Influence of Histamine Receptors on Basal Left Ventricular Contractile Tone in Humans: Assessment Using the H₂ Receptor Antagonist Famotidine and the Beta-Adrenoceptor Antagonist Esmolol as Pharmacologic Probes

KENNETH M. BOROW, MD, FACC, DONNA EHLER, BS, ROGER BERLIN, MD,* ALEX NEUMANN, BS
Chicago, Illinois and West Point, Pennsylvania

Histamine has a positive inotropic action in humans. Recent controversial data have suggested that histamine (H₃) receptor blockade depresses overall left ventricular systolic performance in healthy volunteers. To explore the possibility that H₂ receptors positively influence basal left ventricular contractile tone, 10 normal subjects were studied by using imaging and Doppler echocardiography and calibrated subclavian pulse data in a blinded, randomized, two-period crossover trial with measurements obtained at the end of each 7-day period.

Oral drug administration consisted of either the potent H₂ antagonist famotidine (40 mg/day) or placebo. Left ventricular circumferential end-systolic wall stress-rate-corrected velocity of fiber shortening (Vcfₑₑ) relations were generated over a range of loads with methoxamine. Contractility was assessed by using Vcfₑₑ at a common end-systolic wall stress. During each study, data were obtained before and during high dose intravenous esmolol administration to determine the contributions, if any, of sympathetic reflex responses.

Famotidine did not alter blood pressure, left ventricular percent fractional shortening, circumferential end-systolic wall stress, stroke volume index, cardiac index, total vascular resistance or ventricular contractile state in comparison with placebo but did decrease heart rate by 3 beats/min (p < 0.05). With beta-adrenergic blockade, no differences in contractility were evident between esmolol alone and famotidine plus esmolol.

Thus, H₂ receptor blockade with famotidine does not alter myocardial mechanics or cardiac sympathetic tone, suggesting that in humans basal left ventricular contractile state is not physiologically dependent on the H₂-mediated effects of histamine.

Studies (1-5) performed in animals and humans have suggested that histamine (H₂) receptors exist in the myocardium and peripheral blood vessels. Stimulation of these receptors activates adenylyl cyclase, thereby increasing the intracellular concentration of cyclic adenosine monophosphate (AMP), which results in increases in left ventricular muscle tension and contractility (2-5). In patients with severe left ventricular dysfunction refractory to dobutamine, impromidine, a specific H₂ receptor agonist, has been shown (6,7) to increase cardiac output and decrease pulmonary capillary wedge pressure. H₂-blockers selectively inhibit the binding of histamine to H₂ receptors (2,5), thereby reducing intracellular concentrations of cyclic AMP. Because agents such as cimetidine (Tagamet), ranitidine (Zantac) and famotidine (Pepcid) are an integral part of the clinical treatment of active peptic ulcer disease (5,8,9), it is pertinent to determine whether a potent H₂ antagonist adversely affects contractile state.

Famotidine, which on a weight basis is 8 times more potent than ranitidine and 40 times more potent than cimetidine and has a longer duration of action than either of these drugs, is of particular interest (5,8,9). Recent studies performed by Kirch, Hinrichsen and coworkers (10,11) in normal subjects have raised concerns regarding the possible adverse effect of famotidine on left ventricular contractility. Specifically, these investigators (10,11) reported that oral famotidine (40 mg/day) increased the left ventricular pre-ejection period to ejection time ratio and decreased ventricular stroke volume by impedance cardiography. They concluded that famotidine has a "significant negative effect on cardiac performance." However, other clinical studies (12-15) have failed to confirm these conclusions. If H₂ receptor blockade with famotidine does indeed depress myocardial contractile state in humans in the absence of histamine release from mast and other cells, the implication would be that ambient blood histamine contributes to basal left ventricular contractile tone. If this were true, new approaches...
could be opened for the treatment of left ventricular pump dysfunction because myocardial H₂ receptor density is uniform and does not appear to be subject to the regulatory changes that account for the wide variability in beta-receptor number and density in patients with heart failure (6,7).

All previous reports on the cardiac effects of famotidine have been based on measurements of overall left ventricular performance that are highly dependent on load and heart rate. In no case was it possible to differentiate changes in left ventricular contractility from simultaneously occurring changes in preload and afterload. This is important because intravenously administered H₂ blockers have been reported (13,16) to produce significant changes in peripheral vascular tone and ventricular loading conditions. Furthermore, the indirect cardiac effects of reflex sympathetic activation that may have resulted from treatment with famotidine were not considered. If these occurred, the drug's direct negative inotropic effect might have been even greater than reported previously (10,11). To differentiate between the contributions of load changes, direct inotropic action and reflex sympathetic stimulation, a more specific measurement of contractility is required. By systematically employing a series of pharmacologic probes, it is possible with totally noninvasive techniques to assess the inotropic action of a drug while delineating contributions from the cardiac sympathetic nervous system (17-23).

Using the H₂ receptor antagonist famotidine in conjunction with the beta-adrenoceptor antagonist esmolol, the current study attempted to determine whether circulating histamine has an effect on basal left ventricular contractile tone and loading conditions in humans.

Methods

Study subjects. Ten normal subjects between the ages of 18 and 50 years with a mean systemic blood pressure ≤105 mm Hg, technically adequate echocardiographic images of the left ventricle and normal overall ventricular systolic performance (i.e., percent fractional shortening ≥28%) were eligible for study. Each subject had normal results on a rest electrocardiogram (ECG), physical examination, complete blood count and blood chemistry profile. Exclusion criteria included 1) any contraindication to ingestion of an H₂ antagonist or beta-adrenoceptor blocking agent, 2) any clinical, ECG or echocardiographic findings suggestive of coronary artery or valvular heart disease, or 3) significant cardiac rhythm disturbances. The protocol was approved by the Institutional Review Board of the University of Chicago Medical Center. Packaging of medications was performed by the Medical Center's pharmacy.

Study protocol. Each subject was seen on four separate occasions: visit 1, screening studies; visit 2, start of 1 week of administration of active drug (or placebo); visit 3, imaging and Doppler echocardiographic study 1 followed by start of 1 week of administration of placebo (or active drug); visit 4, imaging and Doppler-echocardiographic study 2 and subsequent termination of study.

All cardiac ultrasound examinations were performed 2 to 3 h after the dose of famotidine or placebo. This timing for data acquisition coincides with the previously reported (5) average time to peak serum concentration after oral ingestion of famotidine. Recordings included left ventricular two-dimensional and targeted M-mode echocardiograms, continuous wave Doppler velocity tracings of aortic valve flow, echocardiographically determined aortic annular cross-sectional area, phonocardiogram. ECG and indirect subclavian pulse tracing. Systolic, diastolic and mean aortic blood pressure determinations were made with the Dinamap 1846 XSP Vital Signs Monitor (Critikon Inc.). In previous comparison studies (24-26), this device was shown to accurately

Figure 1. Schematic presentation of the experimental design employed in the current study. Echo = imaging and Doppler echocardiography.
Pharmacologic probes. After completion of baseline recordings, an intravenous infusion of the specific alpha-adrenergic agonist methoxamine hydrochloride (0.5 to 1 mg/min) was begun. Each subject was premedicated with atropine sulfate (0.005 to 0.01 mg/kg body weight) to maintain a stable heart rate (i.e., prevent baroreceptor-mediated reflex bradycardia). Systolic blood pressure was raised slowly by 20 to 40 mm Hg above the rest value with recordings performed every 1 to 2 min. After the maximal desired systolic pressure was reached, the methoxamine infusion was discontinued. In general, peak pressure was maintained for 3 to 4 min and then decreased by an average of 3 mm Hg/min. When peak left ventricular systolic pressure returned to within 10% of baseline, repeat recordings (as outlined earlier) were performed. Each subject was then given esmolol, an ultrashort-acting cardioselective beta-adrenoceptor blocking agent. This drug has a very rapid onset of action. Esmolol was given intravenously as a 500 µg/kg bolus followed by a continuous infusion at 100 µg/kg per min. After 3 to 7 min, a repeat 500 µg/kg per min bolus was administered followed by continuous infusion at 200 µg/kg per min. After ≥15 min of high dose drug infusion, baseline esmolol data were acquired. We have previously shown that this dosing regimen yields a ≥2.5-fold beta adrenergic blockade as quantified by isoproterenol challenge (23). Finally, with the esmolol infusion maintained at 200 µg/kg per min, the methoxamine challenge was repeated.

Analysis of hemodynamic data. The timing of end-diastole was defined as the peak of the R wave on the ECG. End-systolic measurements were made at the first high frequency component of aortic valve closure on the phonocardiogram. Left ventricular end-diastolic and end-systolic minor-axis dimensions (Dmin, Dsyst) as well as wall thicknesses (Wmin, Wsyst) were measured from parasternal targeted M-mode echocardiographic recordings acquired perpendicular to the left ventricular long axis and through the midline of short-axis images. Care was taken to record the largest left ventricular minor-axis dimensions present between the tips of the mitral valve leaflets and the superior aspect of the papillary muscles. This chordal measurement approximates the mid-equatorial plane of the left ventricle. Left ventricular end-diastolic and end-systolic long-axis dimensions (Lend, Lsyst) were measured from the two-dimensional echocardiographic apical four-chamber view. The apical endocardium was defined as the point within the left ventricle at which the septum and lateral wall formed the most acute angle. This was accomplished by positioning the transducer as far lateral or inferior, or both, as necessary. The distance from the apex to the mid-segment of the mitral valve annulus and the width of the annulus were simultaneously maximized, thus avoiding tangential imaging of the left ventricle.

Cardiac output was determined by multiplying heart rate and left ventricular stroke volume. The latter was calculated as the product of two-dimensional echocardiographically measured aortic annular cross-sectional area and continuous wave Doppler ultrasound-determined flow velocity integral acquired through the aortic valve. Cardiac index and stroke volume index were calculated by dividing by body surface area. Total vascular resistance (TVR; dynes-s-cm⁻²) was determined as:

\[ TVR = \frac{P_{mean} - CO}{CO} \]

where \( P_{mean} \) = mean aortic pressure (mm Hg) and CO = cardiac output (liters/min).

The left ventricular percent fractional shortening (%ΔD) was derived as \( \frac{D_{end} - D_{syst}}{D_{end}} \). Left ventricular end-systolic pressure \( (P_{esyst}) \) was determined from linear interpolation to the height of the incisura by using a calibrated subclavian pulse tracing (29). Left ventricular ejection time \( (LVET) \) was measured from the external pulse tracings in the standard manner (29). The rate-corrected left ventricular mean velocity of circumferential fiber shortening \( (V_{cf}) \) was calculated as (17,29):

\[ V_{cf} = \frac{\%ΔD}{(LVET)/(V/RR) = \%ΔD/ \frac{V}{RR}} \]

where RR = the interval between consecutive cardiac cycles.

Left ventricular circumferential wall stress (σ) was calculated using the equation of Sandler and Dodge (30) as the product of pressure and a geometric factor that includes minor- (D) and long- (L) axis dimensions and wall thickness (h):

\[ σ = \frac{P}{2h} \left( 1 - \frac{D^2}{2L^2(D + h)} \right) \]

where σ is in g/em², P is in mm Hg, D, L, and h are in cm and 1.35 converts pressure from mm Hg to g/cm².

Assessment of left ventricular contractility. Left ventricular contractility was measured by using the load- and heart rate-independent relation between end-systolic circumferential wall stress and rate-corrected velocity of fiber shortening. In each subject, the \( σ_{v_{cf}} \) relation was determined by linear regression analysis (least squares method) using a minimum of four data points acquired over a wide range of afterloads (i.e., circumferential end-systolic stress) generated during methoxamine infusion. For each subject, data were compared for placebo alone, famotidine alone, esmolol alone and famotidine plus esmolol conditions at a common level of value left ventricular end-systolic wall stress.

The following differences in rate-corrected velocity of fiber shortening \( (ΔV_{cf}) \) were determined: 1) famotidine minus placebo, reflecting the effect of famotidine on left ventricular contractile state with a physiologically intact cardiac sympathetic nervous system; 2) esmolol minus placebo, reflecting the inherent negative inotropic effect of esmolol; 3) famotidine plus esmolol minus famotidine.
Hemodynamic Data

The cardiovascular hemodynamic data for the placebo, famotidine and esmolol conditions are summarized in Table I.

- **Heart rate.** Compared with placebo, heart rate decreased by 3 beats/min with famotidine (p < 0.05) and by 4 beats/min with esmolol (p < 0.01). No differences were noted for famotidine plus esmolol versus either famotidine or esmolol.

- **Pressures.** Esmolol with either placebo or famotidine minimally raised mean aortic pressure relative to placebo (p = 0.07) or famotidine (p < 0.05). No other interdrug differences were noted for left ventricular peak systolic, left ventricular end-systolic, aortic diastolic or aortic mean pressures.

- **Left ventricular preload.** This was assessed as left ventricular end-diastolic dimension. Increases tended to occur with esmolol (p = 0.06 vs. placebo) and famotidine plus esmolol (p < 0.05 vs. famotidine). No other interdrug differences were noted.

- **Left ventricular afterload.** Famotidine had no effect on left ventricular afterload. In contrast, esmolol and famotidine plus esmolol increased total vascular resistance (p < 0.001) and left ventricular end-systolic circumferential wall stress (p < 0.01) relative to placebo and famotidine, respectively.

Overall left ventricular systolic performance. Left ventricular end-systolic dimension, percent fractional shortening, rate-corrected velocity of fiber shortening, stroke volume index and cardiac index were not statistically different for placebo and famotidine. Esmolol infusion with either placebo or famotidine increased end-systolic dimension while depressing all other measurements of overall left ventricular performance relative to placebo or famotidine, respectively. No differences were noted for esmolol versus famotidine plus esmolol.

**Left Ventricular Contractility**

Figure 3 shows representative data from one of our study subjects. Left ventricular end-systolic circumferential wall stress is plotted with rate-corrected velocity of fiber shortening. Each line was generated over a wide range of values present at p < 0.0125. Group data are expressed as mean values ± SD.
Table 1. Summary of Hemodynamic Data in 10 Subjects

<table>
<thead>
<tr>
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<th>P</th>
<th>P + E</th>
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<th>F + E</th>
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<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>61 ± 8</td>
<td>57 ± 6</td>
<td>58 ± 6</td>
<td>57 ± 6</td>
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<tr>
<td>Presures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LV peak systolic</td>
<td>112 ± 9</td>
<td>115 ± 8</td>
<td>112 ± 9</td>
<td>113 ± 7</td>
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<tr>
<td>LV end-systolic</td>
<td>95 ± 11</td>
<td>99 ± 8</td>
<td>94 ± 12</td>
<td>99 ± 6</td>
</tr>
<tr>
<td>Ao diastolic</td>
<td>56 ± 8</td>
<td>59 ± 7</td>
<td>69 ± 8</td>
<td>62 ± 6</td>
</tr>
<tr>
<td>Ao mean</td>
<td>83 ± 3</td>
<td>86 ± 5</td>
<td>81 ± 8</td>
<td>87 ± 8</td>
</tr>
<tr>
<td>LV preload Dₜₜ(cm)</td>
<td>4.89 ± 0.34</td>
<td>4.97 ± 0.39</td>
<td>4.85 ± 0.36</td>
<td>4.96 ± 0.41</td>
</tr>
<tr>
<td>LV afterload TVR (dynes·cm⁻²)</td>
<td>1,257 ± 220</td>
<td>1,479 ± 214</td>
<td>1,298 ± 191</td>
<td>1,537 ± 273</td>
</tr>
<tr>
<td>σₑₜ(cm²/cm²)</td>
<td>1.39 ± 0.24</td>
<td>1.63 ± 0.16</td>
<td>1.57 ± 17</td>
<td>1.60 ± 14</td>
</tr>
<tr>
<td>Overall LV systolic perforrance</td>
<td>3.29 ± 0.33</td>
<td>3.54 ± 0.31</td>
<td>3.28 ± 0.26</td>
<td>3.49 ± 0.30</td>
</tr>
<tr>
<td>Dₜₜ(cm)</td>
<td>3.29 ± 0.32</td>
<td>3.54 ± 0.31</td>
<td>3.28 ± 0.26</td>
<td>3.49 ± 0.30</td>
</tr>
<tr>
<td>%ΔDₜₜ</td>
<td>3.29 ± 2.3</td>
<td>28.9 ± 2.7</td>
<td>32.4 ± 2.7</td>
<td>29.6 ± 2.7</td>
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<tr>
<td>Vcfₑ(cm³/cm²²)</td>
<td>1.04 ± 0.09</td>
<td>0.93 ± 0.09</td>
<td>1.05 ± 0.07</td>
<td>0.94 ± 0.08</td>
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<td>SVI(cm³/m²BSA)</td>
<td>48 ± 5</td>
<td>44 ± 4</td>
<td>47 ± 6</td>
<td>43 ± 6</td>
</tr>
<tr>
<td>CI(cm³/m²²BSA)</td>
<td>2.83 ± 0.26</td>
<td>2.49 ± 0.25</td>
<td>2.68 ± 0.31</td>
<td>2.41 ± 0.28</td>
</tr>
</tbody>
</table>

Ao = aortic; BSA = body surface area; CI = cardiac index; Dₜₜ = left ventricular end-diastolic dimension; Dₜₜ = left ventricular end-systolic dimension; E = esmolol; F = famotidine; LV = left ventricular; F = placebo; %ΔDₜₜ = left ventricular percent fractional shortening; σₑₜ = left ventricular end-systolic circumferential wall stress; SVI = stroke volume index; TVR = total vascular resistance; Vcfₑ = left ventricular rate-corrected velocity of fiber shortening.

For left ventricular afterload under conditions of famotidine alone, famotidine plus esmolol, placebo alone and esmolol alone. For this subject, all Vcfₑ values were determined at a level of end-systolic wall stress (i.e., 188 g/cm²) that was common to all four of the σₑₜ – Vcfₑ lines. A similar evaluative process was performed for each subject. For the group, the average end-systolic stress used for comparative purpose was 193 ± 18 g/cm².

Placebo versus famotidine (Fig. 4A). The Vcfₑ for famotidine (0.97 ± 0.10 circumferences/s) did not differ from the value acquired for placebo (0.97 ± 0.09 circumferences/s). The average ΔVcfₑ for famotidine was 0.006 ± 0.013 circumferences/s above the placebo line (p = 0.14). The shaded area of this and all other panels of Figures 4 and 5 delineates the ΔVcfₑ values at ±0.02 circumferences/s from the reference line. This deviation represents the potential error of the method for any individual subject (19). Data for 9 of the 10 placebo versus famotidine comparisons fell within these limits; the remaining data point was slightly above the limits.

Placebo versus esmolol (Fig. 4B). The Vcfₑ for esmolol (0.89 ± 0.09 circumferences/s) was lower (p < 0.001) than the value for placebo. The average ΔVcfₑ for esmolol was 0.076 ± 0.013 circumferences/s below the placebo line (p < 0.001). All data points were well outside the ±0.02 circumferences/s limits.

Famotidine versus famotidine plus esmolol (Fig. 5A). The Vcfₑ for famotidine plus esmolol was 0.90 ± 0.09 circumferences/s. This value differed significantly (p < 0.001) from the value for famotidine alone. The average ΔVcfₑ for famotidine plus esmolol was 0.077 ± 0.013 circumferences/s below the famotidine line (p < 0.001). All data points were well outside the ±0.02 circumferences/s limits.
Esmolol versus famotidine plus esmolol (Fig. 5B). The \( \Delta Vcf \) values for famotidine plus esmolol and esmolol were similar (\( p = 0.90 \)). The average \( \Delta Vcf \) for famotidine plus esmolol was 0.005 ± 0.009 circumferences/s above the esmolol line (\( p = 0.21 \)). All data points were within the ±0.02 circumferences/s limits.

**Discussion**

**Hemodynamic effects of \( H_2 \) receptor blockade.** In this clinical study, the direct and indirect effects of \( H_2 \) receptor blockade on myocardial mechanics and contractility were assessed. By increasing blood pressure with the pure alpha-agonist methoxamine, it was possible to compare data at common left ventricular loading conditions in a given patient regardless of whether famotidine, placebo or the rapidly acting beta-blocker esmolol was administered. This protocol had the unique feature that it allowed analysis of data with the cardiac sympathetic nervous system intact as well as pharmacologically ablated. Within this framework, there was no evidence that circulating blood histamine contributes to basal left ventricular contractile tone. All measurements of overall left ventricular systolic performance were similar for placebo and famotidine data. The only hemodynamic effect of famotidine that approached statistical significance was a 3-beat/min decrease in heart rate compared with that obtained with placebo. This is similar to the previously reported cardiac slowing effect of orally administered cimetidine and ranitidine (5,31,32).

**Comparisons with previous studies.** How can one account for the disparity in conclusions between the current data and the studies of Kirch and Hinrichsen and coworkers (10,11)? The famotidine dosage, route of administration and dosing schedule as well as the study groups cannot be the explanation because they were comparable in all three investigations. The most feasible explanation lies in differences in the hemodynamic variables evaluated and the inherent limitations of the methodologies used. In the studies of Kirch and Hinrichsen et al. (10,11), nonspecific indexes of overall left ventricular performance were employed. Systolic time intervals showed an increase in the ratio of prejection period to left ventricular ejection time. However, values for this ratio vary widely in normal subjects (33,34) and are dependent upon multiple factors including daily variations in left ventricular stroke volume, preload, and afterload (33,35). Similarly, their observation that left ventricular stroke volumes determined by impedance cardiography decreased with famotidine should be assessed critically. The scientific basis for this technique, which records changes in the electrical
impedance of the thoracic cavity with blood flow, is not fully understood (36,37). However, it is generally accepted that the accuracy of stroke volume estimates by impedance cardiography is dependent on many factors including the subject's body size, muscle to fat content ratio, blood resistivity, valvular competence and thoracic shape and composition (37,38).

In contrast, the present randomized, placebo-controlled study used standardized echocardiographic and external pulse tracing techniques to generate preload- and heart rate-independent indexes of myocardial contractile state measured at common levels of left ventricular afterload with and without beta-adrenoceptor blockade. This experimental design eliminated left ventricular load, cardiac frequency and reflex sympathetic responses as possible confounding variables. Thus, while the cause for the differences in conclusions between our data and those of Kirch and Hinrichsen et al. (10,11) cannot be specifically defined, the current study more closely approximates the experimental ideal of controlling as many physiologic variables as is feasible. Furthermore, the results from our investigation are in agreement with the large clinical experience which suggests that histamine H2 antagonists are hemodynamically benign in patients with a wide variety of cardiovascular abnormalities.

Conclusions. Neither circulating blood histamine nor H2 receptor blockade has a significant impact on basal left ventricular contractile state in humans.

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References