Differential \( H_1 \)- and \( H_2 \)-Receptor–Mediated Histamine Responses of Canine Epicardial Conductance and Distal Resistance Coronary Vessels

Wayne L. Miller and Alfred A. Bove

The contributions of histamine (\( H_1 \) or \( H_2 \)) receptor–mediated responses and, therefore, the effects of histamine blocking agents are unclear with regard to regulation of proximal epicardial and distal resistance coronary arteries. This study was designed to evaluate the effects of selective \( H_1 \)- and \( H_2 \)-receptor antagonists on epicardial and resistance vessels in the closed chest dog model. Histamine, diphenhydramine (\( H_1 \) blocker), and cimetidine (\( H_2 \) blocker) were infused into the left anterior descending coronary artery (LAD), and responses were studied by quantitative coronary angiography and flow measurements (\(^{133}Xe \) washout). Histamine infusion alone produced a significant dilation of the proximal LAD (13% above control) only at the highest dose (45 \( \mu \)g/min), while LAD flow was increased by 128%. In the presence of \( H_1 \) blocker, histamine produced significantly greater epicardial dilation (55% above control). The flow response curve was shifted to the right in the presence of \( H_1 \) blocker, but the flow attenuation was overcome by the highest histamine dose. In contrast, the \( H_2 \) blocker attenuated both epicardial dilation (6% below control) and flow response (31% above control) to the highest histamine dose. Results support a differential regulation of proximal epicardial and distal resistance vessels to histamine with epicardial arteries demonstrating \( H_1 \)-mediated vasoconstriction and \( H_2 \)-mediated vasodilation and distal resistance vessels showing \( H_1 \)- and \( H_2 \)-mediated vasodilation. In addition, these findings suggest that \( H_1 \) blockade may antagonize histamine-related vasoconstriction and vasospasm, while \( H_2 \) blockers may permit unopposed \( H_2 \)-mediated vasoconstriction of epicardial arteries and also limit resistance vessel vasodilatory responsiveness in the presence of elevated tissue histamine, as may occur in atherosclerotic coronary artery disease. (Circulation Research 1988;62:226–232)

Current evidence suggests the presence of coronary vasoconstrictor \( H_1 \) receptors and vasodilator \( H_2 \) receptors,\(^{1-3} \) but these findings are not consistent for all studies.\(^{1-4} \) There have been no in vivo studies that demonstrate the effects of \( H_1 \) or \( H_2 \) histamine-receptor antagonists on epicardial conductance and distal resistance vessel responsiveness to histamine. Further, an in vivo study designed to distinguish between histamine receptor–mediated responses of the proximal and distal coronary arteries would help clarify issues regarding discrepant findings of receptor-mediated histamine responses. This study was, therefore, designed to evaluate the integrated effects of histamine-receptor blockade on epicardial and distal resistance vessel responses to intracoronary histamine infusion in the intact closed chest dog model. This would permit testing of the hypothesis that separate \( H_1 \)- and \( H_2 \)-receptor blockades differentially affect proximal epicardial and distal resistance vessel responsiveness to histamine.

Materials and Methods

Twelve male dogs weighing 20–30 kg were studied. Each dog was anesthetized with a combination of Innovar Vet\(^* \) (0.4 mg fentanyl and 20 mg droperidol/ml; 0.2 ml/kg i.m.) and nitrous oxide (70% in oxygen) ventilated with a Harvard respirator (model 807, South Natick, Massachusetts) through an endotracheal tube. A specially constructed coronary sinus catheter (6F) was positioned under fluoroscopy via the right jugular vein for purposes of blood sampling, cardiac pacing, and measurement of coronary sinus blood flow by the thermodilution technique. A polyethylene catheter was also positioned in the abdominal aorta via the left femoral artery and used to monitor systemic blood pressure and to collect arterial blood samples for blood gas and oxygen saturation analysis. In addition, a specially designed coronary artery catheter was advanced under fluoroscopy from the left carotid artery to the ostium of the left coronary artery. The coronary catheter was a double-catheter system consisting of a 2.5-mm (o.d.) guide catheter through which a 1.1-mm (o.d.) catheter was advanced into the left anterior descending artery (LAD) after the guide catheter was positioned in the ostium of the left main coronary artery. The LAD catheter was advanced approximately 1 cm and was used to infuse histamine (0.5, 1.0, 5.0, 15.0, and 45.0 \( \mu \)g/min), cimetidine (\( H_2 \) blocker; 100 \( \mu \)g/min), and diphenhydramine (\( H_1 \) blocker; 100 \( \mu \)g/min). Estimates of the histamine concentrations to which the LAD vessel was exposed correspond to a range of approximately \( 2 \times 10^{-4} \) to \( 2 \times 10^{-6} \) M. Diphenhydramine and cimetidine concentrations were \( 3 \times 10^{-4} \) and \( 4 \times 10^{-6} \) M, respectively. These levels correspond to the concentrations employed in vitro. Systemic plasma concentrations were not determined for histamine antagonists. Xenon-133 was also injected through the LAD.
catheter for measurement of coronary artery flow (LAD flow). Coronary angiograms were obtained during the injection of 6 ml of nonionic contrast media iohexol (Omnipaque 350, Winthrop-Breon Labs, New York) into the left coronary guide catheter. Exposures were obtained at end-expiration in mid-diastole using an R-wave-triggered time-delayed x-ray switch. After all cathereters were in place, the dog was positioned in the right anterior oblique projection to optimize visualization of the LAD. Pressures were recorded from the coronary sinus, distal coronary catheter (LAD), and the proximal left coronary artery (guide catheter). The electrocardiogram was recorded from the standard limb leads. Cardiac pacing was done with the coronary sinus pacing catheter at the rate of 90 beats/min if heart rate decreased below this value. Pressures and electrocardiogram were monitored continuously and recorded for each control and experimental manipulation.

**Coronary Blood Flow Measurements**

Blood flow in the LAD distribution was measured using 0.1–0.2 mCi $^{133}$Xe injected directly into the distal coronary catheter. Isotope washout was monitored by a single crystal detector positioned against the left thorax at midventricular level under fluoroscopy. Count data were transferred directly to a PDP 11/34 computer (Digital Equipment Corp., Marlboro, Massachusetts) for a period of 2 minutes following $^{133}$Xe injection. Flow was determined in milliliters per minute per 100 grams from the monoexponential log-linear least-squares calculation of the slope (k) of the washout curve using $-0.72 k/1.05$ where 0.72 is the xenon blood myocardium partition coefficient and 1.05 is the myocardial density. Flow was also calculated using the height/area method of washout curve analysis; results were comparable by the two methods. Arteriovenous oxygen difference (A-VDO$_2$) was calculated from the difference between arterial and coronary sinus oxygen content (ml O$_2$/dl), which was calculated from the product of hemoglobin content (g/dl) x 1.34 ml O$_2$/g x oxygen saturation. Myocardial oxygen consumption (ml O$_2$/min/100 g) was calculated from LAD flow and A-VDO$_2$. Coronary vascular resistance (CVR; mm Hg/ml/min/100g) was calculated from (mean LAD pressure – mean coronary sinus pressure)/LAD flow.

**Measurement of Epicardial Conductance Vessel Dimensions**

Diameter (mm) and cross-sectional area (CSA; mm$^2$) of the LAD were quantitated by a computerized angiographic analysis system. Single right anterior oblique projection roentgenographic films were exposed at 88 kV for 35 msec in mid-diastole at end-expiration. The luminal edges of the LAD were traced manually and digitized with a quantitative angiography program by the PDP 11/34 computer. The program calculated luminal diameter and cross-sectional area at 1-mm intervals along the length of the artery scanned. Based on the coronary angiograms, a 15-mm long segment of the LAD beginning 10 mm from the catheter tip was designated distal LAD. This segment was identifiedly determined for each experiment and was analyzed within each experiment for responsiveness to the infused histamine and blocker agents. Testing and assessment of the effects of repeated contrast injection on coronary responsiveness and the angiographic method of analysis were previously completed. Also, nonionic contrast medium was used to exclude the problems of possible contrast-induced changes in vascular tone.

**Experimental Protocol**

Once all cannulation procedures were completed, measurements of LAD flow ($^{133}$Xe washout, in duplicate), arterial and coronary sinus oxygen saturation (cooximeter, International Laboratories, Cranbury, New Jersey, aortic, proximal left coronary and coronary sinus blood pressures, heart rate, and a left coronary artery angiogram were obtained (control measurements). Following these measurements, dose-response curves to intracoronary infusion of histamine were obtained ($n = 10$). After a recovery period of 30 minutes, control measurements were again obtained, and then intracoronary infusions of either the H$_1$ blocker diphenhydramine ($n = 5$) or the H$_2$ blocker cimetidine ($n = 5$) were begun. All measurements were repeated after 5 minutes of blocker infusion, and then histamine infusion was begun with the dose-response curve repeated in the presence of either histamine blocker. All measurements were obtained after vessel responses had stabilized (approximately 4–6 minutes). Infusion volume was 0.45 ml/min for the maximum histamine dose and 0.1 ml/min for the blocker doses. Drugs were dissolved in normal saline. In two additional dogs, two dose-response curves to histamine in the presence of H$_2$ blocker were completed in succession. This was done to determine if there were any differences in responsiveness with regard to duration of the experiment or previous drug exposure. No differences, however, were observed in the two groups of dose-response curves with H$_2$ blockade. Dogs were killed under anesthesia by an intracoronary injection of saturated potassium chloride solution.

**Statistical Analysis**

Results are reported as mean ± SEM. Dose-response curves of LAD cross-sectional area, coronary (LAD) flow, or coronary vascular resistance versus dose of histamine infused with and without H$_1$ or H$_2$ blockade are expressed in absolute values and as percent change from control values. Data were analyzed with Student's $t$ test for unpaired observations and two-way analysis of variance. Statistical significance was accepted for $p<0.05$.

**Results**

**Effects of Histamine and H$_1$ and H$_2$ Blockers on Conductance Vessels**

Percent change from control cross-sectional area of the distal epicardial LAD artery for cumulative doses of histamine with and without H$_1$ or H$_2$ blocker is shown in Figure 1. Since control CSA did not differ among the groups, the individual values measured
proximal left coronary artery pressure (MAP) is expressed in
CBF-LAD (ml/min/100 g) 197±10
before each dose-response curve were pooled to
group.
for Hrblocker
for H,-blocker group;
 alone group;
 n = 5
 n = 7
 n = 10 for control values and histamine
experimental value,
mm Hg. *Indicates significant difference between control and
histamine blockade. Responses are expressed as percent change from
control. H,-blocker infusion alone did not affect LAD flow, but with
histamine infusion, H,-blocker did tend to reduce flow

Effects of Histamine and H1 and H2 Blockers on
Resistance Vessels
Percent change from control in LAD blood flow with
histamine infusion in the presence and absence of histamine
antagonists is shown in Figure 1. The absolute values for LAD flows are shown in Table 1
with comparisons made with the control mean. As
shown in Figure 1, histamine infusion produced a
significant dose-dependent increase in coronary blood
flow with a maximum increase of 128±22.8% above
control. H,-blocker infusion alone did not affect LAD
flow significantly but did shift the dose-response curve
to the right. Flow responses to histamine were attenuated at the lower doses (0.5, 1.0, 5.0, and 15.0
µg/min). Statistically significant (p<0.05) reductions
in LAD flow were produced with H2 blocker at the 5.0
and 15.0 µg/min doses compared with histamine
infusion without blocker. Increases in flow above
control, however, were produced by the two highest
doses of histamine with comparable increases in LAD
flow achieved by histamine alone and with the H1
blockade. H2 blockade also significantly attenuated
histamine-induced flow increases, again resulting in a
shift to the right of the dose-response curve. H2-blocker
infusion alone did not affect LAD flow, but with
histamine infusion, H2-blockade did tend to reduce flow

Table 1. Changes in Hemodynamic and Metabolic Parameters With Histamine Infusion in Presence and Absence of Histamine Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>H1 (100 µg/min)</th>
<th>H2 (100 µg/min)</th>
<th>H1 (µg/min)</th>
<th>H2 (µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
<td>1.0</td>
<td>5.0</td>
<td>15.0</td>
<td>45.0</td>
</tr>
<tr>
<td>CBF-LAD (ml/min/100 g)</td>
<td>197±10</td>
<td>207±27</td>
<td>251±20*</td>
<td>246±20*</td>
<td>330±30*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>178±17</td>
<td>194±12</td>
<td>206±28</td>
<td>192±24</td>
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<tr>
<td></td>
<td></td>
<td>207±30</td>
<td>203±35</td>
<td>222±25</td>
<td>209±28</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>91±3</td>
<td>84±3</td>
<td>86±2</td>
<td>88±2</td>
<td>97±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86±6</td>
<td>85±5</td>
<td>85±10</td>
<td>86±7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98±6</td>
<td>97±6</td>
<td>90±3</td>
<td>100±4*</td>
</tr>
<tr>
<td>Arterial-coronary sinus O2</td>
<td>5.78±0.23</td>
<td>5.85±0.37</td>
<td>5.47±0.32</td>
<td>5.18±0.25</td>
<td>4.28±0.38</td>
</tr>
<tr>
<td>difference (ml O2/dl)</td>
<td></td>
<td>5.82±0.28</td>
<td>5.41±0.19</td>
<td>4.93±0.17*</td>
<td>4.14±0.18*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.77±0.60</td>
<td>4.89±0.54</td>
<td>5.92±0.68</td>
<td>5.63±0.43</td>
</tr>
</tbody>
</table>

*p<0.05; values are mean±SEM. n = 10 for histamine alone; n = 5 for H1-blocker group; n = 7 for H2-blocker group.
H1 blocker, diphenhydramine; H2 blocker, cimetidine.
CBF-LAD, coronary blood flow of left anterior descending artery.
below control at the low doses, while LAD flow was significantly elevated above control at the two highest histamine doses. Histamine-induced blood flow increase at the highest dose infused was significantly attenuated by cimetidine compared with the flow response in the presence of the H₂ antagonist.

Figure 1 also shows changes from control in coronary vascular resistance with histamine infusion. CVR was significantly reduced by the three highest histamine doses, but in the presence of H₁ and H₂ blockade, the reductions in CVR were less significant. Infusion of either blocker alone did not significantly affect CVR, but there was a tendency for the CVR dose-response curve to be shifted to the right by both blockers. H₂ blockade also tended to increase CVR above control at the lower histamine doses compared with histamine alone or with H₁ blockade.

Effects of Histamine and H₁ and H₂ Blockers on Blood Pressure, Heart Rate, and Arteriovenous Oxygen Differences

To confirm that the responses observed were due to direct effects of histamine on the coronary vasculature and not secondary to changes in cardiac metabolism, blood pressure, heart rate, and arteriovenous oxygen differences were evaluated. Changes in mean proximal left coronary arterial pressure (MAP) are shown in Figure 1. Control MAP was 93 ± 2.0 mm Hg, and significant changes occurred only at the highest dose of histamine infused where MAP decreased by 12 ± 3 mm Hg in the histamine-alone group and by 13 ± 3 with H₂ blockade. MAP also decreased significantly with H₁ blockade at the 1.0-μg/min dose of histamine but returned to control level with the subsequent dose. Infusion of H₁ or H₂ blocker alone did not alter MAP, but H₂ blockade tended to increase MAP compared with histamine alone or with H₁ blockade; however, differences were statistically nonsignificant. Comparisons among the three groups at each dose level showed no difference in MAP with the exception of the 1.0-μg/min dose where MAP was significantly lower with H₂ blockade compared with the other two groups.

Heart rates as also shown in Table 1 were generally stable but did show a statistically significant increase to 103 ± 7 beats/min from control of 91 ± 3 beats/min with the highest histamine dose, corresponding to the decrease in MAP occurring with this dose. Heart rate was not significantly increased with the highest histamine dose in the presence of H₁ or H₂ blocker, even though H₁ blocker produced a significant decrease in MAP at this dose. Arterial-coronary sinus oxygen differences (Table 1) were reduced in a dose-dependent manner reflecting the increases in LAD flow observed. No increases in A-VDO₂ were observed. Also, histamine infusion did not significantly change myocardial oxygen consumption (MVO₂) from control in any of the groups.

Discussion

This study provides basic information on the integrated but differential regulation by histamine of proximal epicardial and distal coronary resistance vessels and also suggests a basis to evaluate further the potential for beneficial and deleterious effects of H₁ and H₂ blockers, particularly in the circumstances of atherosclerotic coronary artery disease. An H₁-mediated vasodilation mechanism of epicardial coronary arteries of the dog is evidenced in this study by the unmasking of substantial histamine-induced vasorelaxation in the presence of H₂-receptor blocker. In addition, an opposing H₂-mediated vasoconstrictor component of epicardial vasoactivity is supported by the indirect observation that histamine-induced relaxation was antagonized in the presence of H₂-receptor blocker. These results are consistent with findings reported for human epicardial vessels.

Histamine has been shown to be present in the walls of arteries and veins and to be synthesized by endothelial cells. In addition, increased numbers of adventitial mast cells and increased histamine content of epicardial vessels have been demonstrated in human atherosclerotic coronary arteries when compared with nondiseased vessels. Increased constrictor vasoreactivity to histamine has also been demonstrated in isolated atherosclerotic human epicardial arteries. Furthermore, histamine infusion has been shown to induce coronary artery vasospasm in patients being evaluated for variant angina, in the vivo porcine preparation, and in the isolated rabbit heart preparation. Plasma histamine levels have also been shown to be increased by experimental acute coronary thrombosis in the conscious dog. Thus, while a pathophysiologic role for histamine in the mediation of coronary vessel responses has not been definitively established, current data suggest the potential for histamine involvement in epicardial coronary artery spasm. Also, since coronary vasospasm has been reported to be a significant factor in the etiology and clinical manifestations of coronary artery disease, the consideration of histamine effects on coronary vasoactivity in coronary disease states and, particularly, the effects of histamine-blocking agents becomes a relevant issue.

The vascular response to histamine can vary significantly as a function of the receptor type activated. Studies using selective histamine receptor agonists and antagonists have demonstrated the presence of coronary vasoconstricting H₁ receptors and vasodilating H₂ receptors in isolated epicardial vessels. When coronary blood flow is the measured variable, in situ and in vivo data indicate that histamine-induced increases are mediated by both H₁ and H₂ receptor. While this apparent disparity in findings has produced some confusion, it does suggest a basis for the separate regulation and responsiveness of epicardial conductance and distal resistance arteries. Differential responsiveness of proximal and distal vessels to various vasoactive agents has been established. Intracoronary histamine infusion in the intact dog was shown to produce only a modest dilation of epicardial vessels, while coronary blood flow was more than doubled. In human studies, Vigorito et al used intravenous histamine infusion in the presence of H₂ blockade and
demonstrated a decrease in coronary vascular resistance consistent with H1-mediated resistance vessel dilation. In addition, epicardial coronary artery vasospasm was demonstrated suggesting H2-mediated vasoconstriction of epicardial vessels. Decreased aortic pressures and a lack of systematic analysis of the epicardial vessels may, however, limit the conclusion from these data of H2-mediated vasoconstriction in vivo. The potential for a deleterious effect of H2 blockade on coronary blood flow was also suggested by studies using the isolated perfused guinea pig heart where histamine-induced increases in coronary flow were blocked with cimetidine and the vasodilatory effects of specific H2 agonists were abolished. The results of the present study suggest that H1-receptor-mediated vasoconstriction and H2-receptor-mediated vasodilation occur in both proximal epicardial and distal resistance coronary vessels and that selective H2 blockade that would favor unopposed H1-mediated vasoconstriction could be significant in conditions of elevated histamine levels, such as atherosclerotic coronary artery disease.

While the net effect of histamine infusion in the absence of blockers was a small relaxation of the epicardial vessels, the response to H2 blockade with diphenhydramine in this study suggests a potent H1-mediated vasoconstrictor component in epicardial arteries. H2 blockade produced a significant increase in LAD CSA when infused alone and then substantially increased the histamine-induced vasorelaxation when compared with the effects of histamine alone or with H1 blockade. The vasodilator response in the presence of the H2 blocker is out of proportion to the vasoconstriction produced with the H1 blocker; this may reflect an inequality in potency of the antagonists infused and, therefore, receptor binding or it may suggest that the receptor subtypes are not mediating distinctly opposing vasoresponse to histamine. Rather, H1 receptors may mediate both vasoconstrictor and vasodilator responses, and with H2 blockade, the constrictor component is reduced, leaving the dilator component intact. This H2-mediated dilation then augments the H1-mediated vasodilation, resulting in the significant vasorelaxation observed in the present study. These findings would be consistent with the hypothesis of an H1-mediated release of prostacyclin (PGI2) from the endothelium as supported by the experimental results of Toda et al. Such a hypothesis has not been tested in dog coronary arteries in vivo but would be of interest with regard to the findings of this study. In contrast, the H1 blocker, cimetidine, antagonized the dilator responses to histamine. This was most apparent at the highest histamine dose where H2 blockade significantly attenuated the vasodilator effect of histamine.

A separate regulation of the distal vessels to histamine compared with the proximal arteries is supported in part by the contrast in response to histamine by the epicardial and distal resistance vessels. Histamine in the absence of blockers produced a significant dilation of the epicardial LAD artery only with the highest dose infused, and this resulted in a relatively small increase in CSA (+13.1% above control). In contrast, CVR decreased and coronary blood flow increased significantly with histamine indicating a substantial vasodilator effect on distal resistance vessels. The distal resistance vessel response to histamine in the presence of H1 or H2 blocker also supports separate regulation of proximal and distal vessels. Both H1 and H2 blockers shift the histamine dose-flow response curve to the right with cimetidine producing the greater attenuation of flow increase to histamine (128% increase versus 31% increase in flow). These findings indicate that, as others have reported, both H1 and H2 receptors are vasodilatory in the distal vessels but in addition, our findings suggest that the H1-mediated response may provide the larger contribution to vasodilation. This difference could, however, also reflect unequal receptor blockade by the infused histamine antagonists. These findings indicate that H2 receptors mediate vasodilation in the epicardial and distal resistance vessels, while H1 receptors mediate vasoconstriction in the epicardial vessel and vasodilation in the distal resistance vessels.

MAP was generally stable throughout the experiments, but it is possible that the reductions in pressure that occurred with histamine alone and with H2 blocker may have attenuated but not promoted the vasodilatory response observed to histamine. Thus, the LAD flow and epicardial area increases may have been larger at the maximum dose of histamine for the H1-blocker group and the histamine-without-blocker group if pressure had not fallen. This, however, is not a factor in the difference in epicardial vasodilation between the histamine and histamine-plus-H2 blocker groups since MAP dropped to the same extent in both groups (i.e., to 80–81 mm Hg). Furthermore, MAP did not change from control with H2 blockade at the highest histamine dose, but epicardial and resistance vessel dilation responses were significantly attenuated compared with the responses in the H1 and histamine-alone groups. Also, metabolic-induced vasodilator responses secondary to an increased myocardial oxygen demand are not supported by the data. While heart rate did increase with histamine infusion (91–103 beats/min), the increase was not of sufficient magnitude to account for the epicardial and resistance vessel dilations observed. In addition, A-VDO2 was reduced by histamine and not increased as would be expected if histamine or its antagonists had increased myocardial oxygen demand. Therefore, the responses observed reflect the direct effects of histamine and the receptor antagonists without secondary metabolic-induced changes.

In summary, this study supports the hypothesis of differential histamine regulation and responses for epicardial conductance and distal resistance coronary arteries. Histamine effects H1-mediated vasoconstriction and H2-mediated vasodilation in epicardial arteries and H1- and H2-mediated vasodilation in resistance coronary vessels of the dog. Current data suggest that the activation of H1-vasoconstrictor receptors in epicardial arteries may precipitate vasospasm, and our data would indicate that this situation could be further aggravated in the presence of H2-blocking
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agents such as cimetidine, a commonly used medication. H2 blockers may also contribute to myocardial ischemia by significantly limiting flow in resistance vessels under conditions of increased histamine release and increased oxygen demand. The benefit of H2 blockers alone to promote epicardial vasodilation is supported from our data in addition to its effect to enhance histamine-induced epicardial vasodilation. This benefit, however, may be compromised at the resistance vessel level where H1 blockade attenuates the CBF response to histamine.

While experimental animal data cannot unequivocally be extrapolated to human patient management problems, the findings of this study in conjunction with the results of studies of human coronary arteries suggest a basis for further evaluation of histamine antagonists in patients with coronary artery disease. Any potential benefit of H2-receptor antagonists in limiting H1-mediated vasospasm in patients with atherosclerotic coronary disease has not been substantiated. Conversely, the potential deleterious effects of H2-receptor antagonists by permitting unopposed H1-mediated vasoconstriction to histamine in patients with atherosclerotic coronary disease also requires further study.

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W L Miller and A A Bove

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