Transcardiac Serotonin Concentration Is Increased in Selected Patients With Limiting Angina and Complex Coronary Lesion Morphology

Egerton K. van den Berg, MD, James M. Schmitz, MD, Claude R. Benedict, MD, Craig R. Malloy, MD, James T. Willerson, MD, and Gregory J. Dehmer, MD

Serotonin is released by activated platelets and may act as a mediator to initiate or sustain certain unstable syndromes of ischemic heart disease in humans. To determine whether or not serotonin concentration increases across the coronary bed in patients with severe, limiting angina, we measured central aortic and coronary sinus serotonin concentrations by a sensitive radioenzymatic assay in 39 patients with coronary artery disease and 13 patients with minimal or no coronary artery lesions as detected by arteriography. Although no difference existed in the mean aortic or coronary sinus serotonin concentrations between these two groups, elevated coronary sinus serotonin concentrations were detected in 23% of those with coronary artery disease. The coronary sinus and aortic serotonin concentration difference was greater in patients with significant coronary artery disease (0.6±6.62 ng/ml) compared with patients without significant coronary artery disease (−5.6±10.32 ng/ml) (mean±SD) (p<0.05). Further analysis revealed that patients with eccentric, irregular coronary artery lesions or intraluminal filling defects had a significantly elevated coronary sinus and aortic serotonin difference (3.1±5.54 ng/ml) compared with those with smooth concentric lesions (−1.9±6.61 ng/ml) (p<0.02). These data suggest that serotonin is released into the coronary circulation of some patients with coronary artery disease, especially those with frequent angina and complex coronary lesions. Although serotonin may be released in some patients with coronary artery disease, the specific pathophysiologic role of serotonin in the development or perpetuation of certain coronary syndromes in humans remains to be determined. (Circulation 1989;79:116–124)

Factors that initiate or sustain syndromes associated with acute myocardial ischemia in humans have not been defined completely. Speculation on the mechanisms responsible for the development of these syndromes has included consideration of certain humoral mediators whose effects may be augmented at sites of coronary endothelial injury and fixed atherosclerotic stenoses.1–3 Several lines of experimental data indicate that serotonin may be such a mediator. First, serotonin is released by activated platelets, and a close relation between platelet aggregation, thrombus formation, and the release of large amounts of serotonin into the coronary circulation has been established in a canine model.4,5 Second, serotonin concentrations are elevated at sites of fixed coronary artery obstruction and endothelial injury in certain experimental models, and the vasoconstrictor properties of serotonin are potentiated at the sites of endothelial injury.5–7 Finally, transient cyclic coronary blood flow alterations that can be established in severely stenosed canine coronary arteries with superimposed endothelial injury are prevented by a serotonin receptor antagonist and reestablished by the administration of serotonin.5,6,9 Serotonin may have similar effects in humans and, thus, be an important mediator of certain acute ischemic syndromes. Therefore, the purpose of this study was to evaluate alterations in
serotonin concentrations in the coronary circulation of humans and to determine whether or not there are any specific clinical or anatomic factors associated with increased transcardiac serotonin concentrations.

Materials and Methods

Patients

Blood samples for serotonin analyses were collected from the central aorta and coronary sinus in 52 patients (51 men, one woman) referred for cardiac catheterization and coronary arteriography. These patients were randomly selected from the total population referred to the laboratory for the evaluation of severe, limiting angina, or noncoronary conditions, such as valvular heart disease or atypical chest pain that could not be evaluated noninvasively. Therefore, the patients selected for study had either a high or low likelihood of coronary artery disease. Patients with acute (<24 hours) myocardial infarction and those in whom the catheterization procedure began after 1:00 PM were excluded. The latter criterion was necessary because of the time required for processing the serotonin samples after the procedure.

Thirty-nine patients (mean age, 59 ± 9.5 years) had coronary artery disease defined as the presence of at least one epicardial coronary artery having a luminal diameter narrowing of greater than 50% (Table 1). No patient in this group has stenosis confined to the right coronary artery. Six patients had disease of one vessel (five patients had stenosis in the left anterior descending; one patient had stenosis in the large circumflex marginal vessel), 18 had disease of two vessels, and 15 had disease of all three coronary arteries. Thirteen patients (mean age, 56 ± 10.1 years) had no significant coronary artery stenoses; eight had no coronary lesions detectable by angiography, two had a single coronary artery lesion less than 50% luminal diameter narrowing in a secondary branch of a major artery, and three had lesions less than 30% luminal diameter narrowing in a major artery. All patients were evaluated before coronary arteriography, and their symptoms were classified as either stable or unstable. Stable symptoms were defined by the presence of exertional chest pain typical for angina pectoris with symptoms remaining at a constant frequency and severity for the preceding 2 months. Some patients with stable angina had a variable threshold for their symptoms and occasional episodes of rest or nocturnal pain, but these episodes were infrequent and did not increase in number before the catheterization. Unstable symptoms were defined by the presence of episodes of typical ischemic chest pain with the frequency or severity of the pain or both increasing during the preceding 2 months. Patients with the recent onset of angina (<2 months in duration), recent prolonged episodes of angina (>30 minutes) without infarction, and those with angina developing after a recent (<4 weeks) myocardial infarction were considered to have unstable symptoms. Twenty-two of the 39 patients (56%) with coronary artery disease were active cigarette smokers; in contrast, 46% of those without coronary artery disease were smokers at the time of the study.

Because the withdrawal of antianginal medications can be associated with important symptomatic deterioration, no attempt was made to alter medications before the collection of the serotonin samples. Almost all patients were receiving one or more standard cardiac medications, including intravenous, oral, or topical nitrates (n = 39), β-adrenergic blockers (n = 20), or calcium antagonists (n = 41). Twenty-five patients were receiving aspirin, and one was receiving intravenous heparin at the time of study (Table 1). In addition, all patients were premedicated with oral diphenhydramine and chloralzepoxide approximately 30 minutes before the start of the cardiac catheterization procedure.

Blood Sample Collection

The femoral vein and artery were sequentially entered and cannulated with hemostatic sheaths. Through the femoral vein sheath, a 6.5F, 100-cm Simmons II polyurethane catheter (Torcon Green Cook, Bloomington, Indiana) was advanced over a guidewire into the right atrium. After removal of the guidewire and flushing with a small amount of saline containing heparin 2 units/ml, this catheter was positioned in the coronary sinus by a method previously described. The shape of this catheter allows it to be positioned easily in the coronary sinus with its tip resting approximately 2 cm within the coronary sinus. Respiration causes minimal

<table>
<thead>
<tr>
<th>TABLE 1. Clinical and Angiographic Characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Mean age (yr)</td>
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<tr>
<td>Sex (male/female)</td>
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<tr>
<td>Clinical presentation (n)</td>
</tr>
<tr>
<td>Stable angina</td>
</tr>
<tr>
<td>Unstable angina</td>
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<tr>
<td>Noncoronary problem</td>
</tr>
<tr>
<td>Atypical chest pain</td>
</tr>
<tr>
<td>Coronary anatomy (n)</td>
</tr>
<tr>
<td>No CAD</td>
</tr>
<tr>
<td>Minimal CAD</td>
</tr>
<tr>
<td>One-vessel disease</td>
</tr>
<tr>
<td>Two-vessel disease</td>
</tr>
<tr>
<td>Three-vessel disease</td>
</tr>
<tr>
<td>Left main disease</td>
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<tr>
<td>Prior coronary artery bypass graft surgery</td>
</tr>
<tr>
<td>Medications (n)</td>
</tr>
<tr>
<td>Nitrates</td>
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<tr>
<td>β-Adrenergic blockers</td>
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<td>Calcium antagonists</td>
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<tr>
<td>Aspirin</td>
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<tr>
<td>Smoking (n)</td>
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</table>

CAD, coronary artery disease.
movement of this catheter, and the position was
checked often by fluoroscopy to ensure stability. In
a similar fashion, a 110-cm 8F polyurethane pigtail
catheter was advanced through the femoral arterial
sheath over a guidewire. After removal of the wire
and flushing, it was positioned in the ascending
aorta just above the aortic valve. Three milliliters of
blood were gently aspirated from each catheter and
discarded. Then, simultaneously, 2-ml blood sam-
pies for the serotonin assay were collected from
each catheter by gentle aspiration into a plastic
syringe. Previously, we have shown that the sam-
ping of blood in this manner through a long catheter
does not cause an artifactual increase in serotonin
concentration.12 All samples were collected at
the beginning of the cardiac catheterization procedure
before systemic heparin administration or the injec-
tion of angiographic contrast media. After collect-
ton of the samples, hemodynamic measurements,
left ventriculography, and coronary arteriography
were performed. All samples were collected between
8:00 AM and 2:00 PM. Nitroglycerin was not admin-
istered routinely before coronary arteriography. To
assess the reproducibility of the sampling methods,
18 randomly selected patients had duplicate aortic
and coronary sinus samples obtained approximately
5 minutes after the first samples were collected. No
patient developed angina or important hemody-
namic alterations between the collection of the
duplicate samples. The first set of samples collected
was used for the calculation of the coronary sinus
and aortic serotonin differences described later.

Sample Preparation and Serotonin Assay

Samples were prepared for assay according to the
method of Benedict et al.4 Briefly, immediately
after aspiration, 2 ml whole blood was placed in a
plastic tube containing 90 μl 4% ethylenediamine
tetraacetic acid and 0.15% imipramine. Four micro-
grams of prostacyclin was added to this mixture.
Because prostacyclin is unstable in acidic solutions,
-a stock solution was made in 70% acetonitrile
solution and diluted when necessary in phosphate
buffer, pH 8.0, containing 5% albumin. This mix-
ture was spun in a refrigerated centrifuge at 120g for
10 minutes at 10°C to obtain platelet-rich plasma.
The platelet-rich plasma was transferred to another
tube containing a 9:1 sucrose:albumin “cushion” at
the bottom. This was spun in a refrigerated centri-
fuge at 3,000g to obtain platelet-poor plasma, which
was stored at -10°C for subsequent assay. Seroto-
nin was measured by the radioenzymatic assay
method of Hussain and Sole,13 modified by Bene-
dict et al4 as previously described. Results of the
assay are expressed in nanograms per milliliter. The
absolute sensitivity of this assay is 1.2 pg. The
interassay coefficient of variation is 3.75% as deter-
mined by an analysis of plasma samples repeated
six times during 6 days with six different assays.

Angiographic Evaluation

All coronary angiograms were interpreted by
three experienced angiographers who were unaware
of the results of the serotonin assays. Visual anal-
ysis and caliper measurements were used to assess
the percent luminal diameter narrowing. Each lesion
was assessed in two nearly orthogonal projections,
and the view showing the most severe compromise
in lumen caliber was used to determine the actual
lesion severity. Caliper measurements were made
primarily on lesions of intermediate severity (i.e.,
30–70%). These were performed with a back-
projected, magnified (×4) image on a cineangi-
ographic projector (CAP-35, General Electric). The
largest luminal diameter either immediately proxim-
al or distal to the area of stenosis was used to
define the normal vessel. Coronary angiograms
were reviewed simultaneously by the three observers
who each derived an independent interpretation of
the location and severity of the coronary lesions.
The interpretations were then disclosed, and a final
assessment was derived by a discussion among the
observers. Two groups were established based on
the presence or absence of significant coronary
artery stenoses as defined above. In addition to
defining the presence and severity of the coronary
lesions, the morphology of each lesion was evalu-
ated. Previous studies have suggested an associa-
tion between certain coronary lesion morphologies
and unstable coronary syndromes.14-19 Coronary
lesions were classified as either complex or simple
based on the presence or absence of certain mor-
phologic features. Patients were classified as having
a complex lesion if one or more of the following
characterized at least one major epicardial vessel or
large side branch: 1) an eccentric stenosis with a
narrow neck, overhanging edges, or scalloped bor-
ders; 2) sluggish antegrade flow through a severe
(i.e., >90%) stenosis; or 3) an intraluminal filling
defect consistent with a thrombus. Patients were
classified as having simple lesions if none of the
previous criteria was present. These patients typi-
-cally had concentric or eccentric lesions with smooth
surfaces and a broad neck. In this study, a con-
centric stenosis was defined as a symmetric nar-
rowing of a coronary artery with smooth or only slightly
irregular surface and an eccentric stenosis defined
as an asymmetric narrowing of the coronary artery.14
The eccentric coronary lesions were subdivided
further into those with smooth surfaces and a broad
neck and those having more convex intraluminal
obstructions with a narrow base or neck due to one
or more overhanging edges or surfaces that were
very irregular or scalloped.14 Intracoronary throm-
bus was defined as the presence of an ovoid,
spherical, or irregular intraluminal filling defect
located just distal to or within a coronary stenosis
and surrounded on three sides by contrast medium.17
Sluggish antegrade flow was considered present if
contrast filling and washout of the coronary artery
distal to the area of stenosis was delayed compared with that in the other coronary vessels.

Data and Statistical Analyses

Changes in serotonin concentrations across the coronary bed were assessed by determining the difference between the coronary sinus and aortic serotonin concentrations. In this format, a positive number reflects a coronary sinus serotonin concentration higher than the aortic value. All data are expressed as the mean ± SD. Differences between groups were evaluated by a t test for unpaired data or a nonparametric analysis (Mann-Whitney) if the variances of the two groups were dissimilar (Bartlett's test). A least squares linear regression analysis was used for the comparison of the duplicate aortic and coronary sinus samples. A p value less than 0.05 was considered significant.

Results

Validation of Sampling Methods

Platelet activation and serotonin release could occur during the aspiration of blood samples through long catheters. This could lead to an artifactual increase in the serotonin concentration or considerable variability of the measured values. Having established previously that the careful collection of blood samples through long catheters does not cause an artifactual change in serotonin concentration, we evaluated the reproducibility of our sampling methods in the present study by obtaining duplicate aortic and coronary sinus samples. The correlation between the aortic samples was excellent ($r=0.94, p<0.001$, SEE = 5.14 ng/ml) (Figure 1, left panel). Likewise, a significant correlation existed between the duplicate coronary sinus samples ($r=0.74, p<0.001$), although the standard error of the estimate was larger (12.3 ng/ml). This occurred because three values varied widely between the two determinations (Figure 1, right panel). The correlation coefficient for the duplicate coronary sinus serotonin concentrations without these three values was similar to the aortic comparison ($r=0.82, p<0.001$, SEE = 5.67 ng/ml).

Aortic and Coronary Sinus Serotonin Concentrations

The aortic and coronary sinus serotonin concentrations were compared in the patients with and without significant coronary artery disease (Figure 2). In those without coronary disease, the mean aortic serotonin concentration was 14.6 ± 10.49 ng/ml, and the mean coronary sinus serotonin concentration was 9.0 ± 7.36 ng/ml ($p=0.075$). Most of the individual patients in this group had a minimal variation in serotonin concentration across the coronary bed, and the remainder had substantial decreases. In the patients with significant coronary artery disease, the mean aortic serotonin concentration was 13.5 ± 13.62 ng/ml; this value was not different from the mean coronary sinus concentration of 13.4 ± 13.11 ng/ml. Neither the mean aortic nor coronary sinus concentration in the group with significant coronary artery disease was different from the corresponding value in the patients without coronary artery disease. However, in the group with coronary artery disease, several individual patients had substantial increases in the coronary sinus serotonin concentration, a pattern that was not observed in the subjects without significant coronary artery disease.

Coronary Sinus and Aortic Serotonin Concentration Difference

To characterize the change in serotonin concentration across the coronary bed, the coronary sinus and aortic serotonin concentration difference was determined for each patient (Figure 3). In those without significant coronary artery disease, the concentration difference was $-5.6 ± 10.32$ ng/ml, and in those with coronary artery disease, it was $0.6 ± 6.62$ ng/ml ($p<0.05$). Although there was considerable overlap between the two groups, the highest coro-
Coronary sinus and aortic serotonin concentration difference in the group without significant coronary artery disease was 2.94 ng/ml. With 3 ng/ml as a cutoff value, nine patients (23%) with significant coronary artery disease had a concentration difference above this value.

**Relation of Transcardiac Serotonin Concentration to Lesion Morphology and Symptoms**

Coronary lesion morphology in the patients with significant coronary artery disease also was evaluated, and each patient was classified as having complex or simple lesions as defined earlier. To test the hypothesis that serotonin release into the coronary circulation is associated with the presence of complex lesion morphologies, the coronary sinus and aortic serotonin concentration difference was compared in the patients with and without complex morphologies. Fifteen patients (38%) had at least one lesion with complex morphology; the mean concentration difference in this group was 3.1±5.54 ng/ml. This was significantly higher (p<0.02) than the concentration difference in patients with simple lesion morphologies (−1.9±6.61 ng/ml) (Figure 4).

There was no clear association between the presence of unstable symptoms and coronary sinus and aortic serotonin concentration differences. In the patients with significant coronary artery disease, 19 had unstable symptoms. The mean concentration difference in these patients was −1.2±6.06 ng/ml; this value was not significantly different from the value in patients with stable, but severe, limiting angina (1.3±7.05 ng/ml). However, irrespective of the presence or absence of unstable symptoms, the classification of lesion morphology appeared to be important. Ten patients had complex lesion morphologies and stable, though, very limiting angina.
The mean concentration difference in this subgroup was $3.8\pm6.69$ ng/ml. In contrast, the patients with simple lesion morphologies and stable symptoms ($n=10$) had a mean concentration difference of $-1.3\pm6.74$ ng/ml ($p=0.10$). The mean concentration difference in the 14 patients with unstable symptoms and simple lesion morphologies was $-2.3\pm6.73$ compared with $1.7\pm1.67$ ng/ml in the five patients with complex lesion morphologies and unstable symptoms ($p=0.09$).

**Relation to Smoking**

The relation of smoking to the coronary sinus and aortic serotonin concentration difference was evaluated in the groups with and without coronary artery disease. In those without coronary artery disease, the concentration difference was $-9.0\pm13.8$ ng/ml in smokers compared with $-2.7\pm2.2$ ng/ml in the non-smokers (NS). Similarly, there was no difference in the concentration difference in those with coronary artery disease ($-0.7\pm5.4$ in smokers vs. $0.3\pm7.8$ ng/ml in non-smokers).

**Use of Aspirin and Other Medications**

Because it was not possible to withdraw or precisely control all medications before the collection of the samples, the frequency of use of certain medications in the groups with different coronary morphologies was determined. There were no differences in the use of calcium antagonists or $\beta$-blockers between the groups (Table 2). A smaller percentage of the patients without coronary artery disease were receiving nitrates, but this was not statistically significant ($p=0.08$). However, a greater percentage of the patients with simple lesion morphologies (67%) were receiving aspirin compared with the other two groups ($p=0.008$). To determine whether or not aspirin consumption, in general, caused a detectable change in serotonin concentration, aortic and coronary sinus serotonin values, as well as the coronary sinus and aortic serotonin concentration difference, were compared in patients who were and were not receiving aspirin (Table 3). There were no differences in either the mean aortic or coronary sinus serotonin concentrations between the patients who were and were not receiving aspirin. These values were compared separately in those with and without coronary disease, and no detectable differences could be found between the groups. When patients with and without coronary artery disease were considered together, those taking aspirin ($n=25$) had a lower concentration difference than those not taking aspirin ($n=27$). However, when only those with coronary artery disease were considered, there was no difference in the

<table>
<thead>
<tr>
<th>Medication</th>
<th>No CAD (%)</th>
<th>Simple (%)</th>
<th>Complex (%)</th>
</tr>
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<tbody>
<tr>
<td>Calcium antagonists*</td>
<td>62</td>
<td>83</td>
<td>80</td>
</tr>
<tr>
<td>$\beta$-Blockers*</td>
<td>31</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>Nitrates†</td>
<td>23</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Aspirin‡</td>
<td>38</td>
<td>67</td>
<td>20</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease.

*Not significant; †No CAD, less than other groups ($p=0.008$); ‡simple greater than other groups ($p=0.008$).

**TABLE 3. Effect of Aspirin on Serotonin Concentration**

<table>
<thead>
<tr>
<th>Serotonin concentration (ng/ml)</th>
<th>Aspirin</th>
<th>No aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central aorta</td>
<td>$14.2\pm16.46$</td>
<td>$13.9\pm18.40$</td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>$14.8\pm15.34$</td>
<td>$11.8\pm10.45$</td>
</tr>
<tr>
<td>CS-Ao serotonin concentration difference (ng/ml)</td>
<td>All patients ($n=52$)</td>
<td>$-3.79\pm8.83$</td>
</tr>
<tr>
<td></td>
<td>Patients with CAD ($n=39$)</td>
<td>$-1.39\pm5.49$</td>
</tr>
</tbody>
</table>

CS, coronary sinus; Ao, central aorta; CAD, coronary artery disease.
concentration difference between those receiving and not receiving aspirin (Table 3). A meaningful subgroup analysis of patients with simple and complex lesions who were and were not receiving aspirin was not possible because there were too few patients in some of the groups.

Discussion

Numerous experimental and clinical findings have led to speculation regarding the mechanisms that cause unstable angina and their link to the pathogenesis of acute myocardial infarction.1–3,20–22 Hemodynamic, rheologic, and vasomotor stresses may damage atherosclerotic plaques, and such damage may initiate the local release of vasoconstrictor and thrombogenic substances or an imbalance between these substances and intrinsic vasodilating and antithrombotic mediators. In some patients, these interactions may cause the development of an intraluminal thrombus or coronary artery constriction. Evolution of this process to complete coronary occlusion may result in worsening angina or the onset of myocardial infarction.

Role of Serotonin

Considerable experimental evidence indicates that serotonin may have a role in this process,4,5,7–9,23 and this concept has been enhanced by recent clinical observations.24 It has been shown that aliquots of coronary sinus plasma from patients with coronary artery disease cause constriction of isolated canine coronary artery rings, whereas systemic arterial and venous samples from the same patient and coronary sinus samples from patients without coronary artery disease do not.24 Many pharmacologic interventions were tested against this action, and only a serotonin receptor antagonist prevented constriction of the coronary artery rings.24 Although serotonin was not measured directly, these bioassay data indicated that serotonin was important. Moreover, these data suggest that the amount of serotonin released into the coronary sinus is sufficient to have physiologically demonstrable effects.

In this study, we have shown that 23% of the patients with coronary artery disease have a coronary sinus and aortic serotonin concentration difference that is greater than the highest value in those without coronary artery disease. The appreciation of transcardiac alterations in serotonin concentration could be affected by several technical factors related to the sampling methods. For example, a greater variability was noted in the serotonin concentration values obtained from the coronary sinus. This occurred despite a stable catheter position within the coronary sinus and may reflect the incomplete mixing of blood from the various tributaries entering the coronary sinus. Furthermore, it is possible that serotonin is released into the coronary sinus sporadically as platelets aggregate. This coupled with incomplete mixing could result in a failure to detect release of serotonin into the coronary circulation and contribute to an underestimation of the number of patients actually having serotonin production. A few patients had extremely negative coronary sinus and aortic serotonin concentration differences. Whether or not this is related to the variability of the sampling process, the dilution of serotonin in the coronary effluent, or the actual degradation of serotonin as it passes through the myocardial capillary bed cannot be determined by this study.

Relation of Serotonin to Lesion Morphology

Previous studies have shown that certain coronary lesion morphologies occur more often in patients with unstable angina and acute myocardial infarction. Specifically, eccentric coronary artery stenoses with narrow necks, overhanging edges, or scalloped surfaces, and stenoses associated with intraluminal filling defects have been noted with increased frequency.14–19 Our data show that patients who have lesions with one or more complex morphologic features have coronary sinus and aortic serotonin concentration differences that are significantly higher compared with those who have simple coronary lesion morphologies. There is some overlap between these groups, which could occur for several reasons. Arteriography may fail to detect the presence of all lesions with complex morphologic features. Recently, coronary angiography has been used to visualize the morphology of coronary artery lesions in patients with unstable angina.20 Although arteriography correctly identified the absence of complex lesions, it detected only one of four complex plaques and one of seven thrombi detected by angioscopy. Therefore, some patients with elevated coronary sinus and aortic serotonin concentration differences and simple lesion morphology as detected by arteriography may actually have complex lesions. Conversely, all lesions with complex features may not necessarily be responsible for the release of serotonin at the exact time that we sampled coronary sinus blood. Finally, there is the possibility that serotonin is present in high concentrations at the sites of such complex lesions yet not detected in the coronary sinus blood because of dilution, sampling errors, or failure to be released from the local site in substantial amounts.

Relation of Serotonin to Symptoms

In the patients we studied with coronary disease, we did not establish an association between an elevated coronary sinus and aortic serotonin difference and unstable symptoms. Because many of the episodes of ischemia in patients with coronary artery disease may be silent,26 the lack of symptoms in some patients may not be an accurate indicator of the absence of ischemia. Moreover, the occurrence of pain in patients with unstable symptoms may not always be due to platelet activation and the release of serotonin or other mediators. Spontaneous alterations in coronary artery tone and small changes in
myocardial oxygen demand in patients with severe stenoses also could cause pain to occur.

Effect of Smoking and Medications

There was no obvious relation between smoking and the serotonin values measured. The concurrent administration of aspirin and other medications having platelet effects is a confounding variable in the interpretation of these data. Because approximately one half of the patients with coronary artery disease had unstable symptoms, the withdrawal of all medications before the study was not possible. There were no differences in the frequency of use of calcium antagonists and β-blockers between the groups, but a greater percentage of patients with simple coronary lesion morphology were receiving aspirin. The relation of this observation to the lower coronary sinus and aortic serotonin concentration differences in this group is uncertain. The aortic and coronary sinus serotonin concentrations as well as the coronary sinus and aortic serotonin concentration difference were compared in those patients who were and were not receiving aspirin to determine whether or not aspirin caused major changes in the serotonin concentrations. Although no detectable changes could be shown in the various subgroups, it is still possible that aspirin could have some physiologically important effect on the serotonin release from platelets. Because all patients received the same premedications at approximately the same time before the study, it is unlikely that these would have altered the results substantially even though antihistamines could possibly alter serotonin production. Although some of these medications may affect the serotonin concentrations, the results of this study will more closely approximate the clinical situation because most patients with coronary artery disease will be receiving medications a long-term basis.

Clinical Implications

The present study suggests that serotonin release occurs in some patients with important coronary artery disease, especially those with complex coronary lesions that could act as a nidus for platelet activation. Although serotonin release was not detected in every patient, it is possible that the concentration of serotonin was elevated locally around the stenotic site and not detected in the coronary sinus. The finding of an elevated coronary sinus and aortic serotonin concentration difference in some patients with coronary artery disease and an association between these values and complex coronary artery morphology does not prove that the increased transeardiac serotonin concentrations detected are important physiologically. Further studies are necessary to define the role of serotonin in acute ischemic syndromes, but these data are consistent with a hypothesis that serotonin may play an important pathophysiologic role in sustaining certain ischemic heart syndromes in some patients.

Acknowledgments

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References


**KEY WORDS** • serotonin • unstable angina • coronary artery disease • platelets
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