Effect of activation of the H<sub>1</sub> receptor on coronary hemodynamics in man

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ABSTRACT  We evaluated the effects of selective activation of H<sub>1</sub> receptors on coronary hemodynamics in 16 patients divided into two groups: group A, 11 patients with atypical angina or valvular heart disease and normal coronary arteries, and group B, five patients with spontaneous angina, four of whom had significant (>70% stenosis) coronary artery disease and one with normal coronaries. Selective H<sub>1</sub> receptor stimulation was achieved by infusing 0.5 μg/kg/min of histamine intravenously for 5 min after pretreatment with cimetidine (25 mg/kg). Heart rate was maintained constant (100 beats/min) by coronary sinus pacing and coronary blood flow (CBF) was measured by thermodilution. In group A, during histamine infusion mean aortic pressure fell from 99 ± 5 to 77 ± 4 mm Hg (mean ± SEM, p < .001), coronary vascular resistance (CVR) decreased from 1.07 ± 0.17 to 0.82 ± 0.14 mm Hg/ml/min (p < .02), and CBF and myocardial oxygen consumption remained unchanged. None of the patients in this subgroup developed angina during histamine infusion. In group B, while no significant average changes in mean arterial pressure, CVR, or CBF were observed, two of the five patients (40%) developed angina during histamine infusion, accompanied by ST-T elevation, a decrease in CBF, and an increase in CVR. In one of these two patients circumflex coronary arterial spasm was angiographically demonstrated during histamine-induced angina. Our results suggest that stimulation of the H<sub>1</sub> receptor induces a reduction of CVR, probably resulting from vasodilation of small coronary resistance vessels. In a considerable percentage of patients with vasospastic angina with or without coronary artery disease, however, H<sub>1</sub> receptor-induced vasoconstriction of large capacitance coronary arteries may prevail over peripheral vasodilatation. These findings contribute to our understanding of the pathophysiological effects of histamine on CBF in man and may have practical relevance in patients undergoing treatment with H<sub>2</sub> receptor-blocking drugs.

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HISTAMINE is a biological amine, widely distributed in many organs and tissues of mammals, that has effects on cardiac chronotropism, dromotropism, inotropism, and bathmotropism that have been well characterized and attributed to the activation of specific H<sub>1</sub> or H<sub>2</sub> receptors.1

Recent studies have demonstrated the presence of coronary vasodilating H<sub>1</sub> receptors and vasoconstricting H<sub>1</sub> receptors; however, the pathophysiological role of coronary H<sub>1</sub> and H<sub>2</sub> receptors in man is still not well characterized. Studies in vitro on epicardial coronary arterial strips from patients undergoing heart transplantation have confirmed the presence of vasoconstricting H<sub>1</sub> receptors and vasodilating H<sub>2</sub> receptors in man.4 Ginsburg et al.5 have proposed that the stimulation of H<sub>1</sub> receptors in large conductance coronary arteries may induce coronary arterial spasm in some patients with variant angina.

Although the participation of histamine as a chemical mediator of cardiovascular responses has yet to be proven, the systemic release of histamine during immunologic and nonimmunologic reactions is associated with significant cardiovascular changes,6,7 and occasionally with myocardial ischemia8,9 and infarction.10,11 Furthermore, it has been shown that the human heart contains a significant amount of histamine that can be released under appropriate circumstances.12 In addition, histamine released during anaphylactoid reactions might induce deleterious coronary constriction in patients with coronary artery disease being treated with H<sub>2</sub>-blocking drugs.2

These observations have stimulated our interest in investigating the effects of selective activation of H<sub>1</sub> receptors on coronary hemodynamics in man.

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Methods

The study population was divided in two groups (A and B) according to the clinical characteristics of the patients (table 1). Group A was composed of 11 patients, three men and eight women, with a mean age of 46 ± 3 years, who underwent cardiac catheterization and coronary arteriography because of a history of atypical chest pain (nine patients) or for valvular heart disease (two patients). All nine patients with atypical chest pain in this group had borderline exercise stress test results and normal coronary arteries and in each an ergonovine test, performed before coronary arteriography, was negative. Group B was composed of five patients, all men, with a mean age of 47 ± 5 years, who underwent coronary arteriography because they had experienced severe repeated episodes of spontaneous angina within 2 weeks before the study, requiring admission to coronary care unit. No patient had, on admission, electrocardiographic or enzymatic evidence of acute myocardial infarction. Patients 12 and 16 had typical episodes of spontaneous angina with ST elevation in leads II, III, and aVF; patients 13 and 14 had a history of typical effort angina with additional episodes, in the 2 weeks preceding admission, of spontaneous chest pain with ST elevation in leads II, III, and aVF; patient 15 had spontaneous angina only with ST elevation in leads V1–V3. In all patients anginal symptoms were successfully treated with intravenous nitrates and calcium antagonists. However, all drugs were discontinued before our study for at least 5 days, with the exception of sublingual nitrates when required. However, no nitrates were administered to any patient within 12 h before the study. No patient had a history of allergy, peptic ulcer, pehoroecomcytoma, or chronic obstructive lung disease. The study protocol was approved by the Committee on Human Research of our institution and informed consent was obtained from each patient. Patients were studied in the morning after an overnight fast. No premedication was used. Before the procedure was initiated, patients were given 10 mg/kg oral cimetidine and then 15 mg/kg by intravenous injection over a 5 min period.

Hemodynamic measurements in patients were obtained by the Sones technique from the right arm. After the baseline hemodynamic measurements were obtained, a No. 7F Model CCS-7U-90B Wilton Webster coronary thermodilution catheter interfaced with a two-channel Wheatstone bridge was positioned in the coronary sinus with the proximal thermistor within the coronary sinus ostium. Catheter position was confirmed initially by injection of 2 to 3 ml of contrast medium in the coronary sinus and frequently rechecked throughout the procedure by fluoroscopy with reference to thoracic and spinal landmarks. An 18-gauge Teflon cannula was introduced into the right brachial artery for hemodynamic measurements and sampling. Pacing was initiated from the coronary sinus at a heart rate of 100 beats/min, and was maintained at this level for the entire length of the study. After allowing 5 min for stabilization, we measured baseline systolic, diastolic, and mean (MAP) systemic arterial pressures (mm Hg) and coronary sinus blood flow (CBF, ml/min). CBF was evaluated by injecting 20 ml of saline solution through the coronary sinus catheter with a constant infusion pump (60 ml/min). Pressures were measured with Statham P23dB transducers and thermistor signals were recorded on a OTE multichannel photographic recorder. CBF was calculated from the following relationship:

\[
CBF = \frac{60 \times (T_B - T_i) - 1 \times 1.08}{T_B - T_M}
\]

where \(T_B\), \(T_i\), and \(T_M\) represent temperature of blood, injectate, and blood-injectate mixture, respectively, and 1.08 is a constant obtained from the density and specific heat of blood and saline solution. Coronary vascular resistance (CVR) was estimated from the relationship \(CVR = MAP/CBF\), and expressed in millimeters of mercury per milliliter per minute.

In six patients (four from group A and two from group B) we also obtained baseline simultaneous samples of coronary sinus and brachial arterial blood for measurement of oxygen saturation with the use of an American Optical spectrophotometric oximeter. Oxygen content (ml%) was estimated from the following relationship: oxygen content = percent oxygen saturation \(\times\) hemoglobin (g%) \(\times\) 1.34/100. Myocardial oxygen consumption (MVO\(_2\), ml/min) was calculated as MVO\(_2\) = CBF \(\times\) (arterial – coronary sinus) oxygen content/100. Additional samples were obtained from the brachial artery in seven patients.

### TABLE 1

**Clinicoangiographic data on patients studied**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Clinical presentation</th>
<th>Angiographic diagnosis</th>
<th>Coronary spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37/M</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>51/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30/F</td>
<td>Mild mitral regurgitation</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>52/M</td>
<td>Mitral-aortic valve disease</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>56/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33/M</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>56/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>60/F</td>
<td>Atypical chest pain</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>34/M</td>
<td>Spontaneous angina</td>
<td>90% stenosis of RCA</td>
<td>During coronary arteriography (RCA)</td>
</tr>
<tr>
<td>13</td>
<td>56/M</td>
<td>Effort and spontaneous angina</td>
<td>90% stenosis of RCA; 50% stenosis of LAD</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>56/M</td>
<td>Effort and spontaneous angina</td>
<td>90% stenosis of RCA</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>50/M</td>
<td>Spontaneous angina</td>
<td>90% stenosis of LAD</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>38/M</td>
<td>Spontaneous angina</td>
<td>Normal coronary arteries</td>
<td></td>
</tr>
</tbody>
</table>

RCA = right coronary artery; LAD = left anterior descending artery; Cx = circumflex coronary artery.
(five of group A and two of group B) for measurement of plasma catecholamines, which were assayed by techniques described elsewhere.\(^\text{14}\) After baseline values were obtained, we infused histamine intravenously for 5 min at the rate of 0.5 \(\mu\)g/kg/min via a constant-infusion pump, while continuously monitoring arterial pressure and at least two electrocardiographic leads (generally I and III). After 2 min of histamine infusion, we repeated all hemodynamic measurements and sampling. After 5 min the infusion was interrupted, and all measurements were again obtained after 5 min. Subsequently, coronary sinus pacing was discontinued and diagnostic angiography was carried out successfully in all patients. While all 11 patients in group A had normal coronary arteries, four of the five patients of group B had significant coronary artery disease, defined as greater than 70% luminal diameter reduction of a major coronary artery (table 1). Four of the five patients had evidence of coronary spasm: two patients (14 and 16) during the histamine infusion study, both of the circumflex coronary artery; and two patients (12 and 15) who did not develop coronary spasm during the course of histamine infusion, but in whom it spontaneously occurred during the course of the diagnostic coronary arteriography that followed the histamine study protocol. Patient 12 presented with spasm of the right coronary artery and patient 15 with that of the left anterior descending coronary artery. Both cases of spasm were angiographically demonstrated, were accompanied by chest pain and ST elevation on the corresponding electrocardiographic leads, and were immediately resolved by sublingual nitrates. Both episodes occurred between 30 and 60 min after the end of the histamine infusion.

Statistical analysis was performed by Student’s t test for paired samples.

Results

Complaints and complications. All patients developed typical cutaneous flush and pulsating headache during histamine infusion. Patient 12 had mild throat constriction not accompanied by ST-T changes on the electrocardiogram. At the second minute of histamine infusion patient 14 complained of mild retrosternal pain that was associated with ST elevation in lead III, a slight increase in MAP, a decrease in CBF, and an increase in CVR (table 2). When the infusion of histamine was immediately stopped, chest pain quickly disappeared and ST segment elevation as well as coronary hemodynamics returned to normal. During the second minute of histamine infusion, patient 16 complained of crushing substernal pain accompanied by ST segment elevation in lead III, a fall in MAP and CBF, and an increase in CVR (table 2). In this patient angiographic visualization of the left coronary artery through a Sones catheter previously positioned at the left coronary ostium during the episode of histamine-induced angina revealed a 100% occlusion of the circumflex coronary artery and a diffusely decreased caliber of the left anterior descending and of the right coronary artery, without segmental spasm of these latter two vessels. After discontinuation of histamine infusion and injection of 200 \(\mu\)g of nitroglycerin into the left coronary artery, subjective symptoms quickly disappeared and the ST segment in lead III returned to baseline. Repeated coronary arteriographic examination in this patient after the resolution of pain demonstrated a completely normal coronary arterial tree. None of the other patients presented with chest pain or electrocardiographic changes suggestive of ischemia during the histamine infusion. All subjective complaints promptly disappeared within 5 min of the end of the histamine infusion.

Hemodynamic data. Figure 1 shows the effects of histamine infusion (0.5 \(\mu\)g/kg/min) on coronary hemodynamics and MAP. Table 2 shows the individual values for hemodynamic parameters, MVO\(_2\), and cate-

![FIGURE 1. Effects of selective stimulation of H\(_1\) receptors (infusion of 0.5 \(\mu\)g/kg/min of histamine after cimetidine pretreatment) on MAP, CBF, and CVR in groups A and B. B = baseline; H = histamine infusion.](http://circ.ahajournals.org/)

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cholamine plasma levels before and during histamine infusion in group A and B patients. In group A, MAP decreased in all 11 patients (mean values 99 ± 5 to 77 ± 4 mm Hg, p < .001); CBF decreased in five, increased in four, and remained unchanged in two patients (mean values 122 ± 23 to 120 ± 20 ml/min, NS); and CVR decreased in nine patients, increased slightly in one, and remained practically unchanged in the other patient. Mean CVR decreased significantly from 1.07 ± 0.17 to 0.82 ± 0.14 mm Hg/ml/min (p < .02; table 2 and figure 1). MVO₂, measured in four patients in this group, decreased in three patients and increased in one patient (mean values 12.2 ± 5 to 9.9 ± 4 ml/min, NS); plasma epinephrine levels increased in all five patients in whom they were measured (mean values 50 ± 10 to 159 ± 32 pg/ml, p < .005), and plasma norepinephrine levels increased in all five patients (from 258 ± 49 to 523 ± 25 pg/ml; p < .001).

Of the five patients in group B, MAP decreased in four patients and increased slightly in one of the two patients (No. 14) who developed angina during histamine infusion (mean values 101 ± 8 to 89 ± 11 mm Hg, NS). CBF increased in three patients who did not develop angina during histamine infusion and decreased in the two patients (Nos. 14 and 16) who developed angina with ST changes during histamine infusion. Mean CBF values did not significantly change in this group (148 ± 19 to 164 ± 30 ml/min, NS). CVR increased in the two patients with histamine-induced angina but decreased in the other three patients. Mean CVR did not significantly change in this group (0.71 ± 0.08 to 0.61 ± 0.13 mm Hg/ml/min, NS; table 2 and figure 1). MVO₂, measured in only two patients of this group, decreased in patient 14, who developed angina during histamine infusion, and increased in one of the three patients without histamine-induced angina. Plasma levels of epinephrine and norepinephrine increased in both patients in this group in whom they were measured.

**Discussion**

**Stimulation of the H₂ receptor and systemic hemodynamics.** Our results show that the selective stimulation of H₂ receptors by exogenous histamine in man is associated with a significant decrease in arterial pressure, which can be explained by H₂ receptor–induced systemic arteriolar vasodilatation. Several studies have demonstrated that histamine infusion in man is associated with significant hypotension that is synergistically mediated by both H₁ and H₂ receptors. In agreement with the latter studies, our results suggest that even when H₂ receptors are blocked by cimetidine,
The administration of histamine produces a significant decrease in systemic arterial pressure. Although we did not measure plasma levels of cimetidine, the presence of H₂-receptor blockade in our patients was suggested by previous studies in man demonstrating that even doses of cimetidine smaller than that used in the present study were able to produce substantial cardiovascular H₂-receptor blockade.¹⁷

Interestingly, we have also documented a histamine-induced increase in plasma catecholamines. In a previous report we demonstrated that histamine infusion in man was associated with the systemic release of epinephrine and norepinephrine.¹⁴ The present study shows that this release is not prevented by H₂-receptor blockade. Whether epinephrine and norepinephrine release represents a sympathetic response to the acute fall in arterial pressure or a direct histamine effect on adrenal medulla was impossible to assess in the present study. One can speculate that both mechanisms might play a role, since experimental observations have shown that histamine is able to directly release catecholamines from the adrenal medulla and that this effect is mediated by H₁ receptors.¹⁶

Stimulation of the H₁ receptor and coronary hemodynamics in patients with normal coronary arteries and no vasospastic angina (group A). Although several clinical and experimental studies⁴, ⁵, ¹⁹ have suggested that histamine may influence the human coronary circulation, to our knowledge this is the first study demonstrating an effect in vivo of histamine on human coronary hemodynamics. Despite the fall in systemic arterial pressure, CBF (which is controlled by aortic pressure, CVR, and heart rate)²⁰ did not change. Since aortic pressure decreased while heart rate remained constant, the lack of change in CBF must have been the result of the reduction in CVR. It is unlikely that this reduction occurred secondary to an increased myocardial metabolic requirement since MVO₂, which is the principal regulator of CVR,²⁰ did not significantly change. These data also suggest that catecholamines were not responsible for the fall in CVR observed in our patients, since the predominant effect of catecholamines on coronary vasculature is a metabolically mediated peripheral vasodilatation,²¹ which prevails over a less relevant direct increase in large coronary arterial tone mediated by α-adrenergic receptors.²² In addition, it is unlikely that neurogenic reflexes triggered by hypotension were responsible for the observed fall in CVR; in fact, a reduction in carotid sinus pressure is associated with α-adrenergically mediated coronary vasoconstriction and an increase in CVR activated by baroreceptor reflexes.²³ Finally, coronary autoregulation, an intrinsic mechanism for preservation of coronary flow during hypotension,²⁴ cannot account for the reduction in CVR in our patients, since the variations of less than 15 ± 3 mm Hg observed are insufficient to induce autoregulatory changes of coronary circulation.²⁵ Furthermore, autoregulation cannot account for the increase in CBF, despite a fall in MAP, in four of the 11 patients in group A during histamine infusion.

We therefore hypothesize that the fall in CVR observed in our study was due, at least in part, to vasodilation of small resistance coronary vessels through the selective activation of coronary H₁ receptors. The pharmacologic basis of this interpretation resides in experimental studies demonstrating H₁ receptor-mediated coronary vasodilatation associated with an increase in CBF, a decrease in CVR, and no change in MVO₂.²⁵-²⁷ Our study is the first to extend these observations to the coronary circulation of man and suggests that H₁ receptors, presumably located in the small coronary resistance vessels, mediate a vasodilator response similar to what has been observed for other peripheral vessels.¹⁵, ¹⁶, ²⁸ However, it is possible that a reduction in extravascular coronary resistance, which is an important component of total coronary resistance,²⁹ may have contributed to the fall in total CVR during histamine infusion. Extravascular coronary resistance is mainly a function of left ventricular diastol-
ic pressure,29,30 and a histamine-induced decrease in left ventricular end-diastolic pressure has been previously reported.14 Finally, we cannot exclude the possibility that some unknown chemical mediator(s) released by stimulation of the H1 receptor might have been responsible for peripheral coronary dilatation.

**Coronary hemodynamic effects of activation of the H1 receptor in patients with vasospastic angina (group B).** The response of coronary hemodynamics to stimulation of the H1 receptor in patients with vasospastic angina (group B) depended on the occurrence of histamine-induced angina. In fact, in the three patients in this group who did not develop angina during histamine infusion, CBF increased and CVR decreased, a response similar to that in patients with normal coronary arteries and no vasospastic angina (group A). This suggests that in these three patients, as in group A patients, dilatation of small resistance coronary arteries was the most common coronary hemodynamic response to stimulation of the H1 receptor, despite the fact that these three patients had at least one significant coronary stenosis and repeated episodes of spontaneous angina during the 2 weeks before the study that were severe enough to require admission to the coronary care unit and constituted the indication to perform coronary arteriography. However, in the two patients in group B (Nos. 14 and 16) who developed angina during histamine infusion CBF decreased and CVR increased, indicating a primary fall in coronary perfusion most likely due to the occurrence of spasm of a large epicardial coronary artery. Coronary spasm was directly demonstrated in patient 16 by coronary arteriography performed during the histamine-induced anginal episode, disclosing complete occlusion of a circumflex coronary artery that was found on later examination to be patent and free of atherosclerotic obstructions. In patient 14 the occurrence of histamine-induced circumflex coronary spasm superimposed on an organic stenosis was suggested by the development of angina with ST segment elevation in lead III, coupled with the described changes in coronary hemodynamics. Although we cannot exclude the possibility that the occurrence of coronary spasm during histamine infusion might have been a mere coincidence, there is enough previous evidence to suggest that spasm in these patients was the result of activation of the H1 receptors in large epicardial coronary vessels.4,5,31–34 Experimental studies in mammals have demonstrated that histamine may induce contraction of vascular smooth muscle of capacitance arteries in several anatomic areas,31 including the heart,32 and that this response is mediated by H1 receptors.33,34

Recent studies in vitro have demonstrated the presence of vasoconstrictor H1 receptors together with vasodilator H2 receptors in epicardial coronary arterial strips obtained from patients undergoing heart transplantation.4 In addition, Ginsburg et al.3 recently reported that the selective stimulation of H1 receptors was able to provoke coronary spasm in five of 12 patients (41%) presenting with symptoms suggestive of vasospastic angina. In their patients with a positive test result, the selective stimulation of H1 receptors was achieved by infusion of 1 μg/kg/min histamine after pretreatment with 25 mg/kg of cimetidine. Coronary spasm was demonstrated angiographically in one patient and by angina and ST segment elevation in the other four patients. However, coronary hemodynamics were not assessed in their study. These authors attributed coronary spasm to the selective activation of vasoconstricting H1 receptors of large epicardial coronary arteries. In our study, we were able to demonstrate H1-induced coronary spasm (by angiography) and/or angina, ST elevation, a fall in CBF, and an increase in CVR in two of the five patients of group B (40%) with active vasospastic angina. Therefore, our study confirms that in a substantial proportion (about 40%) of patients with vasospastic angina the selective stimulation of H1 receptors is able to reproduce a spontaneous ischemic attack most likely due to coronary arterial spasm.

However, other mechanisms could play a role in the provocation of ischemia during histamine infusion. For example, the possibility of a change in geometry of stenosis due to peripheral coronary vasodilatation with a secondary pressure fall distal to the circumflex stenosis and passive arterial collapse15 should be considered in patient 14. A fall in aortic distending pressure could also, in presence of a tight stenosis, produce a severe reduction in subendocardial perfusion without substantial changes in global coronary flow.36 However, none of the above mechanisms could have played a role in patient 16, who had completely normal coronary arteries. In addition, histamine-induced anginal episodes in both patients were completely similar to those spontaneously occurring in the coronary care unit. Therefore, active H1 receptor–induced coronary vasospasm appears the most likely explanation for the ischemic episodes occurring during histamine infusion, although we have no data to exclude the possibility that other mechanisms, such as passive stenosis or arterial collapse secondary to a pressure fall in the aorta or distal to the stenosis, might play a role.

Also of particular interest are the two patients who developed spontaneous spasm during diagnostic coro-
nary arteriography after the histamine infusion protocol (patients 12 and 15). It is unlikely that spasm in these patients was the result of persistently high plasma levels of histamine, since they are known to return to baseline within a few minutes from the end of infusion of exogenous histamine in man. However, we have no data to completely exclude the possibility that the preceding histamine infusion, coupled with the mechanical trauma of coronary arteriography, might have somewhat facilitated the occurrence of spontaneous coronary spasm in these two patients.

Since we did not systematically perform coronary arteriography during histamine infusion, we cannot comment on caliber changes that may have occurred in large coronary arteries, even in association with a decrease in CVR. In our patients with normal coronary arteries and atypical angina, an associated H2-induced reduction in diameter of the large coronary artery is not likely to have influenced the coronary hemodynamic response, since dimensional changes in large coronary arteries do not affect coronary flow or resistance. However, an H1-induced increase in epicardial coronary arterial tone might assume larger clinical and hemodynamic importance in patients with severe organic stenosis and residual vasomotive capacity, possibly enhanced by supersensitivity of H1 receptors, in the coronary wall surrounding the plaque. In these patients even a slight reduction in diameter may critically increase resistance of the stenosis and reduce coronary flow, even in the presence of peripheral vasodilatation. This mechanism was probably in effect in patient 14 but not in the patient with vasospastic angina and stenosis of the left anterior descending artery (patient 15) or the two patients with vasospastic angina and stenosis of the right coronary artery (patients 12 and 13), in whom vasospasm should have been revealed by changes in coronary hemodynamics and/or angina with ST segment elevation. The case of patient 16, who also developed histamine-induced angina, and had normal coronary arteries, suggests that all patients with vasospastic angina, with or without organic atherosclerotic narrowings, have a particular supersensitivity of large epicardial coronary arteries to stimulation of the H1 receptors.

In light of studies in dogs and in man demonstrating a separate regulation and responsiveness of proximal conductance and distal resistance coronary arteries to several stimuli, histamine included, we can hypothesize that, in man, the coronary hemodynamic response to stimulation of the H1 receptors is characterized by both vasoconstriction of large coronary conductance arteries and vasodilatation of small resistance coronary arteries. In our studies, performed with infusions of 0.5 μg/kg/min of histamine, the prevailing response of patients with normal coronary arteries and atypical angina was vasodilatation, but the response of the individual patient with vasospastic angina was unpredictable. Our results suggest that the vasodilator response may be observed even in patients with active spontaneous vasospasm and significant organic stenosis. However, we cannot exclude the possibility that, with higher or longer histamine infusion rates or when endogenous histamine is directly released at the level of coronary arterial wall, the type and the intensity of the response might be different from those observed in our study.

Conclusions. In summary, our study demonstrates that the stimulation of H1 receptors in man with a histamine infusion at a rate of 0.5 μg/kg/min for 5 min is associated with significant coronary vasodilatation most likely due to the activation of vasodilating H1 receptors of small resistance coronary vessels. This response is consistently observed in patients with normal coronary arteries and atypical angina or other heart disease, but can also be found in patients with vasospastic angina with or without organic stenosis. However, our data show that, in a substantial proportion of patients of the latter group (40%), an H1-induced increase in coronary vascular resistance and fall in CBF may prevail. This response is most likely due to the stimulation of vasoconstricting H1 receptors of large epicardial coronary arteries, although it is possible that in some patients there is a change in geometry of stenosis secondary to hypotension or peripheral coronary vasodilatation. Our data confirm that, even in patients with active vasospastic angina, the sensitivity of coronary arterial spasm to histamine provocation at the rate of 0.5 mg/kg/min does not favorably compare with that of the standard ergonovine test.

Finally, our results support the concept that histamine may precipitate coronary spasm during systemic histamine release, such as in the course of anaphylactic reactions or during therapeutic or diagnostic interventions, in a subset of patients with vasospastic angina with or without coronary artery disease who are under treatment with H2-blocking drugs. Our study provides a basis for a better understanding of the changes in coronary hemodynamics in these clinical situations, and constitutes an initial contribution to the characterization of the presence and role of coronary H1 receptors in man.

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