Heart Failure

Impact of Blockade of Histamine H$_2$ Receptors on Chronic Heart Failure Revealed by Retrospective and Prospective Randomized Studies

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OBJECTIVES	The goal of this work was to determine whether the blockade of histamine H$_2$ receptors is beneficial for the pathophysiology of chronic heart failure (CHF).
BACKGROUND	Because CHF is one of the major life-threatening diseases, we need to find a novel effective therapy. Intriguingly, our previous study, which predicts the involvement of histamine in CHF, suggests that we should test this hypothesis in patients with CHF.
METHODS	We selected 159 patients who received famotidine among symptomatic CHF patients for the retrospective study. We blindly selected age- and gender-matched CHF patients receiving drugs for gastritis other than histamine H$_2$ receptor blockers as a control group. For the prospective study, 50 symptomatic CHF patients were randomly divided into 2 groups. One group received famotidine of 30 mg/day for 6 months, and the other group received teprenone.
RESULTS	In the retrospective study, famotidine of 20 to 40 mg decreased both left ventricular end-diastolic and end-systolic lengths (LVDd and LVDs, respectively) and the plasma B-type natriuretic peptide (BNP) levels (182 ± 21 vs. 259 ± 25 pg/ml, $p < 0.05$) with unaltered fractional shortening (FS). In a randomized, open-label study, compared with teprenone, famotidine of 30 mg prospectively decreased both New York Heart Association functional class ($p < 0.05$) and plasma BNP levels (183 ± 26 pg/ml vs. 285 ± 41 pg/ml, $p < 0.05$); this corresponded to decreasing both LVDd (57 ± 2 mm vs. 64 ± 2 mm, $p < 0.05$) and LVDs (47 ± 2 mm vs. 55 ± 2 mm, $p < 0.05$) with unaltered FS ($15 \pm 1\%$ vs. $17 \pm 1\%$). The frequency of readmission because of worsening of CHF was lower in the famotidine group (4% and 24%, $p < 0.05$). On the other hand, teprenone had no effects on CHF.
CONCLUSIONS	Famotidine improved both cardiac symptoms and ventricular remodeling associated with CHF. Histamine H$_2$ receptor blockers may have therapeutic benefits for CHF. (J Am Coll Cardiol 2006;48:1378–84) © 2006 by the American College of Cardiology Foundation

Despite current medical therapy for patients with chronic heart failure (CHF) such as angiotensin-converting enzyme (ACE) inhibitors or beta-adrenergic receptor blockers (1), CHF remains one of the major causes of high morbidity and mortality worldwide. Chronic heart failure is characterized by cardiac symptoms, impaired cardiac performance, cardiac

mechanical stress, and neurohormonal imbalance (2). Indeed, increased levels of catecholamines, cytokines, and angiotensin II are thought to play important roles in the

pathophysiology and development of CHF (3,4). Histamine is one of the neurohormonal factors that provoke various cellular functions via stimulation of histamine H$_1$-H$_3$ receptors (5,6). Specifically, because histamine H$_2$ receptors are known to be located in gastric cells and enhance the production of acids that cause gastric ulcers, the blocker of histamine H$_2$ receptors is developed as the drug for the treatment of gastric ulcers (7). Interestingly, we have previously predicted that histamine H$_2$ receptor blockers may be cardioprotective in patients with CHF using the data mining technique (8). The histamine H$_2$ receptor is also located in the cardiomyocytes, and this receptor is coupled to Gs protein as well as is the beta receptor (9–13). Indeed, it is reported that: 1) histamine provokes positive inotropic effects (11,14); and 2) the blocker of histamine H$_2$ receptors decreases cardiac output (14). The important roles of mast cells and released histamine are also accepted in the cardiovascular system (15).

We tested the hypothesis that the blockade of histamine H$_2$ receptors by famotidine is beneficial for the pathophys-

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Abbreviations and Acronyms
ACE    = angiotensin-converting enzyme
AMP    = adenosine monophosphate
BNP    = brain natriuretic peptide
CHF    = chronic heart failure
FS     = fractional shortening
GERD   = gastroesophageal reflux disease
LVDd   = left ventricular end-diastolic volume
LVDs   = left ventricular end-systolic volume
NYHA   = New York Heart Association
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iology of CHF in retrospective and prospective randomized studies.

METHODS

This study was approved by the ethical committee of National Cardiovascular Center. Informed consent was obtained from all patients before participation in this study in accordance with institutional approved protocols.

Study population and protocols. THE RETROSPECTIVE STUDY. A total of 1,104 consecutive subjects who were admitted to our hospital for treatment of CHF between January 2002 and April 2004 were candidates for this study. The criteria for enrollment in this study were: 1) clinical evidence of heart failure despite the conventional therapy; and 2) left ventricular fractional shortening (FS) below 30%, as assessed by 2-dimensional echocardiography. All the patients had New York Heart Association (NYHA) functional classifications of II to III, but were stable for 2 months after their discharge. Among these patients, we selected the patients who received famotidine of 20 to 40 mg (n = 159, the famotidine group). In the control group, the patients were selected so as to be matched for age, gender, and the cause of CHF (n = 159). We randomly selected age-, gender-, and cause-matched patients for the other drug of non-histamine H_2 blocker for gastritis (n = 159). Among the 159 patients in each group, the number of patients who suffered from dilated cardiomyopathy, hypertensive heart disease, ischemic cardiomyopathy, and valvular heart disease were 71, 11, 39, and 38, respectively. Clinical parameters of the plasma brain natriuretic peptide (BNP) levels and echocardiography were obtained. We estimated the NYHA functional classification of each patient by 3 independent cardiologists who were blinded to the medical treatment of CHF. If the estimations of all 3 doctors did not agree, we decided to take the median among 3 values of NYHA functional classification.

The prospective studies: the effects of famotidine. We studied 50 patients with symptomatic CHF and gastroesophageal reflux disease (GERD) in our institute. Gastroesophageal reflux disease was diagnosed by questionnaires reported previously (16). The criteria for enrollment in this study were clinical evidence of heart failure despite the conventional therapy and a left ventricular FS below 30%, as assessed by 2-dimensional echocardiography, and existence of GERD. All the patients had NYHA functional classifications of II to III. There were 32 men and 18 women with a mean age of 65 years. The number of patients diagnosed as CHF because of dilated cardiomyopathy, hypertensive heart disease, ischemic cardiomyopathy, and valvular heart disease were 17, 2, 4, and 2 in each group, respectively. Exclusion criteria included chronic obstructive pulmonary disease, pregnancy, and severe liver disease as defined by having hepatic enzymes >2 times the upper limit of normal values. All patients were treated by optimal and stable doses of beta-blockers and ACE inhibitors for at least 3 months before screening echocardiography and randomization. We did not change the doses of these drugs after the enrollment. Patients were randomly divided into 2 treatment groups: famotidine (n = 25, the famotidine group) and teprenone (n = 25, the control group). The doses of famotidine and teprenone were 30 and 150 mg per day, respectively, and there were no patients who discontinued the intake of either famotidine or teprenone, and drugs for CHF.

In the current study, we tested the hypothesis that famotidine, the histamine H_2 receptor blocker, may have therapeutic benefits for CHF in the clinical settings. The primary end point is to assess the changes in NYHA functional class and the plasma BNP levels from the baseline to 24 weeks. We estimated the NYHA functional classification of each patient by 3 independent cardiologists who were blinded to the treatment assignment of famotidine. If the estimations of all 3 doctors did not agree, we decided to take the median among 3 values of NYHA functional classification. Additional analyses were done using the echocardiogram to obtain the changes in left ventricular or atrial volume, and the pressure differences across the tricuspid valve from baseline to 24 weeks. Furthermore, the frequency of readmission because of worsening of CHF within 24 weeks was investigated.

Estimating from retrospective study results showing that the reduction of the plasma BNP levels was about 30%, 25 patients were required for each study group. A randomization was performed according to a computer generated randomization list by central telephone call or fax to Clinical Study Support Center Japan (Suita Osaka, Japan).

Effects of teprenone. There is a possibility that teprenone has deleterious effects on the pathophysiology of CHF, and if this were the case, famotidine would appear to be beneficial, when famotidine has no cardioprotective effects. To examine this possibility, we administered teprenone to 10 patients with CHF for 24 weeks, and compared 10 CHF patients without the teprenone treatment. The criteria for the enrollment, evaluated parameters, and the evaluation procedure were the same as in the study of famotidine described earlier in the text.

Analysis of parameters for CHF. Blood samples were collected in test tubes containing ethylenediaminetetraacetic acid at baseline and after 24 weeks of the treatment. The plasma was separated from blood cells by centrifugation and frozen at −80°C. Plasma concentrations of BNP were

measured using a specific immunoradiometric assay (17). The personnel performing these assays were blinded to the patients' treatment assignments.

M-mode echocardiography was performed with 2-dimensional monitoring using a Sono layer phased-array sector scanner (SONOS 5500, Hewlett Packard, Palo Alto, California) before and after 24 weeks of the treatment with famotidine or teprenone (18). All echocardiograms were read by the same physician, at baseline and after 24 weeks of the treatment, who was blinded to patients' treatment, assignment, and time point.

Statistical analysis. Data are presented as mean ± SEM. Statistical analysis was performed using paired or unpaired t test for numerical values, and either chi-square tests or Wilcoxon signed rank test for categorical values. B-type natriuretic peptide levels were logarithmically transformed to perform the statistical analysis. Furthermore, we used two-way repeated-measures analysis of variance when we compared the changes of each parameter in 2 groups. The chi-square tests were also performed to test the differences of the incidence of the readmission. All statistical analyses were performed using Stat View version 5.0 for Windows (SAS Institute, Cary, North Carolina) and SPSS 10.0.5J software (SPSS Inc., Chicago, Illinois).

Table 1. Clinical Parameters of CHF With or Without Famotidine

	Control Group (n = 159)	Famotidine Group (n = 159)
Age (yrs)	66 ± 1	66 ± 1
M/F gender (%)	97/62 (61/39)	97/62 (61/39)
Hypertension (%)	11 (7)	11 (7)
Duration of CHF (yrs)	8.7 ± 0.7	8.5 ± 0.8
Systolic blood pressure (mm Hg)	112 ± 9	105 ± 8*
Diastolic blood pressure (mm Hg)	67 ± 4	62 ± 5*
Heart rate (beats/min)	73 ± 5	66 ± 5*
Fractional shortening (%)	24 ± 1	23 ± 1
LV diastolic diameter (mm)	58 ± 2	54 ± 1*
LV systolic diameter (mm)	44 ± 1	41 ± 1*
LA diameter (mm)	40 ± 3	39 ± 3
Pressure across tricuspid valve (mm Hg)	30 ± 2	28 ± 2
Plasma BNP levels (pg/ml)	259 ± 25	182 ± 21*
NYHA functional class: II/III (%)	75/84 (47/53)	97/62 (61/39)*
Concomitant drugs, n (%)		
Digoxin	126 (80)	134 (84)
Diuretics except spironolactone	140 (88)	137 (86)
Nitrates	80 (25)	32 (20)
Beta-blockers	143 (90)	137 (86)
ACE inhibitors	127 (80)	121 (76)
ARB	118 (20)	38 (24)
Spironolactone	25 (20)	25 (20)

Values are either numbers of each group, range, or mean ± SEM. *p < 0.05 vs. the control group.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; CHF = chronic heart failure; LA = left atrium; LV = left ventricular; NYHA = New York Heart Association; Fractional shortening (%) = (left ventricle end-diastolic diameter − left ventricle end-systolic diameter)/left ventricle end-diastolic diameter.

Table 2. Baseline Characteristics of the Study Population

|	Teprenone Group (n = 25)	Famotidine Group (n = 25)
Age (yrs)	65 ± 2	65 ± 2
M/F gender (%)	16/9 (64/36)	16/9 (64/36)
NYHA functional class: II/III (%)	8/17 (32/68)	10/15 (40/60)
Hypertension (%)	4 (16)	6 (24)
Duration of CHF (yrs)	11.2 ± 1.7	13.2 ± 2.3
Systolic blood pressure (mm Hg)	113 ± 3	112 ± 3
Diastolic blood pressure (mm Hg)	68 ± 3	67 ± 2
Heart rate (beats/min)	83 ± 3	83 ± 2
Fractional shortening (%)	15 ± 1	15 ± 1
LV diastolic diameter (mm)	65 ± 2	64 ± 2
LV systolic diameter (mm)	55 ± 2	55 ± 2
LA diameter (mm)	43 ± 2	42 ± 2
Pressure across tricuspid valve (mm Hg)	33 ± 3	36 ± 3
Plasma BNP levels (pg/ml)	268 ± 28	286 ± 41
Concomitant drugs, n (%)		
Digoxin	24 (96)	22 (84)
Diuretics except spironolactone	25 (100)	25 (100)
Nitrates	7 (28)	4 (16)
Beta-blockers	25 (100)	25 (100)
ACE inhibitors	23 (92)	21 (84)
ARB	2 (8)	4 (16)
Spironolactone	10 (40)	8 (32)

Values are either numbers of each group, range, or mean ± SEM.
Abbreviations as in Table 1.

RESULTS

After age and gender matching, as shown in Table 1, the gender ratio and the average age of the 2 groups were similar. There were no significant differences of the variety of medical treatment drugs between the 2 groups. Blood pressure, heart rate, NYHA functional class, the plasma BNP levels, and left ventricular dimensions were smaller in the famotidine group compared with the control group. There were no differences between FS in the 2 groups. This result suggests that famotidine may be beneficial for pathophysiology of CHF.

As for the prospective randomized famotidine treatment protocol, medications were well tolerated over the 24-week period. The participants were recruited from September 2004 to October 2004. Participants attended clinic visits at the time of randomization (baseline) and at 4- to 8-week intervals for 24 weeks. All patients completed the protocol (50 of 50). No patients died during the 24-week study. In addition, the doses of beta-blockers, ACE inhibitors, and diuretics were not altered during the course of the entire study.

There were no differences in age, gender, or concurrent medications between the control and famotidine groups (Table 2). Blood pressure and heart rate were not different between the groups with and without famotidine before the treatment. Famotidine administration slightly decreased blood pressure (systolic and diastolic blood pressure 107 ± 3 mm Hg vs. 112 ± 3 mm Hg, p < 0.01 and 60 ± 3 mm Hg vs. 67 ± 2 mm Hg, p < 0.05) and heart rate (79 ± 2
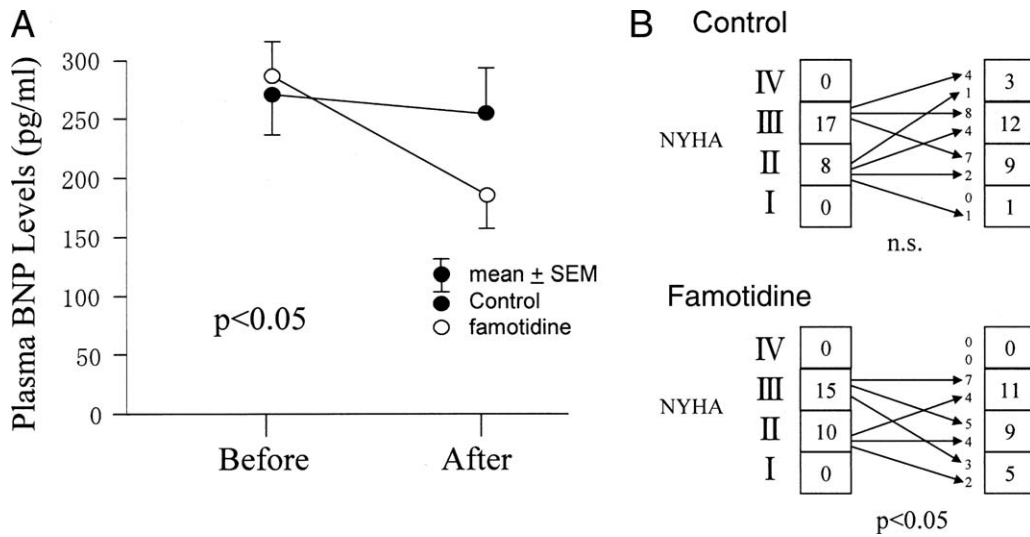
Figure 1. Changes in the plasma B-type natriuretic peptide (BNP) levels **(A)** and New York Heart Association (NYHA) functional classification **(B)** before and after the treatment with (the famotidine group) or without famotidine (the control group). The plasma BNP levels are statistically analyzed after the log transformation. The p values are obtained using 2-way repeated-measures analysis of variance **(A)** or Wilcoxon signed rank test **(B)**.

min^{-1} vs. 83 ± 2 min^{-1}, $p < 0.05$), whereas the control group did not exhibit changes in either blood pressure (systolic and diastolic blood pressure 113 ± 3 mm Hg vs. 113 ± 3 mm Hg and 68 ± 3 mm Hg vs. 68 ± 3 mm Hg) or heart rate (81 ± 3 min^{-1} vs. 83 ± 3 min^{-1}) before and 24 weeks after the treatment. The patients who received famotidine demonstrated improved functional capacity assessed by the plasma BNP levels and NYHA functional

class (Fig. 1). Plasma BNP level and NYHA functional class were unchanged after 24 weeks in the group without famotidine. The functional improvement in the famotidine group was associated with improved cardiac performance. Compared with the group without famotidine, the patients treated with famotidine had lower left ventricular end-diastolic volume (LVDd) and left ventricular end-systolic volume (LVDs) while keeping FS unchanged (Fig. 2). The
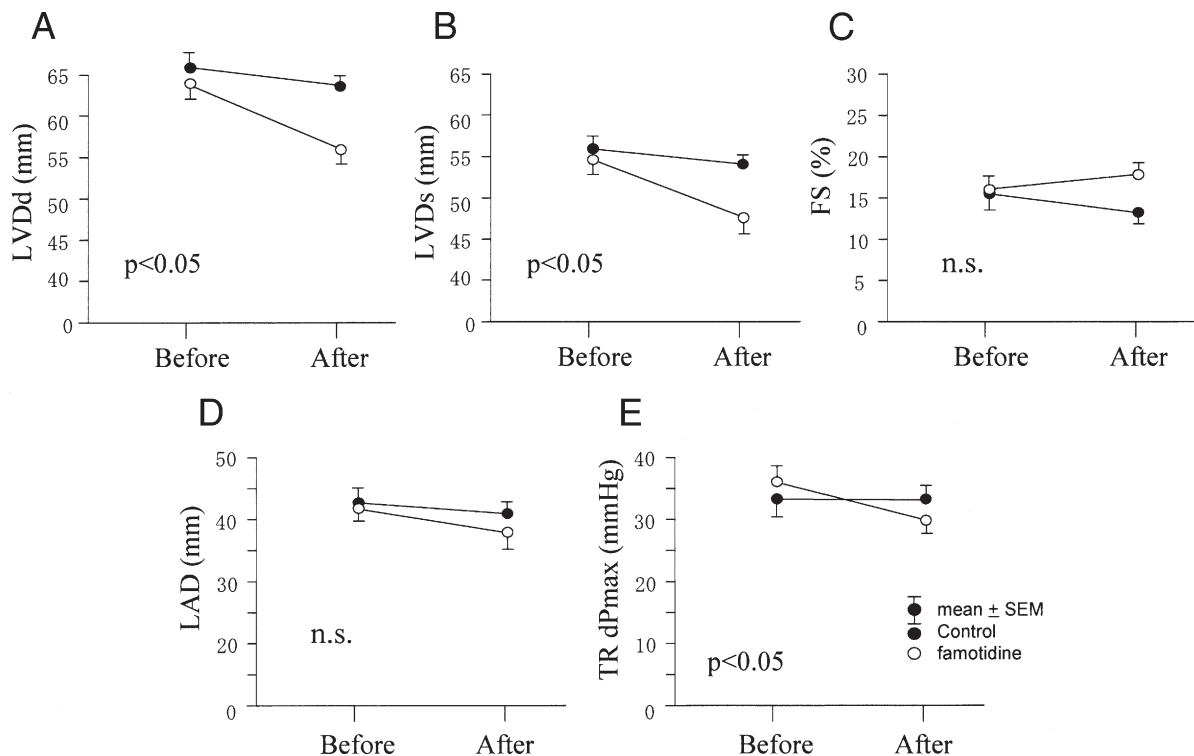
Figure 2. Changes in left ventricular (LV) end-diastolic volume (LVDd) **(A)** or end-systolic volume (LVDs) **(B)**, LV fractional shortening (FS) **(C)**, left atrial diameter (LAD) **(D)**, and the pressure differences across the tricuspid valve (TR dPmax) **(E)** before and after 24 weeks of treatment in the control and famotidine groups. The p values are tested using 2-way repeated-measures analysis of variance.

Table 3. Baseline Characteristics of the Study Population

	Teprenone Group (n = 10)	No Treatment Group (n = 10)
Age (yrs)	67 ± 4	68 ± 3
M/F gender (%)	7/3 (70/30)	7/3 (70/30)
NYHA functional class: II/III (%)	2/8 (20/80)	2/8 (20/80)
Hypertension (%)	2 (20)	2 (20)
Duration of CHF (yrs)	12.1 ± 2.8	12.0 ± 1.3
Systolic blood pressure (mm Hg)	109 ± 5	114 ± 4
Diastolic blood pressure (mm Hg)	64 ± 4	65 ± 32
Heart rate (beats/min)	75 ± 4	75 ± 2
Fractional shortening (%)	18 ± 3	18 ± 1
LV diastolic diameter (mm)	66 ± 4	65 ± 1
LV systolic diameter (mm)	53 ± 3	54 ± 1
LA diameter (mm)	45 ± 2	45 ± 2
Pressure across tricuspid valve (mm Hg)	36 ± 3	34 ± 2
Plasma BNP levels (pg/ml)	246 ± 48	248 ± 26
Concomitant drugs, n (%)		
Digoxin	10 (100)	10 (100)
Diuretics except spironolactone	10 (100)	10 (100)
Nitrates	2 (20)	1 (10)
Beta-blockers	10 (100)	10 (100)
ACE inhibitors	9 (90)	7 (70)
ARB	0 (0)	3 (30)
Spironolactone	5 (50)	5 (50)

Values are either numbers of each group, range, or mean ± SEM.
Abbreviations as in Table 1.

frequency of readmission because of worsening of CHF was lower in the famotidine group compared with the control group (1 [4%] and 6 [24%], difference [95% confidence interval] 20% [2 to 38], p < 0.05).

As for the prospective randomized teprenone treatment protocol, medications were well tolerated over the 24-week period. The participants were recruited from September 2004 to October 2004. Participants attended clinic visits at the time of randomization (baseline) and at 4- to 8-week intervals for 24 weeks. All patients completed the protocol (20 of 20). No patients died during the 24-week study. In addition, the doses of beta-blockers, ACE inhibitors, and diuretics were not altered during the course of entire study. There were no differences in age, gender, or concurrent medications between the control and famotidine groups (Table 3). We found that teprenone does not affect the severity of CHF (the plasma BNP levels: 246 ± 48 pg/ml vs. 234 ± 49 pg/ml, LVDd: 65.8 ± 3.6 mm vs. 65.6 ± 3.7 mm, LVDs: 53.2 ± 2.9 mm vs. 53.8 ± 3.6 mm, FS: 18.7 ± 2.8% vs. 18.3 ± 1.3% before and 24 weeks after an administration of teprenone) in comparison with the patients without the teprenone treatment (the plasma BNP levels: 248 ± 26 pg/ml vs. 238 ± 18 pg/ml, LVDd: 65.1 ± 1.3 mm vs. 66.7 ± 1.5 mm, LVDs: 53.6 ± 1.4 mm vs. 55.1 ± 1.2 mm, FS: 17.7 ± 1.3% vs. 17.2 ± 1.0% at observation time of 0 and 24 weeks). The frequency of readmission because of worsening of CHF was identical between the teprenone and control groups (2 [20%] and 2 [20%]).

DISCUSSION

In the present study, we demonstrate that the blockade of histamine H_2 receptors favors the improvements of the pathophysiology of CHF via retrospective and prospective clinical trials. These conclusions propose the novel findings that histamine that stimulates histamine H_2 receptors is one of the neurohumoral factors for the worsening of CHF, and that the blockade of histamine H_2 receptors becomes the novel strategy for the treatment of CHF.

Histamine in failing hearts. We have shown that histamine release is augmented in the ischemic myocardium compared with the non-ischemic myocardium in dogs (unpublished data). When the mast cells that store histamine are stimulated by ischemia or mechanical stress, mast cells actively release histamine. There are reports that mast cells are found in the human heart (19) and have been implicated in cardiovascular diseases (15,20,21). Indeed, the increase of mast cells have been observed in the hearts of patients with hypertrophy (22), dilated cardiomyopathy, ischemic cardiomyopathy (23), and ischemia/reperfusion (24), and the infarction-related coronary arteries (25). Furthermore, histamine is present in high concentrations in cardiac tissues in most animal species, including humans (10,26,27), and its release from cardiac stores and the subsequent actions on the heart may be of importance in the pathophysiology of heart disease. These lines of evidence agree with the present observation that the blockade of histamine H_2 receptors in failing hearts has an impact on the pathophysiology of CHF.

The role of histamine receptors in failing hearts. The histamine receptors (H_1, H_2, H_3, and H_4) are all G protein-coupled molecules, and they transduce extracellular signals via Gq, Gs, and Gi/o, respectively (5,6,28). Specifically, histamine H_2 receptors are linked to Gs proteins that facilitate the production of cyclic adenosine monophosphate (AMP) as beta-adrenoreceptors are (29). Histamine H_2-receptor-stimulated cAMP accumulation or adenylyl cyclase activator has been demonstrated in a variety of tissues including gastric cells (10,30), vascular smooth muscle cells (31), brain (10,32), and cardiac tissue (10,33). Beta-adrenoreceptor blockers are known to be cardioprotective in failing hearts because the accumulation of cyclic AMP after the activation of beta-adrenoreceptors enhances both myocardial contractility and oxygen consumption, which deteriorates heart function in patients with CHF (34,35). In addition, it has been reported that histamine is a powerful vasoconstrictor in atherosclerotic coronary arteries (36), which may locally provoke coronary spasm and thus contribute to the onset of myocardial infarction (23). The importance of beta-adrenoreceptor blockers depends on the presence of both catecholamine and beta-adrenoreceptors in the heart. Therefore, because histamine H_2 receptors and histamine are located in failing human hearts, it is likely that blockers of histamine H_2 receptors are as cardioprotective against failing hearts as beta-adrenoreceptor blockers are.

Because famotidine decreases both blood pressure and heart rate, this may improve the pathophysiology of CHF. Indeed, the reduction of afterload or preload and heart rate seems to be an important factor in the treatment of CHF. This is also the case in either beta-adrenoreceptor blockers or ACE inhibitors in patients with heart failure. Either beta-adrenoreceptor blockers or ACE inhibitors are still effective independent of the reduction of loading condition to the heart, because they inhibit the signal transduction for deterioration of cardiac function. Because histamine increases cyclic AMP levels in the cardiomyocytes via histamine H_2 receptors, famotidine may be beneficial through both load-reduction-dependent and -independent mechanisms.

Clinical importance. Beta-adrenoreceptor blockers have been shown to be effective for treating ischemic heart diseases and heart failure (37), and histamine receptor blockers are similar to beta-adrenoreceptor blockers. Histamine plays an important role in the regulation and mal-regulation of cardiac and coronary function. Furthermore, the histamine receptor blockers such as famotidine that are used for peptic ulcers or GERD all over the world could be used for ischemic heart diseases. Furthermore, beta-adrenoreceptor blockers ameliorate the severity of heart failure, and histamine receptor blockers may be beneficial for patients with CHF. However, we should note that the 3 H_2 receptor blockers administered for 7 days at clinical dosages had no significant effect on left ventricular systolic function, aerobic metabolic performance, or exercise capacity in men with class II or III stable CHF (38). This suggests that a relatively long-term administration of histamine receptor blockers is necessary to mediate the cardio-protective effects of histamine receptor blockers in patients with CHF as a relatively long-term administration of beta-adrenoreceptor blockers is necessary for the treatment of CHF (37).

Moreover, because famotidine was administered in addition to the aggressive treatments with beta-adrenoreceptors blockers, ACE inhibitors, and diuretics, and we proved that famotidine further improves the pathophysiology of CHF, it is possible to develop famotidine for the drug of CHF, although we need to plan and perform a large-scale clinical trial for the investigation of the effects of famotidine on CHF. We also need to clarify the best dose of famotidine for the treatment of CHF.

Study limitations. The present study has several limitations that we need to pay attention to. First of all, the first part of the data was obtained from the retrospective analysis, and seemed to be influenced by many factors, although Table 1 showed low BNP levels and low ventricular volumes in the famotidine group suggested the preventive effects of famotidine on cardiac remodeling. To strengthen the hypothesis obtained by the retrospective study, we performed the prospective analysis using either famotidine or teprenone.

The second limitation is that the second part of the study was an open-labeled, randomized trial using small sampling size. However, to decrease these weaknesses, we used the objective end points such as the plasma BNP levels and left ventricular dimensions, and we also tried to exclude the subjective scope of the assessment of NYHA functional classification.

Third, the severities of pathophysiology of CHF in the retrospective and prospective studies were different. The severity of CHF in enrolled patients in prospective study is higher than that in the retrospective study. This is because we enrolled the patients from the different protocols. Nevertheless, because both studies suggest that famotidine is effective for patients with CHF, we may be able to suggest the beneficial effects of famotidine to treat patients with CHF.

Fourth, if teprenone could be deleterious to the pathophysiology of CHF, famotidine seemed to be beneficial compared with teprenone even if famotidine has no beneficial effects on CHF. Before planning the present study, we tested the effects of pathophysiology of CHF, and we found that teprenone has no beneficial or deleterious effects on CHF in the present study.

Fifth, either famotidine or teprenone may directly affect the plasma half-life or excretion of BNP. If this is the case, the plasma BNP levels may be altered independent of the improvements of CHF. We cannot deny this possibility, however, because left ventricular dimension becomes smaller in the famotidine group, suggesting that famotidine is beneficial for the heart of CHF patients.

Sixth, we should notice that an interaction of gastritis with heart failure could confound their conclusion regarding the effect of histamine blockade. Indeed, it may be still possible to consider that famotidine improves cardiac function via an improvement of GERD if GERD worsens CHF, because we have no positive or negative data to link GERD and CHF. We should investigate this possibility to explain the effects of H_2 receptor blockers on CHF in further study.

In summary, despite these limitations, we proposed the hypothesis that H_2 receptor blockers are effective for the treatment of CHF, and we need to verify the beneficial effects of H_2 receptor blockers such as ranitidine or cimetidine as well as famotidine in CHF patients with a large-scale trial.

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