Why Do Patients With Congestive Heart Failure Tolerate the Initiation of \( \beta \)-Blocker Therapy?

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**Background.** Despite its negative inotropic effects, the initiation of \( \beta \)-adrenergic blockade is tolerated by patients with congestive heart failure (CHF). Accordingly, we examined the acute hemodynamic effects of \( \beta \)-adrenergic blockade on systolic and diastolic left ventricular (LV) function and ventriculo-arterial coupling. In addition, isolated myocardium from patients with CHF shows selective \( \beta_1 \)-receptor downregulation, implying a greater role for the \( \beta_1 \)-receptor in maintaining in vivo LV contractility. As a secondary aim, we hypothesized that nonselective \( \beta \)-adrenergic blockade would have greater negative inotropic effect than \( \beta_1 \)-blockade in patients with CHF.

**Methods and Results.** Patients with clinical CHF (n=24) and control patients without CHF (n=24) were given either the nonselective \( \beta \)-blocker propranolol or the \( \beta_1 \)-selective blocker metoprolol. LV pressure-volume relations were obtained before and after the administration of intravenous \( \beta \)-blocker, and measures of LV systolic and diastolic function were examined. Patients with CHF had a deterioration in LV systolic function with a fall in LV systolic pressure (1139±6 to 125±6 mm Hg), cardiac index (2.56±0.11 to 2.20±0.11 mL·min\(^{-1}\)·m\(^{-2}\)), dP/dt\(_{max}\) (1173±63 to 897±50 mm Hg/s), and end-systolic elastance (0.88±0.10 to 0.64±0.10 mm Hg/ml), \( P<.05 \) for all. Although there was deterioration of active LV relaxation (isovolumetric relaxation 63±2 to 73±3 milliseconds, peak filling rate 43±3 to 464±28 ml/s, \( P<.05 \) for both), there was no change in passive LV diastolic function (pulmonary capillary wedge, 24±2 to 24±1 mm Hg; chamber stiffness, 0.0154±0.0005 to 0.0163±0.0005 ml/m\(^{-1}\), \( P=NS \) for both), and a decrease in afterload (arterial elastance 3.85±0.31 to 3.38±0.24 mm Hg/ml, \( P<.05 \)). Control patients had no change in these parameters other than a prolongation of isovolumetric relaxation (48±1 to 55±2 milliseconds, \( P<.05 \)). The effects of propranolol (n=12) versus metoprolol (n=12) on these parameters in patients with CHF were similar.

**Conclusions.** These data do not support a greater in vivo physiological role of the myocardial \( \beta_1 \)-receptor in CHF. The preservation of passive diastolic function and ventriculo-arterial coupling provide possible explanations of why \( \beta \)-adrenergic blockade is tolerated by patients with CHF. (Circulation. 1993;88(part 1):1610-1619.)

**Key Words** • \( \beta \)-adrenergic receptors • elastance • cardiomyopathies

*Chronic* congestive heart failure (CHF) is associated with activation of the sympathetic nervous system.\(^1,2\) It has been suggested that this sympathetic activation is compensatory, maintaining basal left ventricular (LV) cardiac output and ejection fraction (EF)\(^3-5\); however, there is evidence that it may be cardiotoxic and play an important role in the progression of CHF.\(^6-8\) Therefore, the use of chronic \( \beta \)-blockers in the treatment of CHF has been suggested. Chronic \( \beta \)-adrenergic blockade has been demonstrated to improve many of the hemodynamic, functional, and neurohormonal abnormalities of patients with CHF.\(^9-13\) The initiation of \( \beta \)-blockade in these patients might be expected to cause worsening heart failure by interfering with the positive inotropic and lusitropic actions of endogenous catecholamines. If this were the case, most patients with CHF would be expected to have clinical and hemodynamic deterioration with the initiation of \( \beta \)-blocker therapy. However, in clinical trials using \( \beta \)-blockers in patients with mild-to-moderate CHF, the majority of patients tolerate the careful initiation of \( \beta \)-blocker therapy.\(^10,12-16\) It is the unusual patient who does not tolerate \( \beta \)-blockade and must be excluded from published studies. Why patients with CHF tolerate the initiation of \( \beta \)-blockade has not been previously examined. Accordingly, we examined the acute hemodynamic effects of \( \beta \)-adrenergic blockade on systolic and diastolic left ventricular function and ventriculo-arterial coupling.

As a secondary aim, we examined whether \( \beta_1 \)-selective blockade had different hemodynamic effects than nonselective \( \beta \)-blockade in patients with CHF. The potential physiological advantage of \( \beta_1 \)-selective compared with nonselective blockade in patients with idiopathic dilated cardiomyopathy has been suggested by Swedberg et al.\(^9\) After several clinical successes using the \( \beta_1 \)-selective agent practolol they administered the
nonselective agent alprenolol to nine subsequent patients. However, alprenolol administration was associated with clinical deterioration and three early deaths. Therefore, blockade of both β1 and β2 receptors was poorly tolerated, whereas blockade of the β1 receptor alone was clinically well tolerated. More recently, Bristow and coworkers\textsuperscript{17} demonstrated preservation of an inotropic response to selective β2 but not β1 agonists in isolated heart muscle from patients with CHF demonstrating selective downregulation of β1- but not β2-adrenergic receptors. Therefore, we hypothesized that nonselective β-blockade would result in greater negative inotropic and lusitropic effects than selective β1 receptor blockade in patients with CHF.

To examine these aims, patients with clinical CHF and control patients without heart failure were given either the nonselective β-blocker propranolol or the β1 selective blocker metoprolol. LV pressure-volume relations were obtained before and after the administration of intravenous β-blocker, and measures of LV systolic and diastolic function were examined.

Methods

Patient Selection Criteria

Patients scheduled for elective cardiac catheterization at the University of Virginia were eligible for enrollment. The CHF group consisted of patients with a history of dyspnea on exertion or fatigue for at least 2 months, a pulmonary capillary wedge (PCW) pressure >14 mm Hg, and a LVEF <40%. The etiology of heart failure was either idiopathic dilated cardiomyopathy (global LV systolic dysfunction in the absence of significant coronary artery disease) or ischemic cardiomyopathy (LV systolic dysfunction due to coronary artery disease). Patients in the non-CHF group were referred for cardiac catheterization for chest pain syndromes and did not have any history of congestive symptoms. No patient in this group had any history of myocardial infarction or any segmental wall motion abnormality during left ventriculography. Patients in any group were excluded from study if they had atrial fibrillation, any exposure to β-blockers within 2 weeks of study, a history of myocardial infarction within 1 month, significant LV thrombus, primary valvular disease, or any contraindication to β-blockade (such as bronchospastic pulmonary disease or heart block). All medications were held for 24 hours before the cardiac catheterization, with the exception of diuretics in patients with CHF. Written informed consent was obtained from each patient, and the protocol was approved by the Human Investigation Committee at the University of Virginia.

Data Acquisition

Conductance catheter technique. A full description of the principles and technique of the conductance catheter are described elsewhere.\textsuperscript{18,19} The present study was performed using an 8F conductance catheter (Webster Labs, Baldwin Park, Calif) and a 2F micromanometer catheter (Millar Instruments, Houston, Tex) fully extended within its lumen. The catheters were positioned under fluoroscopic guidance along the long axis of the left ventricle and connected to a digital stimulator microprocessor (Sigma V, Leycom, Netherlands) operating at 20 kHz. The system uses a dual excitation algorithm and a pair of stimulating electrodes at the apex and base (single field). Resistance differences between intervening electrode pairs are inversely related to segmental volumes, and individual segment volumes are summed to yield total chamber volume. Segmental pressure-volume signals were displayed. Viewing each signal from ventricular apex to base allowed use of all interventricular segments, but the basal segment was excluded if its volume remained constant or increased with systole. Real-time pressure-volume loops could be displayed using total or segmental volumes by two-channel analog/digital conversion (at 200 Hz) and a 16-bit microcomputer system (Halcom Inc, Baltimore, Md).

Protocol. Patients underwent routine right and left heart catheterization, left ventriculography, and coronary angiography. Nonionic contrast was used (Isovue, Squibb Diagnostics, New Brunswick, NJ) to minimize the negative inotropic effects of contrast media. After the diagnostic study, the 8F conductance and 2F micromanometer catheters were advanced into the LV cavity as described previously. Baseline hemodynamic parameters recorded at least 30 minutes after the diagnostic cardiac catheterization included heart rate (HR), mean right atrial (RA), mean pulmonary artery (PAM), PCW, LV systolic, and LV end-diastolic (LVEDP) pressures; thermodilution cardiac index; stroke volume index; and the first derivative of LV pressure rise (dP/dt\textsubscript{max}) and fall (dP/dt\textsubscript{min}). Subsequently, an intravenous bolus of nitroglycerin was administered, and pressure-volume loops were recorded on a beat-by-beat basis for 50 seconds. All hemodynamic parameters returned to baseline before the administration of β-blockade (>30 minutes after baseline measurements).

Patients received intravenous β-blockade with either the nonselective β-blocker propranolol (maximum dose, 0.1 mg/kg) or the β1-selective blocker metoprolol (maximum dose, 0.2 mg/kg). Intravenous β-blocker was administered until the heart rate decreased by 25% or the maximum dose was achieved. Hemodynamic measurements were then repeated and pressure-volume loops recorded after a repeat bolus of intravenous nitroglycerin as described.

Nitroglycerin dose. In pilot studies, the dose of nitroglycerin necessary to reliably produce at least a 15 mm Hg fall in systolic arterial pressure was 200 μg in control patients and 400 μg in CHF patients. This reliable fall in systolic arterial pressure was necessary to calculate end-systolic elastance (E\textsubscript{syst}) and diastolic chamber elastic stiffness accurately. A lower dose of 200 μg was used in the control patients since higher doses could result in severe hypotension.

Data Analysis

Data obtained from the conductance and micromanometer catheters were analyzed off-line by computer (Halcom Inc, Baltimore, Md). The pressure and volume recordings were smoothed with a three-point, non-weighted moving average before determining hemodynamic parameters. Absolute volume measurements from the conductance catheter were calibrated with a correction for offset and gain. The gain correction was calculated as the ratio between thermodilution stroke volume and conductance stroke volume. The offset correction was calculated as the ratio between the right
anterior oblique left ventriculographic end-diastolic volume (calculated using the Kennedy-Dodge regression) and the gain, subtracted from the end-diastolic volume of the baseline conductance volume signal. The offset was then subtracted from the continuous conductance volume signal, and this difference was multiplied by the gain.

The series of pressure-volume loops used to generate \( E_a \) and the diastolic pressure-volume relation commenced with the beat preceding a visual fall in pressure or volume and ended either at nadir pressure or volume with baroreflex activation (defined as a 5% increase in heart rate on three consecutive beats). All premature and post-premature beats were excluded from the analysis. The following variables were determined.

**Diastolic Parameters**

*Maximal rate of LV pressure decline (dP/dt\( _{\text{max}} \)).* The LV pressure signal was digitized at 200 Hz and differentiated to obtain the maximal rate of LV pressure decline. 

*Diastolic filling time (DFT).* The diastolic filling period was calculated as the time period after the onset of dP/dt\( _{\text{max}} \) until end diastole, occurring at the peak of the R wave on the ECG.

*Time constant of isovolumetric LV pressure relaxation (\( \tau _a \)).* \( \tau _a \) was calculated by two methods. The first used a plot of ln(LVP) versus time, as derived by Weiss et al.\(^{21} \) (\( \tau _a \)), which assumes that during isovolumetric relaxation, LV pressure decayed in a monoexponential manner to zero. The second method computed the time needed for LV pressure to fall to one half of its value from the pressure at dP/dt\( _{\text{max}} \), using the method of Mirsky\(^{22} \) (\( \tau _a _{\text{ECG}} \)). The method of Mirsky (\( \tau _a _{\text{ECG}} \)) does not require a calculation of the exponential decay of pressure but merely the time required for pressure to reach one half of its value of the pressure at dP/dt\( _{\text{max}} \).

Both \( \tau _a _{\text{LVP}} \) and \( \tau _a _{\text{ECG}} \) measure the active diastolic properties of the left ventricle.

*Peak LV filling rate (dV/dt\( _{\text{max}} \)).* The peak LV filling rate was calculated from the maximum value of the first derivative of the calibrated conductance volume signal.

*Chamber elastic stiffness (B).* The diastolic pressure-volume relation was derived from the last 50% of diastolic filling ending immediately before atrial systole. A single point within this interval was selected for the baseline pressure-volume loop and each subsequent pressure-volume loop obtained during a load change with bolus intravenous nitroglycerin. These points were fixed at a set interval before end diastole. The diastolic pressure-volume relation was obtained by connecting these points. Chamber elastic stiffness was calculated by fitting these diastolic pressure-volume points to an elastic model, \( P = P_s + a(e^{bV} - 1) \), with a Marquardt non-linear least-squares algorithm, where \( P \) is passive chamber elastic stiffness (mL\(^{-1} \)), \( P_s \) is the baseline pressure (mm Hg), and \( a \) is a constant. Thus, chamber elastic stiffness is a measure of the passive late diastolic properties of the left ventricle. An example of the diastolic pressure-volume relation and calculated chamber elastic stiffness is shown in Fig 1.

**Systolic Parameters**

*LV stroke work index (SWI).* Stroke work index was calculated from the integrated area circumscribed by each pressure-volume loop normalized to body surface area.

*Maximal rate of LV pressure rise (dP/dt\( _{\text{max}} \)).* The LV pressure signal was digitized at 200 Hz and differentiated to obtain the maximal rate of LV pressure rise.

*End-systolic elastance (\( E_s \)).* The end-systolic pressure-volume point of each loop was selected as the data point with the maximum (\( P/[V-V_s] \)). A least-squares linear regression of those points was applied, generating slope (\( E_s \)) and intercept (\( V_s \)) estimates. With this estimate of intercept, points of maximal (\( P/V-V_s \)) for each cycle were obtained, and a subsequent regression was used to determine new estimates for \( E_s \) and \( V_s \). This process was repeated until there was no change in either parameter with subsequent iterations.

*Left ventricular afterload.* Effective arterial elastance (\( E_a \)) was calculated from the ratio of end-systolic pressure (\( P_s \)) and stroke volume (SV), or \( E_a = P_s/\text{SV} \) as previously defined.\(^{23,24} \)

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=24)</th>
<th>CHF (n=24)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±2</td>
<td>55±3</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (67%)</td>
<td>19 (79%)</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54±3</td>
<td>24±1</td>
<td>.0001</td>
</tr>
<tr>
<td>EDVI, mL/M(^2)</td>
<td>81±3</td>
<td>121±5</td>
<td>.0001</td>
</tr>
<tr>
<td>ESVI, mL/M(^2)</td>
<td>33±2</td>
<td>90±6</td>
<td>.0001</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>9 (38%)</td>
<td>12 (50%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (54%)</td>
<td>8 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; LVEF, angiographic left ventricular ejection fraction; EDVI, angiographic left ventricular end-diastolic volume index; and ESVI, angiographic left ventricular end-systolic volume index.
TABLE 2. Hemodynamic Response to Acute β-Blockade

<table>
<thead>
<tr>
<th></th>
<th>Control (n=24)</th>
<th>CHF (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>73±2</td>
<td>88±2†</td>
</tr>
<tr>
<td>Post</td>
<td>60±2*</td>
<td>73±1*†</td>
</tr>
<tr>
<td><strong>Ejection fraction, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>54±3</td>
<td>24±1‡</td>
</tr>
<tr>
<td>Post</td>
<td>56±3</td>
<td>26±2‡</td>
</tr>
<tr>
<td><strong>LVEDV, mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>164±7</td>
<td>248±11‡</td>
</tr>
<tr>
<td>Post</td>
<td>163±6</td>
<td>241±11‡</td>
</tr>
<tr>
<td><strong>LVESV, mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>79±7</td>
<td>190±10‡</td>
</tr>
<tr>
<td>Post</td>
<td>74±7</td>
<td>182±11‡</td>
</tr>
<tr>
<td><strong>Diastolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCW, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>14±1</td>
<td>24±2‡</td>
</tr>
<tr>
<td>Post</td>
<td>15±1*†</td>
<td>24±1‡</td>
</tr>
<tr>
<td>dP/dt min, mm Hg/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>-1713±71</td>
<td>-1254±62‡</td>
</tr>
<tr>
<td>Post</td>
<td>-1628±80</td>
<td>-1085±54*††</td>
</tr>
<tr>
<td>DFT, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>454±23</td>
<td>339±11‡</td>
</tr>
<tr>
<td>Post</td>
<td>551±30*</td>
<td>434±13‡</td>
</tr>
<tr>
<td>T1, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>48±1</td>
<td>63±2‡</td>
</tr>
<tr>
<td>Post</td>
<td>55±2*</td>
<td>73±3*‡</td>
</tr>
<tr>
<td>T12, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>36±1</td>
<td>47±1‡</td>
</tr>
<tr>
<td>Post</td>
<td>41±2*</td>
<td>52±2*‡</td>
</tr>
<tr>
<td>DFT/T1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>9.7±0.5</td>
<td>5.6±0.2‡</td>
</tr>
<tr>
<td>Post</td>
<td>10.4±0.7</td>
<td>6.1±0.3*‡</td>
</tr>
<tr>
<td>dV/dt max, mL/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>537±25</td>
<td>543±33</td>
</tr>
<tr>
<td>Post</td>
<td>542±31</td>
<td>464±28*</td>
</tr>
<tr>
<td>Chamber stiffness, mL⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.0198±0.0009</td>
<td>0.0154±0.0005‡</td>
</tr>
<tr>
<td>Post</td>
<td>0.0188±0.0008</td>
<td>0.0163±0.0005‡</td>
</tr>
</tbody>
</table>

Note: CHF indicates congestive heart failure; bpm, beats per minute; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PCW, pulmonary capillary wedge; dP/dt max, maximal first derivative of left ventricular pressure fall; DFT, diastolic filling time; T1, time constant of isovolumetric pressure decay logarithmic; T12, time constant of isovolumetric pressure decay one-half; dV/dt max, peak filling rate; LVSP, left ventricular systolic pressure; SWI, stroke volume index; CI, cardiac index; SWI, stroke work index; Ees, end-systolic elastance; and Em, arterial elastance.

TABLE 2. Continued

<table>
<thead>
<tr>
<th></th>
<th>Control (n=24)</th>
<th>CHF (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>150±6</td>
<td>139±6‡</td>
</tr>
<tr>
<td>Post</td>
<td>148±6</td>
<td>125±6*†‡</td>
</tr>
<tr>
<td>SVI, mL/M²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>43±2</td>
<td>29±2‡</td>
</tr>
<tr>
<td>Post</td>
<td>44±2</td>
<td>30±2‡</td>
</tr>
<tr>
<td>CI, mL · min⁻¹ · M⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>3.06±0.10</td>
<td>2.56±0.11‡</td>
</tr>
<tr>
<td>Post</td>
<td>2.65±0.11*</td>
<td>2.20±0.11*‡</td>
</tr>
<tr>
<td>SWI, mm Hg · mL⁻¹ · M⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>3983±195</td>
<td>2023±161‡</td>
</tr>
<tr>
<td>Post</td>
<td>3796±159</td>
<td>1826±200$</td>
</tr>
<tr>
<td>dP/dt max, mm Hg/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1504±61</td>
<td>1173±63‡</td>
</tr>
<tr>
<td>Post</td>
<td>1238±39*</td>
<td>897±50*†‡</td>
</tr>
<tr>
<td>Em, mm Hg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.13±0.15</td>
<td>0.88±0.10‡</td>
</tr>
<tr>
<td>Post</td>
<td>2.01±0.16</td>
<td>0.64±0.10*‡†</td>
</tr>
<tr>
<td><strong>Afterload</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective Em, mm Hg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.55±0.25</td>
<td>3.85±0.31†</td>
</tr>
<tr>
<td>Post</td>
<td>2.41±0.18</td>
<td>3.38±0.24*‡</td>
</tr>
<tr>
<td><strong>Ventriculo-arterial coupling</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Em/Es ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.99±0.11</td>
<td>0.25±0.03‡</td>
</tr>
<tr>
<td>Post</td>
<td>0.94±0.11</td>
<td>0.20±0.03‡</td>
</tr>
</tbody>
</table>

**Relations between LV systolic function and afterload: ventriculo-arterial coupling (Em/Es).** The relation between systolic function and afterload was determined by the ratio of end-systolic elastance and effective arterial elastance.

**Statistical Analysis**

Data were compiled and analyzed on a minicomputer (VAX 8200, Digital Equipment Corp, Maynard, Mass) using RS/1 (Bolt, Beranek and Newman, Cambridge, Mass). Continuous variables were expressed as mean±SEM, and differences between groups were estimated by either a t test with pooled variance or an ANOVA (one- or two-way). Categorical data were expressed as proportions, and differences between groups were estimated using the Fisher exact test. Differences between groups were considered significant at P<.05 (two-tailed).

**Results**

**Clinical Patient Characteristics and β-Blocker Dose**

The characteristics of the 48 patients enrolled in this study are shown in Table 1. Patients with CHF (n=24)

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had greater LV volumes and lower LVEFs than control patients (n=24). The etiology of CHF was ischemic cardiomyopathy in 12 patients (50%) and idiopathic dilated cardiomyopathy in 12 patients. Although all patients in the control group were referred for cardiac catheterization due to chest pain syndromes, only nine patients (38%) had epicardial coronary artery disease. Thirteen patients (54%) in the control group and eight patients (33%) in the CHF group had a clinical history of hypertension that had required medical therapy.

Intravenous metoprolol was administered to 11 control and 12 CHF patients, while propranolol was administered to 13 control and 12 CHF patients (P=NS, control vs CHF). The average metoprolol dose was 14±1 mg in control patients and 12±1 mg in CHF patients (P=NS). The average propranolol dose was 9±1 mg in control patients and 8±1 mg in CHF patients (P=NS).

**Hemodynamic Response to β-Blockade in Patients With and Without CHF**

The hemodynamic parameters of the 24 patients with and 24 patients without CHF before and after β-blockade are shown in Table 2. At baseline, patients with CHF had faster resting heart rates than control patients. Baseline indices of active diastolic function (dP/dt min, Tau, and Tau1/2) demonstrated impaired active relaxation in CHF patients. Patients with CHF had a higher baseline pulmonary wedge pressure but a lower chamber elastic stiffness than control patients. When chamber stiffness was calculated using the end-diastolic point of the LV diastolic pressure-volume relation, patients with CHF still had a lower chamber stiffness than control patients (0.0154±0.0008 vs 0.0178±0.0009, P<0.05). Patients with CHF had evidence of LV systolic dysfunction with a lower cardiac index, stroke volume index, and stroke work index, as well as lower dP/dt max and E a than control patients. CHF patients had greater LV afterload (effective E a) and impaired ventriculo-arterial coupling (E a/E a) compared with control patients.

After intravenous β-blockade, patients with and without CHF had similar reductions in heart rate. Left ventricular ejection fraction, end-systolic volume and end-diastolic volume did not change with β-blockade.

**FIG 2. Examples of pressure-volume loops and calculated end-systolic elastance (E a) and chamber elastic stiffness (B) are shown at baseline (above) and after (below) administration of intravenous β-blocker (BB) for a control (left) and congestive heart failure (CHF) (right) patient plotted on the same pressure-volume axes. At baseline (Pre-BB), the control patient had higher values for E a and B than the CHF patient. After β-adrenergic blockade (Post-BB), there was no change in E a in the control patient, whereas there was a reduction in E a in the CHF patient. On the other hand, neither the control nor the CHF patient had any change in chamber elastic stiffness with β-blockade.**

### Table 3. Chamber Elastic Stiffness

<table>
<thead>
<tr>
<th>Chamber stiffness, mL⁻¹</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+HTN (n=13)</td>
</tr>
<tr>
<td>Pre</td>
<td>0.0204±0.0011</td>
</tr>
<tr>
<td>Post</td>
<td>0.0178±0.0008*</td>
</tr>
</tbody>
</table>

+HTN indicates previous history of hypertension; −HTN, no previous history of hypertension; CHF, congestive heart failure.

*P<0.05 Pre vs Post; †P<0.05 CHF vs control +HTN.
Haber et al  Acute Effects of β-Adrenergic Blockade in Cardiomyopathy  1615

**TABLE 4. Hemodynamic Response to β-Blockade in Patients With Congestive Heart Failure With Idiopathic Versus Ischemic Cardiomyopathy**

<table>
<thead>
<tr>
<th>Heart rate, bpm</th>
<th>Idiopathic (n=12)</th>
<th>Ischemic (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>88±3</td>
<td>89±3</td>
</tr>
<tr>
<td>Post</td>
<td>73±2*</td>
<td>72±2*</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>25±2</td>
<td>23±2</td>
</tr>
<tr>
<td>Post</td>
<td>25±3</td>
<td>26±3*†</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>263±16</td>
<td>234±13</td>
</tr>
<tr>
<td>Post</td>
<td>258±17</td>
<td>226±12</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>200±16</td>
<td>181±11</td>
</tr>
<tr>
<td>Post</td>
<td>197±18</td>
<td>168±12</td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCW, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>20±2</td>
<td>29±2‡</td>
</tr>
<tr>
<td>Post</td>
<td>21±2</td>
<td>26±2</td>
</tr>
<tr>
<td>dP/dt_{min}, mm Hg/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>-1116±53</td>
<td>-1393±100‡</td>
</tr>
<tr>
<td>Post</td>
<td>-1001±54*</td>
<td>-1169±91*</td>
</tr>
<tr>
<td>T_L, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>66±4</td>
<td>61±3</td>
</tr>
<tr>
<td>Post</td>
<td>77±4*</td>
<td>70±4*</td>
</tr>
<tr>
<td>T_{1/2}, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>47±3</td>
<td>46±2</td>
</tr>
<tr>
<td>Post</td>
<td>53±2*</td>
<td>51±2*</td>
</tr>
<tr>
<td>dV/dt_{max}, mL/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>561±60</td>
<td>527±34</td>
</tr>
<tr>
<td>Post</td>
<td>438±43</td>
<td>481±42</td>
</tr>
<tr>
<td>Chamber stiffness, mL⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.0152±0.0005</td>
<td>0.0161±0.0011</td>
</tr>
<tr>
<td>Post</td>
<td>0.0155±0.0007</td>
<td>0.0171±0.0008</td>
</tr>
</tbody>
</table>

bpm Indicates beats per minute; LVEDV, left ventricular end-systolic volume; PCW, pulmonary capillary wedge; dP/dt_{min}, maximal first derivative of left ventricular pressure fall; T_L, time constant of isovolumetric pressure decay logarithmic; T_{1/2}, time constant of isovolumetric pressure decay one-half; dV/dt_{max}, peak filling rate; LVSP, left ventricular systolic pressure; SVI, stroke volume index; CI, cardiac index; SWI, stroke work index; E_{es}, end-systolic elastance; and E_s, arterial elastance.

*P<.05 Pre vs Post; tP<.05 percent change in idiopathic greater than percent change in ischemic; 4P<.05 idiopathic vs ischemic.

Active diastolic function worsened in patients with CHF and in control patients after β-blockade, as demonstrated by a prolongation of Tau_L (P<.02) and a reduction in peak LV filling rate (P=.01) than patients given metoprolol. PCW pressure increased minimally in control patients and did not change in patients with heart failure. Chamber elastic stiffness calculated before atrial systole or from the end-diastolic point remained unchanged in both groups, indicating no significant changes in passive diastolic function. Patients with CHF had a significant reduction in LV systolic pressure, dP/dt_{max}, E_{es}, and LV afterload (E_s) after intravenous β-blockade. Ventriculo-arterial coupling, however, did not change after β-blockade. Although control patients had a significant reduction in dP/dt_{max} with β-blockade, the magnitude of this reduction was small, and there were no decreases in LV systolic pressure, E_{es}, or LV afterload (E_s). Examples of the effect of intravenous β-blockade on E_{es} and chamber elastic stiffness for a patient with CHF and a control patient are shown in Fig 2.

**TABLE 4. Continued**

<table>
<thead>
<tr>
<th>Systolic function</th>
<th>Idiopathic (n=12)</th>
<th>Ischemic (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>125±7</td>
<td>154±9†</td>
</tr>
<tr>
<td>Post</td>
<td>113±6*</td>
<td>136±9*</td>
</tr>
<tr>
<td>SVI, mL/M²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>32±2</td>
<td>26±2</td>
</tr>
<tr>
<td>Post</td>
<td>31±3</td>
<td>29±2*</td>
</tr>
<tr>
<td>CI, mL·min⁻¹·M⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.76±.0.14</td>
<td>2.36±.0.16</td>
</tr>
<tr>
<td>Post</td>
<td>2.23±.0.17†</td>
<td>2.15±.0.18*</td>
</tr>
<tr>
<td>SWI, mm Hg·mL⁻¹·M⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1975±220</td>
<td>2068±243</td>
</tr>
<tr>
<td>Post</td>
<td>1748±279</td>
<td>1912±298</td>
</tr>
<tr>
<td>dP/dt_{max}, mm Hg/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1037±51</td>
<td>1309±102†</td>
</tr>
<tr>
<td>Post</td>
<td>827±44*</td>
<td>968±86*</td>
</tr>
<tr>
<td>E_{es}, mm Hg·mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.76±0.13</td>
<td>0.99±0.12</td>
</tr>
<tr>
<td>Post</td>
<td>0.54±0.09*</td>
<td>0.73±0.15*</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective E_s, mm Hg·mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>3.66±0.44</td>
<td>4.05±0.45</td>
</tr>
<tr>
<td>Post</td>
<td>3.14±0.36</td>
<td>3.64±0.32</td>
</tr>
<tr>
<td>Ventriculo-arterial coupling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E_{es}/E_s ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.23±0.05</td>
<td>0.27±0.04</td>
</tr>
<tr>
<td>Post</td>
<td>0.20±0.04</td>
<td>0.20±0.04</td>
</tr>
</tbody>
</table>
Chamber elastic stiffness (calculated before atrial systole) before and after β-blockade is shown in Table 3 in control patients with and without a clinical history of hypertension as well as in CHF patients. At baseline, control patients with hypertension had a higher chamber elastic stiffness than CHF patients. Chamber elastic stiffness calculated at end diastole demonstrated similar trends at baseline (0.0181±0.0011 [+HTN] vs 0.0175±0.0015 [−HTN] vs 0.0154±0.0008 [CHF]; P<.05, CHF vs HTN).

Hemodynamic Response to β-Blockade in CHF Patients According to Etiology of Cardiomyopathy

The hemodynamic parameters of the patients with idiopathic dilated cardiomyopathy (n=12) and the patients with ischemic dilated cardiomyopathy (n=12) are shown in Table 4. At baseline, patients with idiopathic dilated cardiomyopathy had lower PCW pressure than those with ischemic dilated cardiomyopathy. In addition, patients with idiopathic dilated cardiomyopathy had lower LV systolic pressure, lower dP/dt min, and dP/dt max compared with patients with ischemic dilated cardiomyopathy. After intravenous β-blockade, all hemodynamic effects occurred equally in CHF patients regardless of the etiology of cardiomyopathy despite the administration of similar doses of β-blocker to both groups.

Hemodynamic Effect of Selective Versus Nonselective β-Blockade in Patients With CHF

The hemodynamic parameters before and after β-selective blockade with metoprolol (n=12) and nonselective β-blockade with propranolol (n=12) in CHF patients are shown in Table 5. At baseline, CHF patients receiving either metoprolol or propranolol were similar with respect to all hemodynamic parameters. The percent decrease in heart rate after β-blockade was similar in those treated with a selective or nonselective β-blocker. Of all hemodynamic indices of diastolic function, systolic function, or afterload (E), only peak filling rate (dV/dt max) was affected more in those treated with propranolol compared with those treated with metoprolol.

Effects of β-Blockade in the Absence of Intravenous Nitroglycerin

To demonstrate that the decrease in LV systolic pressure and lack of change in PCW pressure reported in Table 2 were due to β-adrenergic blockade and not to persistent nitroglycerin effects, an additional four patients with CHF were treated with intravenous propranolol but not nitroglycerin. In these four patients, LV systolic pressure decreased (131±3 vs 120±3 mm Hg, P=.01) and PCW pressure remained unchanged (23±1 vs 24±1, P=NS). These effects were similar to those seen in patients with CHF (Table 2) and suggest that the results reported in the present study were indeed due to β-adrenergic blockade.

Discussion

There is increasing evidence that chronic β-adrenergic blockade may provide long-term hemodynamic, symptomatic, and perhaps even prognostic benefit in patients with CHF.9-13,16 Nevertheless, many clinicians are hesitant to initiate β-blocker therapy in patients with CHF because of a fear of clinical deterioration from the negative inotropic effects of β-blockade. Several controlled trials using chronic β-blockers in patients with CHF reveal, however, that most patients with CHF tolerate the initiation of therapy.10,12-16 In the present study, we identified two potential explanations for this phenomenon. The reduction in LV systolic function was accompanied by a reduction in afterload, thus preserving ventriculo-arterial coupling. Furthermore, passive late diastolic function (PCW pressure and chamber elastic stiffness) did not change.

The present study demonstrated that although intravenous β-adrenergic blockade retarded active relaxation, it did not affect the passive late diastolic properties of the left ventricle. These observations demonstrate an uncoupling of active and passive diastolic function in patients with both normal and abnormal active relaxation. Weisfeldt et al10 demonstrated that the end-diastolic pressure-volume relation of the normal filling canine left ventricle was unaffected by changes in active relaxation provided that end diastole occurred more than 3.5 Tau, after maximal dP/dt max. More recently, Nikolic et al26,27 examined the effects of early diastolic loading on myocardial relaxation in filling and nonfilling canine hearts. They concluded that the duration of myocardial relaxation was prolonged by LV filling. In these studies, the time to end relaxation in nonfilling hearts was 3.7 Tau but increased to 5.4 Tau in filling hearts. In the present study, the time to end diastole in both normal and CHF patients was greater than 5.5 Tau, before or after β-blockade (Table 2), which would imply that end relaxation occurred before end diastole in these patients regardless of whether the time to end relaxation was 3.5 Tau25 or 5.4 Tau27. Thus, a prolongation of active relaxation caused by β-blockade would not be expected to increase PCW pressure or chamber elastic stiffness even in patients with prolonged active relaxation secondary to congestive cardiomyopathy.

The physiological importance of alterations in the number and coupling of β-adrenergic receptors to adenylate cyclase in CHF has been the subject of much recent interest. Bristow et al17 reported a 25% to 50% decrease in myocardial β-receptor density in failing human myocardium that was mostly due to selective β1-receptor downregulation. They also reported a greater contractile response to selective β2 stimulation than to β1 stimulation despite a greater number of β2-receptors in papillary muscle preparations from failing hearts in idiopathic cardiomyopathy.17 This suggests a potential role for β2-receptors in maintaining contractility in the failing heart. However, several investigators have demonstrated partial uncoupling of the β2-receptor apparatus in isolated failing myocardium;28,29 probably mediated by alterations in guanine regulatory (G) proteins. Thus, whether the β2-receptor has developed greater hemodynamic importance than the β1-receptor in the intact circulation of patients with CHF is unclear. In the present study, there were no differences in the magnitude of the negative inotropic effects of nonselective β-receptor blockade compared with β1-selective blockade in patients with CHF. Thus, our data do not support a greater in vivo physiological role of the myocardial β2-receptor in the maintenance of left ventricular systolic function in CHF. However, nonselective β-blockade caused a greater deterioration in parameters that measure active diastolic function (ie, Tau and...
TABLE 5. Hemodynamic Response to Metoprolol Versus Propranolol in Patients With Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol (n=12)</th>
<th>Propranolol (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>91±3</td>
<td>85±3</td>
</tr>
<tr>
<td>Post</td>
<td>73±2†</td>
<td>72±2</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>20±2</td>
<td>27±2‡</td>
</tr>
<tr>
<td>Post</td>
<td>24±3†</td>
<td>27±3</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>257±16</td>
<td>240±13</td>
</tr>
<tr>
<td>Post</td>
<td>243±17*</td>
<td>240±14</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>205±15</td>
<td>176±12</td>
</tr>
<tr>
<td>Post</td>
<td>187±17*</td>
<td>177±14</td>
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<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCW, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>24±2</td>
<td>24±3</td>
</tr>
<tr>
<td>Post</td>
<td>24±2</td>
<td>24±2</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
<td>-1211±96</td>
<td>-1298±83</td>
</tr>
<tr>
<td>Post</td>
<td>-985±50*</td>
<td>-1185±90*</td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>63±3</td>
<td>63±3</td>
</tr>
<tr>
<td>Post</td>
<td>72±3*</td>
<td>75±5*</td>
</tr>
<tr>
<td>T&lt;sub&gt;12&lt;/sub&gt;, milliseconds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>48±2</td>
<td>45±2</td>
</tr>
<tr>
<td>Post</td>
<td>53±2*</td>
<td>51±2*</td>
</tr>
<tr>
<td>dV/dt&lt;sub&gt;max&lt;/sub&gt;, mL/s</td>
<td>496±50</td>
<td>586±42</td>
</tr>
<tr>
<td>Post</td>
<td>492±52</td>
<td>438±25*</td>
</tr>
<tr>
<td>Chamber stiffness, mL&lt;sup&gt;-1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.0149±0.0002</td>
<td>0.0156±0.0006</td>
</tr>
<tr>
<td>Post</td>
<td>0.0156±0.0009</td>
<td>0.0168±0.0008</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; LVEDV, left ventricular end-systolic volume; PCW, pulmonary capillary wedge; dP/dt<sub>max</sub>, maximal first derivative of left ventricular pressure fall; T<sub>1</sub>, time constant of isovolumetric pressure decay logarithmic; T<sub>12</sub>, time constant of isovolumetric pressure decay one-half; dV/dt<sub>max</sub>, peak filling rate; LVSP, left ventricular systolic pressure; SVI, stroke volume index; CI, cardiac index; SWI, stroke work index; E<sub>as</sub>, end-systolic elastance; and E<sub>a</sub>, arterial elastance.

*<i>P</i> < .05 Pre vs Post; †<i>P</i> < .05 percent change in propranolol greater than percent change in metoprolol; ‡<i>P</i> < .05 metoprolol vs propranolol.

Bristow et al<sup>30</sup> demonstrated that ischemic cardiomyopathy is characterized by less β-adrenergic receptor downregulation but more uncoupling of β-adrenergic receptors to the effector apparatus compared with idiopathic cardiomyopathy. These differences in myocardial β-adrenergic receptor number have led some to the hypothesis that cardiac β-adrenergic drive is higher in patients with idiopathic cardiomyopathy than in ischemic cardiomyopathy for a given degree of myocardial dysfunction.<sup>30</sup> Therefore, patients with idiopathic dilated cardiomyopathy might be expected to be more sensitive to the negative inotropic effects of acute β-blockade compared with patients with ischemic dilated cardiomyopathy. Despite lower baseline LV systolic pressures, dP/dt<sub>max</sub>, dP/dt<sub>min</sub>, and a trend toward lower end-systolic elastances, patients with idiopathic cardiomyopathy had similar acute hemodynamic responses to β-adrenergic blockade compared with those with ischemic cardiomyopathy. These results are consistent with both of these groups having similar cardiac β-adrenergic drive, although plasma catecholamines were not measured.

TABLE 5. Continued

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol (n=12)</th>
<th>Propranolol (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>136±10</td>
<td>143±9</td>
</tr>
<tr>
<td>Post</td>
<td>120±7*</td>
<td>131±9*</td>
</tr>
<tr>
<td>SVI, mL/M&lt;sup&gt;2&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>Pre</td>
<td>26±2</td>
<td>31±2</td>
</tr>
<tr>
<td>Post</td>
<td>29±3</td>
<td>31±2</td>
</tr>
<tr>
<td>CI, mL·min&lt;sup&gt;-1&lt;/sup&gt;·M&lt;sup&gt;-2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.35±0.14</td>
<td>2.77±0.16</td>
</tr>
<tr>
<td>Post</td>
<td>2.10±0.17*</td>
<td>2.31±0.14*</td>
</tr>
<tr>
<td>SWI, mm Hg·mL&lt;sup&gt;-1&lt;/sup&gt;·M&lt;sup&gt;-2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1980±214</td>
<td>2062±245</td>
</tr>
<tr>
<td>Post</td>
<td>1967±274</td>
<td>1968±296</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
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<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1163±67</td>
<td>1184±93</td>
</tr>
<tr>
<td>Post</td>
<td>862±59*</td>
<td>932±81*</td>
</tr>
<tr>
<td>E&lt;sub&gt;as&lt;/sub&gt;, mm Hg/mL</td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>0.88±0.15</td>
<td>0.88±0.10</td>
</tr>
<tr>
<td>Post</td>
<td>0.62±0.15*</td>
<td>0.66±0.11*</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective E&lt;sub&gt;as&lt;/sub&gt;, mm Hg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>3.50±0.41</td>
<td>4.16±0.47</td>
</tr>
<tr>
<td>Post</td>
<td>3.00±0.36*</td>
<td>3.74±0.31</td>
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<tr>
<td>Venticulo-arterial coupling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E&lt;sub&gt;as&lt;/sub&gt;/E&lt;sub&gt;a&lt;/sub&gt; ratio</td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>0.27±0.06</td>
<td>0.23±0.03</td>
</tr>
<tr>
<td>Post</td>
<td>0.21±0.05</td>
<td>0.19±0.03</td>
</tr>
</tbody>
</table>
The baseline differences in passive diastolic function between patients with and without CHF merit further consideration. Although patients in the control group had higher chamber elastic stiffness at baseline than those with CHF (Table 2), this was in part due to the high chamber elastic stiffness seen among those hypertensive patients in the control group (Table 3). Although myocardium of CHF patients might be expected to be stiffer than nonhypertensive controls because of the cardiac hypertrophy associated with congestive cardiomyopathy, this was not demonstrated in the present study since chamber stiffness was measured rather than myocardial stiffness. The differences between chamber and myocardial properties of the left ventricle would be accentuated in CHF because of the loss of eccentricity and larger chamber size present in congestive cardiomyopathy.

The hemodynamic effects of intravenous $\beta$-blockade on LV systolic pressure and afterload (effective $E_v$) merit further comment. Patients with CHF demonstrated significant reductions in LV systolic pressure and $E_v$ after $\beta$-blockade, whereas control patients had no such effects. The mechanism of this decrease is uncertain. In CHF patients, it is possible that the negative inotropic effects of $\beta$-blockade on the left ventricle decreased the distending pressure on their noncompliant arterial system. Alternatively, acute $\beta$-blockade may have exerted a direct beneficial effect on the arterial tree in patients with CHF. This explanation seems unlikely since stimulation of vascular $\beta_2$-receptors should cause arterial dilation, and $\beta$-blockade could be expected to produce arterial constriction. However, the opposite effect was observed. The explanation for this result is not apparent from the data obtained in this study. Nevertheless, this reduction in afterload was responsible for the preservation of ventriculo-arterial coupling in CHF patients treated with $\beta$-adrenergic blockade.

There are several potential limitations to this study. The first involves the accuracy and linearity of the gain and offset calibration of the conductance volume signal. The use of thermodilution-derived stroke volume for gain correction may be inaccurate in patients with depressed LV function. Furthermore, although the gain calibration for the conductance volume signal is nonlinear over a large volume range, previous investigators have demonstrated that even during an acute load change, the calibrated conductance volume signal is accurate within the range of volume from end-diastolic volume to end-systolic volume of the baseline loop. Since bolus intravenous nitroglycerin did not reduce late diastolic volumes below that of the end-systolic volume of the baseline loop, the LV diastolic pressure-volume relations reported in the present study should be accurate. The offset calibration caused by the parallel conductance of adjacent structures was assumed to be constant in the present study. Previous investigators have demonstrated that the offset calibration of the conductance volume signal is relatively insensitive to changes in right ventricular volume or LV thickness and shape changes during the cardiac cycle.

Another potential limitation involves the use of bolus intravenous nitroglycerin to change loading conditions in these patients. Although intravenous nitroglycerin has a very short half-life in patients with normal ventricular function, it has a longer half-life in patients with CHF. Some of the effects ascribed to acute $\beta$-blockade in patients with CHF could in part be due to persistent blood levels of nitroglycerin. However, this is unlikely since hemodynamics had returned to baseline before the administration of intravenous $\beta$-blockade, and the four CHF patients receiving $\beta$-blockade without intravenous nitroglycerin had similar hemodynamic effects to those reported in the present study.

The small numbers of patients in each of the subgroups shown in Tables 3 through 5 may limit the statistical power in those analyses. Nevertheless, the effect of $\beta$-blockade on the primary end points of end-systolic elastance and chamber stiffness was very similar in these subgroups, and it is unlikely that the addition of more patients would alter our results. Finally, the baseline cardiac index of CHF patients was only slightly below the lower range of normal and hence limits any generalization regarding the safety of $\beta$-blockade in some CHF patients. However, these results can be generalized to those patients examined in this study with symptomatic CHF with a mean ejection fraction of 24% and a mean pulmonary capillary wedge pressure of 24 mm Hg.

Conclusions

Our conclusions are (1) intravenous $\beta$-blockade administration reduces LV systolic and active diastolic function but not passive late diastolic function in patients with CHF; (2) nonselective and $\beta_1$-selective blockade caused similar hemodynamic effects in patients with CHF; (3) hypertensive control patients had a higher chamber elastic stiffness than patients with CHF; (4) $\beta$-adrenergic blockade lowered LV systolic pressure and afterload ($E_v$) in patients with CHF but not in control patients; and (5) the negative inotropic effects of $\beta$-adrenergic blockade on patients with CHF were similar in patients with ischemic versus idiopathic cardiomyopathy. The preservation of passive late diastolic function and ventriculo-arterial coupling provides possible explanations of why $\beta$-adrenergic blockade is tolerated by many patients with CHF.

Acknowledgments

This study was supported by a fellowship (H.L.H.) from the American Heart Association, Virginia Affiliate, Inc (VA-91-F-61), and by a FIRST Award (M.D.F.) from the National Heart, Lung, and Blood Institute (R29HL-47046-01). This study could not have been performed without the assistance and excellent clinical care offered by the entire staff of the Cardiac Catheterization Laboratory at the University of Virginia and Robert Owens. Excellent editorial skills were provided by Jerry Curtis.

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Why do patients with congestive heart failure tolerate the initiation of beta-blocker therapy?

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*Circulation.* 1993;88:1610-1619
doi: 10.1161/01.CIR.88.4.1610

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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