Short-Term and Long-Term Effects of Bisoprolol on Chronic Heart Failure Related to Rheumatic Heart Disease and Atrial Fibrillation

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ABSTRACT

Objective: We investigated whether a selective beta, blocker, bisoprolol, improved chronic heart failure (HF) related to rheumatic heart disease (RHD) and atrial fibrillation (AF).

Methods: We randomly assigned 88 chronic HF patients with RHD, a cardiothoracic ratio below 65%, and AF with a resting ventricular rate of 70 beats/minute or more for at least three months to either a treatment group or a control group. All patients received basic therapy: a diuretic, digoxin, an angiotensin-converting enzyme (ACE)–inhibitor/angiotensin receptor blocker (ARB), or nitrates, depending on their blood pressure level and the presence of valvular lesions. All patients also received warfarin. Patients in the treatment group received bisoprolol. We then compared the short-term and long-term clinical and hemodynamic variables between the two groups.

Results: Basic Characteristics. Thirty-three treated patients (75.0%) and 34 control patients (77.3%) completed the study. The follow-up period for both groups of patients was similar. There were no significant differences in age, sex, duration, the use of diuretics and ACE-inhibitors or ARBs, left ventricular (LV) end-diastolic dimension, or left atrial (LA) diameter. The LV ejection fraction (LVEF) for all patients was found to be higher than 40% in the two groups. Only three patients had an LVEF below 45%. The average maximum bisoprolol dose was 6.52 ± 2.7 mg/day in the treatment group; 54.5% of the patients tolerated at least 5 mg of bisoprolol once daily.

Short-Term Results. The length of hospital stay was significantly shorter for the treated patients. At hospital discharge, these patients had a slower 24-hour average ventricular rate and were able to walking farther over a period of six minutes, compared with the control group.

Long-Term Results. During the follow-up period, the combined endpoint of chronic HF-related and thromboembolism-related death or hospitalization in the treated patients was significantly lower than that in the control patients. After six to 12 months, only the control patients had a higher 24-hour average ventricular rate, a worse New York Heart Association (NYHA) class, and a lower exercise capacity. In contrast, the treatment group showed improved NYHA class and exercise capacity as well as a lower 24-hour average ventricular rate, lower systolic blood pressure; and a significantly decreased LA diameter. However, no significant changes in the LVEF or LV end-diastolic dimension were noted in the two groups during follow-up.

Summary: The data suggest that a selective beta, blocker might improve NYHA class and exercise tolerance for patients with chronic HF related to RHD and AF. Furthermore, the advantage of these effects provided by this agent might be mediated by a reduction in ventricular rate and LA volume.

KEY WORDS: beta blocker, heart failure, rheumatic heart disease, atrial fibrillation

INTRODUCTION

Traditionally, chronic heart failure (HF) has been attributed to a reduced systolic left ventricular (LV) function, accompanied by an increase in LV filling pressures and volumes (also called “systolic HF”). The important role of neurohormones in the pathophysiology of chronic HF is well recognized. Chronic HF is characterized by an increased activity of the neurohormonal system, such as the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS).

Beta-adrenergic blocking agents (beta blockers) and angiotensin-converting enzyme (ACE)–inhibitors or angiotensin II receptor blockers (ARBs) are well known as keystones in the medical treatment of systolic HF because of their ability to suppress sympathetic drive and the RAAS.1,2 However, during the past decade, it has become clear that about 50% of all patients with chronic HF have preserved LV systolic function (also called “diastolic HF”).3 Diastolic HF is suspected in patients with signs and symptoms of HF and a normal or mildly reduced systolic LV ejection fraction (LVEF) greater than 40% and normal LV end-diastolic volumes.4,5 Diastolic HF may arise as a consequence of various underlying conditions that result in a modification of the physical properties of the myocardium. These conditions (e.g., hypertension, ischemic heart disease, atrial fibrillation [AF], and valvular heart disease) can cause a structural impairment of the heart.6,7

One study identified many patients with isolated AF or valvular heart disease, or both, who had dyspnea and normal or near-normal LV function.6 There is no doubt today that diastolic HF is a pathophysiological clinical condition, distinct from or concomitant with systolic HF.9 However, many questions remain, not the least of which concerns methods of treatment, because these two syndromes are not identical.

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Previous studies have confirmed that the sympathetic nervous system is activated prior to the RAAS during the development of chronic HF, and plasma norepinephrine is one of the most powerful predictors of mortality in early chronic HF. The Metoprolol CR/XL Randomized Intervention in Congestive Heart Failure (MERIT-HF) trial demonstrated consistent and similar improvement in outcomes of patients receiving controlled-release or extended-release metoprolol when combined with either a high or low dose of an ACE-inhibitor or digitalis or no digitalis at all.

Long-term beta-blocker treatment in chronic HF patients who have already been treated with ACE-inhibitors showed plasma renin levels comparable to those without ACE-inhibitors. Indeed, the suppression of angiotensin II by an ACE-inhibitor is more effective in patients who are also receiving a beta blocker, and the escape (inhibitive effect) of angiotensin II from ACE-inhibitors is attenuated in such patients. Beta blockers have a renin-inhibiting effect and therefore hinder the sympathetic nervous system as well as the RAAS. These results suggest that beta blockers probably have a more pronounced protective effect than ACE-inhibitors against elevations in neurohormones.

Rheumatic heart disease (RHD) often results in two main pathophysiological changes: mitral valve stenosis and AF. AF is the most common cause of chronic HF resulting from a loss of atrial contraction and an associated rapid ventricular rate in patients with RHD. Both mitral stenosis and AF result in a low cardiac output that activates the sympathetic nervous system. Ozdenir et al. noted increased sympathetic activity in patients with RHD, especially in patients whose disease was complicated by AF. AF was an independent predictor of a higher risk of diastolic HF in patients hospitalized with chronic HF.

Several studies have shown important differences in efficacy among different agents. Metoprolol succinate (e.g., Toprol®, AstraZeneca) and bisoprolol (e.g., Concor®, Merck) are both selective beta_1_ antagonists, whereas carvedilol (Coreg®, GlaxoSmithKline) is a nonselective beta blocker with additional beta_2_-blocking and antioxidant properties. A selective beta_1_ blocker without a vasodilatory effect can decrease the ventricular rate by suppressing sympathetic drive and without having a deteriorative effect on low cardiac output. Therefore, we thought that a selective beta_1_ blocker might be more feasible for treating chronic HF related to RHD concomitant with AF. However, the effects and mechanisms of this agent in this subgroup of patients remain to be explored.

The aim of our study was to analyze the effects of bisoprolol therapy for six to 12 months on the clinical symptoms and prognosis in patients with chronic HF and normal or near-normal systolic function related to RHD and AF.

METHODS

Study Population

We identified 143 patients with HF related to RHD and AF from our hospital’s cardiology ward between August 2000 and March 2002. Thirty-seven patients did not meet all of the inclusion criteria for enrollment, and 18 patients had clinical or echocardiographic data that caused them to be ineligible. Thus 88 patients were included in the study.

We obtained admission data by using case notes and a computerized hospital information system. The study was approved by the Ethics Committee of Southwest Hospital. We carefully explained the nature and purpose of the investigation to the patients, who gave their written informed consent.

Inclusion Criteria

 Patients were included in the study if they had (1) a history of uncorrected rheumatic heart valvular disease or New York Heart Association (NYHA) functional class III or IV disease, necessitating hospitalization; (2) a cardiothoracic ratio of less than 65%; (3) AF with a resting ventricular rate of 70 beats/minute or more for at least three months, as depicted on the electrocardiogram (ECG); and (4) an echocardiogram showing a significant mitral stenosis or aortic lesions and mitral valve regurgitation.

Exclusion Criteria

 Patients were excluded from the study if they had uncorrected congenital heart disease, sustained ventricular tachycardia, severe liver and kidney dysfunction, chronic obstructive pulmonary disease, bronchial asthma, obstructive or restrictive cardiomyopathy or myocarditis, myocardial infarction, or unstable angina within the previous three months. Patients were also ineligible for enrollment if they required intensive care or concurrent intravenous therapy or if they were using calcium-channel blockers, class I or III antiarrhythmic drugs, monoamine oxidase (MAO)–inhibitors or beta_2_-agonists.

On the basis of admission sequence, patients were randomly assigned to a treatment group or a control group. Concomitant therapy was kept as stable as possible throughout the study. All patients received warfarin for anticoagulation. At the discretion of the treating physicians, all patients were given concomitant therapy consisting of one of the following:

- diuretics, as required, to control fluid retention
- digoxin, extracted from Digitalis lanata
- ACE-inhibitors (or ARBs when ACE-inhibitors were not tolerated) unless there were specific contraindications
- nitrates, depending on the presence of valvular lesions and on blood pressure readings

Patients with predominant (pure or non-pure) mitral stenosis or a systolic blood pressure below 100 mm Hg did not receive an ACE-inhibitor or an ARB but often received nitrates unless nitrates were not well tolerated. The physicians followed the recommended titration schedule.

All patients in the treatment group received bisoprolol at the initial dose of 1.25 mg/day. The recommended maximal dose was 10 mg/day. The dose schedule for titration of the selective beta_1_ blocker was gradually increased over three to five days, by two to three weeks, to as high as 10 mg/day, with adjustments of diuretics and ACE-inhibitors, as clinically indicated.

If the resting heart rate was lower than 50 beats/minute or if patients had symptomatic postural hypotension (systolic blood pressure below 90 mm Hg), the upward titrated dose of bisoprolol was deferred, interrupted, or stepped down in the case of an increase in heart failure symptoms. The treatment period was six to 12 months.
Clinical Observations

The diagnosis of HF was confirmed if two or three of these criteria were met while patients were in the cardiology unit:22

- a documented history of heart failure necessitating hospitalization
- the presence of symptoms (orthopnea, dyspnea, asthenia, or respiratory rate over 28 breaths/minute at rest)
- physical findings (S3 gallop, rales, raised jugular distention, hepatojugular reflux, ascites, or edema and heart murmur)
- clinical or radiological signs of HF

Heart valve disease was classified as significant only if the following were present:23

- aortic stenosis with a gradient greater than 20 mm Hg
- mitral stenosis with a valve area of less than 1.5 cm²
- mitral valve regurgitation lesions of at least moderate severity

RHD was defined as significant mitral stenosis with accompanying mitral valve regurgitation or aortic lesions or with no other lesions at all.

The decrease in NYHA class I or greater was regarded as an improvement in heart function. The discharge markers included (1) NYHA class improvement, (2) a reduced number of chronic HF symptoms, and (3) increased signs of relief.

The combined endpoint included chronic HF-associated and thromboembolism-associated hospitalization or death but not hospitalization or death unrelated to chronic HF and thromboembolism.

An adverse drug event (ADE) was defined as (1) drug intolerance, particularly weakness, fatigue or dizziness, dyspnea, severe hypotension (below 90 mm Hg), and (2) a resting ventricular rate below 50 beats/minute.

All patients underwent 24-hour ambulatory ECG studies at hospital discharge and after six to 12 months of treatment. During the day of the test, patients were instructed to conduct their activities as usual. The 24-hour average ventricular rates were calculated according to the ambulatory ECG.

We obtained follow-up information by conducting telephone interviews with the patients or with follow-up visits by two physicians (one physician for the controls and another physician for the treated group). Topics included survivorship, the NYHA classification, chronic HF symptoms or signs, hospitalization, and the use of medications. The interviewer was not informed of the immediate outcome, the presence of valvular lesions, echocardiographic data, or the 24-hour ECG at discharge.

Echocardiography

Echocardiographic studies were performed with the HDI 5000 ultrasound system (Philips, The Netherlands). Both groups of patients received Doppler echocardiographic examinations at hospital discharge and after six to 12 months with an acceptable two-dimensional registration. All images were recorded and subsequently analyzed by experienced ultrasound physicians who did not know the patients’ classification or treatment.

LA diameters and LV end-systole and end-diastole dimensions were assessed by apical four-chamber views. The longest RR intervals (pauses between heartbeats) were selected to measure the ejection fraction (EF) as the best function seen for AF. The single-plane ellipse formula was used to calculate the EF.24 LV function was categorized as definitely impaired if the EF was less than 40%.

Predominant mitral stenosis23 was defined as (1) being of at least moderate severity, with a mitral valve area smaller than 1.4 cm²; (2) a dilated left atrium and a hypertrophic right ventricle (RV); (3) mild mitral valve regurgitation or mild aortic lesions without a dilated left ventricle or mild mitral valve regurgitation without any other lesions.

Six-Minute Walking Distance

At discharge and after six to 12 months of treatment, walking distances over a period of six minutes were measured for all patients. Instruction on walking exercise was given two or three times before the formal walking distance was determined. After a rest of at least 30 minutes, the average six-minute walking distance, measured in meters, was obtained two or three times.

Statistical Analysis

Measurement data are presented as mean ± standard deviation (SD). To compare baseline values and changes at the end of six to 12 months, we used the paired Student’s t test for continuous variables within groups and the non-paired t test between groups. We used the x² test to evaluate between-group differences in enumeration data assessment. A P value of less than .05 was considered statistically significant. NYHA classes I, II, III, and IV, respectively, were calculated as scores of 1, 2, 3, and 4.

RESULTS

Fundamental Characteristics

Eleven treated patients (25%) and nine control patients (20.5%) did not complete the study. Among the treated patients, five (11.3%) withdrew because of suspected ADEs from bisoprolol: weakness, dizziness, and dyspnea. No severe hypotension occurred in either group. Fourteen patients were excluded from the evaluation at follow-up. Seven patients had echocardiographic or 24-hour ECG data of insufficient quality, and seven patients withdrew because of telephone-connection difficulties. Their withdrawal from this study did not affect our conclusions because these patients were equally distributed in the treated and control groups.

Among all patients, 67 (76.1%) fulfilled complete clinical, ECG, and echocardiographic data and six to 12 months of follow-up data. The follow-up period was similar for the controls (263 ± 56 days, or 207–319 days) and for the treated patients (247 ± 74 days, or 173–321 days). There were no significant differences in age, sex, NYHA class, disease duration, or the use of diuretics and nitrates (Table 1).

The severity of mitral or aortic lesions did not differ in either group: (1) two treated patients (6.1%) and one control patient (2.9%) had mitral valve regurgitation of at least moderate severity and/or mild stenosis; (2) six treated patients (18.2%) and eight control patients (23.5%) had combined mitral stenosis of
at least moderate severity and mitral valve regurgitation; and (3) 21 treated patients (63.6%) and 22 control patients (64.7%) had combined mitral and aortic valve disease. Sixteen treated patients (48.5%) and 17 control patients (50.0%) had significant mitral stenosis. In both groups, approximately 50% of patients had pure and non-pure (predominant) mitral stenosis. The LVEF was higher than 40% in all patients in the two groups and was below 45% in three patients (two patients in the treatment group and one in the control group). All patients had combined mitral and aortic valve disease.

During follow-up, the use of ACE-inhibitors/ARBs and digoxin was similar for all patients. Thirteen treated patients (39.4%) and 16 controls (47.1%) received ACE-inhibitors/ARBs, and 30 treated patients (90.9%) and 32 controls (94.1%) received digoxin. The average maximum bisoprolol dose was 6.52 ± 2.7 mg/day in the treatment group; 54.5% of the patients tolerated at least 5 mg of bisoprolol once daily. Nineteen treated patients (55.9%) and 20 controls (60.6%) received nitrates.

### Short-Term Clinical Effects

At hospital admission, the resting ventricular rate was similar in both treated and control patients. Both groups had a similar NYHA class from admission to discharge. However, the treatment group showed a significantly lower 24-hour average ventricular rate at discharge (80 ± 14 beats/minute, 95 ± 14 beats/minute; \( P < .001 \)) (see Table 1). The length of hospital stay for the treated patients (6.8 ± 3.4 days) was significantly shorter than that for the control patients (9.5 ± 4.3 days, \( P = .046 \)). Further, the treated patients had better exercise capacity at discharge (391 ± 32 meters, 309 ± 28 meters; \( P < .001 \)) (see Table 1). At discharge, although the treated group had a mild higher systolic blood pressure than the controls, the LV end-diastolic dimension and the average LA diameter did not differ between the two groups (see Table 1).

### Long-Term Clinical Effects

During follow-up, the combined endpoint accounted for 11 cases of HF in the controls (32.4%) and four cases in the treated patients (12.1%, \( P = .048 \)) (Table 2). Ten controls and three treated patients were hospitalized for complaints associated with chronic HF; one treated patient and one control were admitted with these complaints.

Also at follow-up, NYHA class in the treated patients remained stable. The condition of only two patients deteriorated to NYHA class IV, and 75.8% of patients were in class I or II. However, NYHA class in the controls worsened to some extent.

### Table 1  Fundamental Characteristics of Patients with Heart Failure (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Patients (n = 34)</th>
<th>Treated Patients (n = 33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.5 ± 7.4</td>
<td>40.6 ± 6.8</td>
<td>( P = .120 ) (t = 1.671)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>12/22 (35.3%)</td>
<td>12/21 (36.4%)</td>
<td>( P &gt; .200 ) (( \chi^2 = 0.015 ))</td>
</tr>
<tr>
<td>Resting ventricular rate at admission (beats/minute)</td>
<td>105 ± 19</td>
<td>110 ± 21</td>
<td>( P = .32 ) (t = 1.210)</td>
</tr>
<tr>
<td>24-hour average ventricular rate at hospital discharge (beats/minute)</td>
<td>95 ± 14</td>
<td>80 ± 14*</td>
<td>( P &lt; .001 ) (t = 4.385)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension (mm)</td>
<td>57 ± 21</td>
<td>55 ± 19</td>
<td>( P &gt; .200 ) (t = 0.409)</td>
</tr>
<tr>
<td>Average left atrial diameter (mm)</td>
<td>41 ± 6</td>
<td>43 ± 5</td>
<td>( P = .182 ) (t = 1.484)</td>
</tr>
<tr>
<td>Six-minute walking distance at hospital discharge (meters)</td>
<td>309 ± 28</td>
<td>391 ± 32*</td>
<td>( P &lt; .001 ) (t = 11.149)</td>
</tr>
<tr>
<td>Systolic pressure at discharge (mm Hg)</td>
<td>121 ± 14</td>
<td>115 ± 12</td>
<td>( P = .008 ) (t = 1.885)</td>
</tr>
<tr>
<td>NYHA Class at hospital discharge (score)</td>
<td>2.2 ± 0.6</td>
<td>2.1 ± 0.8</td>
<td>( P &gt; .200 ) (t = 0.577)</td>
</tr>
</tbody>
</table>

\* \( P < .05 \) compared with the control group of patients.

mm = millimeters; Hg = mercury; NYHA = New York Heart Association; SD = standard deviation.

### Table 2  Clinical Characteristics for the Follow-up Period in Patients with Heart Failure (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Patients (n = 34)</th>
<th>Treated Patients (n = 33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined endpoint (%)</td>
<td>11 (32.4%)</td>
<td>4 (12.1%)*</td>
<td>( P = .048 ) (( \chi^2 = 3.944 ))</td>
</tr>
<tr>
<td>NYHA Class (score)</td>
<td>3.2 ± 0.8</td>
<td>2.2 ± 0.7*</td>
<td>( P &lt; .001 ) (t = 5.445)</td>
</tr>
<tr>
<td>24-hour average ventricular rate (beats/minute)</td>
<td>110 ± 27</td>
<td>68 ± 17*</td>
<td>( P &lt; .001 ) (t = 7.645)</td>
</tr>
<tr>
<td>Decreased left atrial diameter (mm)</td>
<td>2.2 ± 0.5</td>
<td>–3.9 ± 0.6*</td>
<td>( P &lt; .001 ) (t = 45.138)</td>
</tr>
<tr>
<td>Six-minute walking distance (meters)</td>
<td>290 ± 23</td>
<td>423 ± 25*</td>
<td>( P &lt; .001 ) (t = 22.644)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>118 ± 16</td>
<td>105 ± 15*</td>
<td>( P &lt; .001 ) (t = 3.453)</td>
</tr>
</tbody>
</table>

\* \( P < .05 \) compared with the control group of patients.

mm = millimeters; Hg = mercury; NYHA = New York Heart Association; SD = standard deviation.
degree; the health of nine patients deteriorated to class IV, and 50% were in class III. NYHA class scores of the treated patients were significantly lower than those of the controls (2.2 ± 0.7 score, 3.2 ± 0.8 score; P < .001). In addition, compared with the controls, the treated patients receiving the study regimen had lower 24-hour average heart ventricular rates, decreased systolic blood pressure readings (P < .001), and longer six-minute walking distances (see Table 2).

Compared with the findings at discharge, the LV end-diastolic dimension in both groups did not differ significantly at follow-up. For all patients in the two groups, the LVEF was higher than 40%. The LVEF was below 45% in four patients (one treated patient and three controls). Thus, no significant changes in EF or LV end-diastolic dimension were found in either group during the follow-up evaluation. However, the treated patients did show a significantly decreased LA diameter compared with the control group at follow-up.

**DISCUSSION**

**Do Selective Beta-Blockers Affect Chronic Heart Failure Related to Rheumatic Fever?**

The evidence supports a profound protective effect of beta blockers in their ability to inhibit activation of the neuroendocrine system in regard to chronic HF: (1) the early activation of the sympathetic nervous system in chronic HF; (2) the beneficial effect of beta blockers on sudden death, especially important in early stages of chronic HF; and (3) the dual inhibitory effect of beta blockers on renin and the sympathetic nervous system. 

ACE-inhibitors have been shown to decrease mortality by approximately 25% in patients with chronic HF. Some large outcome studies and several meta-analyses have documented a reduction in mortality of approximately 35% with the addition of a beta blocker. The escape of angiotensin II from ACE-inhibitors is attenuated in the patients who take beta blockers. 

RHD is still an important cause of chronic HF in developing countries, including China. The predominant pathological change associated with RHD is rheumatic mitral stenosis. Numerous studies have reported increased sympathetic activity in patients with mitral stenosis, because low cardiac output mediated by mitral stenosis activates the sympathetic nervous system.

As shown by Razoolini et al., sympathetic activity decreased after mitral balloon valvuloplasty was significantly correlated with the increase in the cardiac index. ACE-inhibitors or nonselective beta blockers with alpha-adrenergic activity have an obvious vasodilatory effect, which can worsen a low cardiac output, whereas a selective beta adrenoceptor antagonist (e.g., bisoprolol with a half-life of 10 to 12 hours) does not have any partial agonist or vasodilatory effect. On the basis of these assumptions, the selective beta blocker bisoprolol was used to treat chronic HF patients with RHD in this study.

We assessed 67 patients: 16 treated patients (48.5%) and 17 control patients (50.0%) had significant mitral stenosis. Thus, approximately 50% of patients with RHD had pure and non-pure mitral stenosis; for these patients, the use of vasodilators might not be appropriate. In our study, only 13 treated patients (39.4%) and 16 controls (47.1%) used an ACE-inhibitor/ARB.

The average maximum bisoprolol dose was 6.52 ± 2.7 mg/day. In the treatment group, 54.5% of patients tolerated at least 5 mg of bisoprolol once daily during the maintenance phase. Five patients (11.3%) withdrew from the study because of suspected ADEs from bisoprolol. No severe hypotension or bradycardia occurred. Bisoprolol decreased the length of hospital stay, reduced the incidence of cardiac events, and improved exercise capacity over six to 12 months of treatment.

Our results were similar to the findings of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS), and the MERIT–HF trial. In our study, the average maximum bisoprolol dose was lower, but the tolerance of at least 5 mg of bisoprolol once daily was not significantly different from that of the CIBIS-II trial (54.5% versus 67%), probably because the cause of chronic HF in our study differed from that in other studies.

Chronic HF caused by RHD is associated with a lower cardiac output, which can bring about deterioration in the increased sympathetic nervous system. However, our results and those of other studies showed that the benefits derived from bisoprolol, when used to treat patients with chronic HF, clearly outweighed the risk of ADEs.

In clinical practice, these patients cannot usually tolerate optimum doses of both an ACE-inhibitor and a beta blocker. This lack of tolerance is especially common among the elderly. The CIBIS–III findings indicated that chronic HF therapy should be not started with both an ACE-inhibitor and a beta blocker simultaneously, especially in elderly patients or in those with special circumstances. Therefore, we concluded that a selective beta blocker might be a reasonable choice of therapy for chronic HF patients with RHD.

**Do Selective Beta-Blockers Affect Chronic Heart Failure Related to Atrial Fibrillation?**

In patients with RHD, AF is the most common sustained arrhythmia and it is the most common cause of chronic HF resulting from a loss of atrial contraction and an associated rapid ventricular rate. One study showed that decreased sympathetic activity after balloon mitral valvuloplasty occurred only in patients with mitral stenosis and sinus rhythm but not in patients with AF. The results indicated that patients with mitral stenosis and AF experienced a more adverse neurohormonal change. However, the effects of selective beta blockers on chronic HF accompanying AF remain to be explored.

In patients without HF, beta blockers improved ventricular rate control in AF when they were added to digoxin or when they were used alone. Among patients with AF and HF, only a few trials have suggested that beta blockers reduce ventricular rate, improve ventricular function, and are well tolerated. However, these studies used agents with high intrinsic sympathomimetic activity, and these agents are now generally thought to be contraindicated for patients with HF.

In our study, all patients in the treated group received bisoprolol. Thirty patients (90.9%) in the treated group and 32 patients (94.1%) in the control group used digoxin. Compared with the control patients, the treated patients showed a shorter length of hospital stay (–2.4 ± 3.8 days) and better exercise tolerance at discharge.

During six to 12 months of follow-up, the combined endpoint
of chronic HF-related and thromboembolism-associated hospitalization or death decreased significantly, from 32.4% in the controls to 12.1% in the treated patients. The 24-hour average ventricular rate did not change significantly in the control group, but the rate did decrease in the treated patients (see Table 1). The difference in the absolute change between the two groups was statistically significant ($P < .001$).

We found that bisoprolol benefited patients with chronic HF related to RHD and AF. A study by Fung et al. supported the idea that the benefits of the beta blocker in patients with HF extend to patients with HF complicated by AF. The beta blocker had an incremental benefit when added to digoxin for the management of AF in patients with HF.

**Are Selective Beta-Blockers More Useful in Chronic Heart Failure Accompanying Normal or Near-Normal Systolic Function?**

LV diastolic dysfunction usually precedes systolic dysfunction, but it can also be present for a longer period of time, even years. Impairment of diastolic function appears to be age-related. Although fewer than 10% of patients with heart failure younger than 50 years of age tend to have diastolic dysfunction, the number rises to 70% in patients older than 80 years of age. However, the prognosis of chronic HF patients with preserved systolic function (or diastolic HF) is similar to that for those with systolic dysfunction.

Although there is currently no worldwide accepted definition of diastolic HF, the American College of Cardiology/American Heart Association Guidelines have proposed that if patients have symptoms of HF but normal systolic function, they should be classified as having HF with preserved systolic function; thus, it is no longer mandatory for diastolic function to be assessed objectively in these patients.

Diastolic HF may originate because of conditions that alter the myocardial structure (i.e., AF and valvular heart disease). A certain pattern of LV diastolic filling always results from a complex interaction of various factors such as heart rate and rhythm, preload, aortic or mitral valve disease, right ventricular (RV) competence, ventricle–septum interaction, active LV relaxation, LV elasticity properties, and LA contraction. Aging, disease progression, and changes in loading conditions may lead to diastolic dysfunction. It is known that atrial contraction is very important for the filling of the heart, especially in elderly patients. Thus, abbreviated filling, in terms of sudden onset of AF, may exacerbate diastolic dysfunction and may even cause dramatic symptoms and signs (pulmonary congestion). We found the incidence of AF to be higher in subjects with diastolic HF, that is, in a quarter to a third of patients.

In the Italian Network on Congestive Heart Failure (IN–CHF) registry, 16% of patients with a low LVEF had AF, compared with 25% of patients with an LVEF above 45%.

In a multivariate analysis, AF was an independent predictor of a higher risk of diastolic HF in patients hospitalized with chronic HF. According to pathophysiological changes, patients with RHD may be classified into two groups: (1) those with predominant mitral stenosis and (2) those with predominant mitral valve regurgitation and/or aortic lesions. Predominant mitral stenosis may result in dilation of the LA and a hypertrophic right ventricle. The latter condition may cause an increased left-sided heart preload or afterload. Eventually, patients with either condition exhibit an elevated pulmonary artery pressure.

Various factors may lead to diastolic dysfunction by complex interactions because of a hemodynamic coupling of RV and LV functions. Patients with a cardiothoracic ratio below 65% and without severe hepatic or renal dysfunction were included in our study. There was no significant age difference between the controls and the treated patients (see Table 1). For all patients at discharge, the LVEF was higher than 40%. Only three patients had an LVEF below 45% (two treated patients and one control).

At the end of the study, we observed a significant change in LVEF; it measured below 45% in four patients (in one treated patient and in three control patients). All of the patients with an LVEF below 45% had combined mitral and aortic valve disease. Our findings supported the phenomenon that chronic HF related to AF and valvular heart disease without an advanced course had a normal or near-normal LV function.

How to best treat diastolic HF remains to be determined. The IMPROVEMENT–HF study and the IN-CHF registry showed that beta blocker use was higher in patients with diastolic HF, and patients with diastolic HF tolerated beta blockers well. Beta blockers were associated with decreased resting and peak exercise heart rates and blood pressure and an increased early and late (atrial) phase (E/A ratio). Many patients with impaired RV function or pulmonary hypertension have also benefited from beta blockers.

Some studies showed that a six-month course of carvedilol therapy did not reduce the LV diameter at end-diastole and at end-systole, but it did restore physiological early diastolic filling by complex interactions between relaxation and chamber stiffness. Our study also indicated the same phenomenon; the beneficial effect of bisoprolol was not significantly related to the changes in LV volume and systolic function.

It is known that baseline heart rates and changes in heart rates are related to the prognosis in patients with chronic HF. Perhaps resting heart rate, as a simple clinical surrogate for sympathetic nervous system activity, might prove to be a simple and clinically useful predictor of benefit from beta-blocker therapy. A short diastolic period is always detrimental if myocardial function is compromised. Beta blockers prolong the diastolic period more than they prolong the systolic period, which promotes diastolic filling, improves myocardial perfusion and metabolism, and might offer direct protective action on the myocytes against catecholamine excess.

Bergström et al. noted that patients with higher heart rates benefited more from carvedilol than patients with lower heart rates. Patients with a heart rate above 71 beats/minute who took carvedilol showed an improved E/A ratio and E-wave velocity, whereas there was less effect on the A-wave velocity, compared with the placebo group.

These findings indicate that patients with diastolic dysfunction and higher heart rates experience improved diastolic filling through a shift of diastolic volumes from late to early diastole. It appears that this redistribution of filling volumes toward a more normal pattern is brought about by an improvement in early filling in particular, thereby inducing a more normal filling pattern.

However, it is difficult to differentiate the effects on heart rate...
output, thereby leading to a decreased atrial diameter. Other drugs with heart rate-reducing effects (e.g., calcium-channel blockers and digitals) do not share the positive effects of beta blockers in HF treatment. The exact mechanism of their effect is not entirely clear, but the data suggest that the primary mechanism of action of beta blockers in chronic HF is to prevent and reverse adrenergically mediated intrinsic myocardial dysfunction and remodeling.

Our study included patients with a resting ventricular rate of at least 70 beats/minute. The 24-hour average ventricular rate decreased significantly in the treatment group, in contrast to the control patients. The significantly decreased LA diameter and reduced systolic blood pressure were observed only in the treated patients. This difference in ventricular rates might be attributable to the fact that a selective beta blocker can allow longer diastolic filling by decreasing resting and exercise ventricular rates and may produce a higher cardiac output, thereby leading to a decreased atrial diameter. Thus, we concluded that a selective beta blocker might be feasible for chronic HF accompanying normal or near-normal systolic function; we were less concerned about the negative inotropic effect of the beta blocker in patients with diastolic HF than we were about systolic HF. In our study, patients were somewhat younger, had higher basic ventricular rates, and did not have end-stage disease. This was also an important reason why bisoprolol exerted beneficial effects in this subgroup.

Study Limitations

We focused on patients with RHD and AF who had no complications associated with chronic HF, such as myocardial dysfunction and liver or renal dysfunction. It was necessary to include this highly selective population as a first step to identifying the feasibility and effectiveness of bisoprolol without confounding variables. Further studies are needed to address the effect of bisoprolol in patients with advanced RHD.

Another element of potential bias was the use of an unblinded treatment, which might affect hospital patient discharges and subsequent admissions.

CONCLUSION

We suggest that a selective beta blocker, such as bisoprolol, can improve NYHA class and exercise tolerance for patients with chronic HF related to RHD and AF. The advantage of these effects provided by this agent might be mediated by a reduction in ventricular rate and LA volume.

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