60)</td>
<td>47 (66)</td>
</tr>
</tbody>
</table>

*P for trend = 0.057.
Values in parentheses are percentages.

may induce endothelial injury and thereby lay the groundwork for thrombosis.

The effects of serotonin as a mitogen could be of importance for the initiation or progression of vascular disease. Serotonin has growth-promoting effects both on vascular smooth muscle cells and endothelial cells, the effects depend on its concentration and duration of action. This may contribute both to the restenotic lesions seen after angioplasty procedures and to the proliferation that is found in the advancing native atherosclerotic lesions. Furthermore, in an experimental model the development of arteriosclerosis was preceded by an augmented vasoconstrictor response to serotonin.

Clinically, there is firm evidence for important actions of serotonin, although cardiovascular complications have not been convincingly reduced by ketanserin. Serotonin release during coronary angioplasty and infusion of serotonin at coronary angiography both have contributed to clinically relevant vasoconstriction in patients with coronary artery disease. The effects were seen with plasma levels of serotonin equivalent to those resulting from local platelet activation, and were blocked by ketanserin. In nonrandomized studies, administration of ketanserin has been reported to decrease mortality among patients with angiographically demonstrated coronary stenosis, and ketanserin also reduced mortality in patients with intermittent claudication and no medication of potassium loosing diuretics. In a small placebo-controlled study, ketanserin has been shown to prevent early restenosis, but a larger study failed to show effect on minimal lumen loss 6 months after angioplasty and did not significantly improve clinical outcome. However, there was a trend toward fewer events in the ketanserin group. There is also experimental evidence suggesting that a combination of serotonin receptor antagonist and a thromboxane A2 inhibitor may be useful for attenuation of restenosis.

Platelet count and platelet hyperreactivity have been associated with acute myocardial infarction and prognosis, and increased platelet serotonin has been detected in patients with clinically suspected coronary artery disease or myocardial infarction compared with controls. An experimental animal model also suggests that serotonin could be important for acute clinical syndromes showing that serotonin and thromboxane A2 receptor blockade protected against epinephrine-induced cyclic flow variation. In our study, serotonin adjusted for conventional risk factors was associated with acute cardiac events known to be precipitated by coronary thrombosis. Although the design of our cross-sectional study would neither observe transient rises in epinephrine and serotonin during acute chest pain, nor does it prove a causal relationship with coronary artery disease, the absolute levels during stable phases of the disease seem to be important for subsequent clinical exacerbation. Serotonin levels were not higher in patients with previous infarctions. There is no obvious explanation for this, but factors such as therapeutic or lifestyle changes after the infarction could play a role. Consumption of large platelets during the thrombotic process with subsequent decrease of serotonin levels is less likely to have occurred in our patients who had long-term symptomatic stability before blood sampling.

Age had an expected relationship with cardiac endpoints during follow-up. Whereas risk factors, such as cholesterol and homocysteine, normally have increasing blood levels with age, serotonin seems to be inversely related to age, having higher levels in younger age groups in which it also had a significant relationship with acute cardiac events. We have no clear explanation for this observation or for the reduction in serotonin with advancing age (also has been shown previously). However, because morbidity and mortality increase with age, and the finding that serotonin is most important in the younger age groups, the decline in serotonin with age may support the concept that it is not only a passive marker of coronary artery disease and cardiac events.

The stability of serotonin levels is an issue for the interpretation of our results. Only traces of serotonin are normally found in plasma where it is bound to proteins. The measurements of total serotonin in platelet rich plasma reflect both serotonin in platelets and the protein bound contents in the circulation. Serotonin levels vary within a relatively wide range during the day and may show a modest reduction with age. There is also a gender difference with slightly higher levels in women than in men. In our male study population, blood was sampled at the same time in the day in all subjects and thus some possible confounders were avoided. It
has been shown that when sampled at the same time of the day, serotonin levels are stable over long periods of time.40 Factors associated with coronary artery disease and acute events are probably not exclusively either thrombogenic or atherogenic; there is evidence to support both effects for serotonin. High serotonin levels may also augment the effects of other platelet activation agonists39,43 and may thereby take part in the spontaneous aggregation and platelet hyperreactivity observed in patients with atherosclerotic disease.28,33,44,45 Thus we cannot exclude confounding by other substances that promote platelet activation like thromboxane A2, oxygen-derived free radicals, activated thrombin, ADP, tissue factor, fibroblast growth factor, fibrinogen, β-thromboglobulin, platelet factor 4, and platelet derived growth factor.46 The concentration of platelet aggregation inhibitors (prostacyclin, endothelium-derived relaxing factor, tissue plasminogen activator) has also been shown to be reduced at sites of vascular endothelium injury46 and may further contribute to increased platelet aggregation, thrombus formation, and vasospasm.

In conclusion, we found that total blood serotonin is associated with the presence of angiographically confirmed coronary artery disease and subsequent cardiac events, particularly in younger age groups and gives further evidence that serotonin is related to clinical disease.

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