Effect of $\beta$-Adrenergic Blockade on Myocardial Function and Energetics in Congestive Heart Failure

Improvements in Hemodynamic, Contractile, and Diastolic Performance With Bucindolol

Eric J. Eichhorn, MD, John B. Bedotto, MD, Craig R. Malloy, MD, Barbara A. Hatfield, RN, David Deitchman, PhD, Marilyn Brown, RN, BSN, John E. Willard, MD, and Paul A. Grayburn, MD

The hemodynamic effects of $\beta$-adrenergic blockade with bucindolol, a nonselective $\beta$-antagonist with mild vasodilatory properties, were studied in patients with congestive heart failure. Fifteen patients (New York Heart Association class I–IV) underwent cardiac catheterization before and after 3 months of oral therapy with bucindolol. The left ventricular ejection fraction increased from 0.23±0.12 to 0.29±0.14 ($p=0.007$), and end-systolic elastance, a relatively load-independent determinant of contractility, increased from 0.60±0.40 to 1.11±0.45 mm Hg/ml ($p=0.0049$). Both left ventricular stroke work index (34±13 to 47±19 g-m/m², $p=0.0059$) and minute work (5.5±2.2 to 7.0±2.6 kg-m/min, $p=0.0096$) increased despite reductions in left ventricular end-diastolic pressure (19±8 to 15±5 mm Hg, $p=0.021$). There was an upward shift in the peak $+dP/dt_{max}$–end-diastolic volume relation ($p=0.0005$). These data demonstrate improvements in myocardial contractility after $\beta$-adrenergic blockade with bucindolol. At a matched paced heart rate of 98±15 min⁻¹, the time constant of left ventricular isovolumic relaxation was significantly reduced by bucindolol therapy (92±17 versus 73±11 msec, $p=0.0013$), and the relation of the time constant to end-systolic pressure was shifted downward ($p=0.014$) with therapy. The slope of the logarithm left ventricular end-diastolic pressure–end-diastolic volume relation was unchanged ($p=0.51$) after bucindolol. These data suggest that chronic $\beta$-adrenergic blockade with bucindolol improves diastolic relaxation but does not alter myocardial chamber stiffness. Myocardial oxygen extraction, consumption, and efficiency were unchanged despite improvement in contractile function and mechanical work. Thus, in patients with congestive heart failure, chronic $\beta$-adrenergic blockade with bucindolol significantly improves myocardial contractility and minute work, yet it does not do so at the expense of myocardial oxygen consumption. Additionally, bucindolol improves myocardial relaxation but does not affect chamber stiffness. (Circulation 1990;82:473–483)

Several studies have suggested that chronic $\beta$-adrenergic blockade may reduce mortality in patients with congestive heart failure.¹⁻³ More recent studies indicate that exercise tolerance, ejection fraction, and stroke work may improve with $\beta$-adrenergic blockade.⁴⁻⁷ However, the effect of chronic $\beta$-adrenergic blockade on left ventricular hemodynamics, contractility, and relaxation have not been extensively evaluated. Therefore, we examined the effects of bucindolol, a $\beta_1$, $\beta_2$-antagonist with mild vasodilatory properties,⁸⁻¹¹ in patients with longstanding congestive heart failure. Although a
small amount of intrinsic sympathomimetic activity has been noted in some in situ model system studies,9,10 this drug appears to have no such intrinsic activity in humans.5,11 Because earlier trials showed beneficial effects of β-antagonists on ejection fraction, we tested the hypothesis that β-adrenergic blockade with bucindolol could improve contractility without increasing myocardial oxygen consumption. We examined bucindolol’s effect on left ventricular contractility, myocardial relaxation, chamber stiffness, coronary blood flow, myocardial oxygen consumption, and efficiency.

Methods

Patient Population

Fifteen male patients 32–62 years old (mean±SD, 50±11 years) with clinical congestive heart failure (New York Heart Association [NYHA] class I–IV) and a left ventricular ejection fraction less than 0.45 by radionuclide or contrast angiographic methods within 30 days of entry comprised the study group. To bias the study population toward nonischemic etiology, we entered patients who were suspected of having no coronary artery disease. All patients with a presumptive diagnosis of a dilated cardiomyopathy were approached for entry into the study unless they had a complicating illness. Patients with severe renal (creatinine, >2.5 mg/dl), hepatic (SGOT or SGPT, >3 times that of normal), pulmonary (reactive airways disease), rheumatological (e.g., systemic lupus erythematous, polyarteritis nodosa, scleroderma, dermatomyositis), or endocrine disease (e.g., primary aldosteronism, pheochromocytoma, hyperthyroidism, hypothyroidism, insulin-dependent diabetes) were excluded. Patients with myocardial infarction within 3 months or constrictive, restrictive, hypertrophic, or primary valvular disease were excluded as were patients with a recent (<3 months) history of ethanol abuse. Myocarditis was ruled out in high-suspicion patients (i.e., patients with <6 months of clinical heart failure of unclear etiology) by endomyocardial biopsy.

All medications were allowed, except β-adrenergic blocker therapy within 3 months of entry. In addition, angiotensin converting enzyme inhibitors were allowed as long as the dosage remained constant for at least 2 months before entry and unchanged during the study period. All medications remained constant during the study period except for diuretics, which were altered as clinically indicated. Written informed consent was obtained from each patient, and the protocol was approved by the Human Studies Subcommittee of the Dallas Veterans Administration and University of Texas Southwestern Medical Centers.

Hemodynamic Measurement

Each study was performed in the Dallas Veterans Administration Cardiac Catheterization Laboratory. Patients were studied before and after 3 months of oral bucindolol therapy. All patients were studied within 1 week before initiating therapy.

A 7F Wilton-Webster coronary sinus thermodilution catheter and a 7F Simmons II catheter were placed in the coronary sinus for sampling blood for oximetry. Using a femoral approach, a 7F balloon-tipped thermodilution pulmonary artery catheter was advanced under fluoroscopic guidance to the pulmonary artery. An 8F doublechep Millar (Millar Instruments, Houston, Tex.) micromanometer pigtail catheter was positioned in the left ventricle so one transducer recorded left ventricular pressure while the other transducer recorded simultaneous aortic pressure. This catheter contains a central lumen that allows performance of a left ventriculogram while simultaneous micromanometer pressures are recorded.

Baseline left and right heart pressure recordings were performed before initiation of overdrive (coronary sinus) pacing. These measurements included pulmonary capillary wedge, pulmonary artery, right atrial, aortic, and left ventricular pressures. dP/dt was recorded by electronic differentiation of the simultaneous left ventricular pressure wave form. Recording was made on an optical strip-chart recorder (Honeywell Electronics for Medicine model VR-16) at a paper speed of 100 mm/sec. Thermodilution cardiac outputs were then obtained, and the results of three to five consecutive measurements were averaged. Forward stroke volume was determined by dividing the cardiac output by heart rate. Coronary sinus blood flow measurements were performed with previously established methods,12 and near-simultaneous coronary sinus and arterial blood was sampled for oximetry and determination of myocardial oxygen consumption.13,14

Ten minutes after initiation of atrial pacing at 15 beats/min above the intrinsic heart rate, left and right heart pressures and cardiac outputs were repeated. This was followed by digital ventriculography with 15–25 ml (total volume) of diluted (60:40) nonionic contrast media (Iohexol, Winthrop-Breon Laboratories, New York). Ventriculography was performed at 30 frames/sec with cineradiographic equipment (Philips model Optimus M200, Eindhoven, The Netherlands) interfaced directly to a digital radiographic computer (ADAC, model DPS-4100C, Milpitas, Calif.) and stored as a 512×512×8 bit image matrix. An R wave gated mask was derived from the cardiac cycle before the appearance of radiographic contrast and subtracted from the respective frames containing contrast. During digital ventriculography, simultaneous left ventricular pressures were acquired and stored by the ADAC computer. Left ventriculography was performed in a 30° right anterior oblique projection. Before the first ventriculogram, a standardized grid, at the mid left atrial level, was imaged at the same focal length and image intensifier height as the ventriculograms.

After these measurements were recorded, loading conditions were altered while maintaining atrial pac-
ing. Intravenous sodium nitroprusside was initiated at a dose of 0.25–0.50 μg/kg/min and increased by 0.25 μg/kg/min every 2–5 minutes to achieve a reduction of 10–20 mm Hg in aortic end-systolic pressure. Care was used to avoid symptomatic hypotension. Repeat simultaneous ventriculograms and hemodynamic recordings were performed at one or two time points after aortic end-systolic pressure had been altered. There was a delay of at least 10 minutes between ventriculograms to allow the left ventricle to return to equilibrium.

After 3 months of therapy, the same procedure was used with care to match the original atrially paced heart rate used in the baseline study.

Selective coronary arteriography was performed on all patients at the end of their first catheterization to document the etiology of their cardiomyopathy.

Drug Titration

Bucindolol was initiated the day after initial catheterization in all but two cases. Therapy was started in the remaining two patients within 1 week of catheterization. The drug was titrated weekly at the rate of 12.5, 25, 50, 75, and 100 mg twice daily.

Hemodynamic Data Analysis

Left ventricular volumes were measured by analysis of digital left ventriculography. The cardiac cycle selected was not a premature or postpremature beat. Analysis of the cardiac cycle was performed by computer gating of the RR interval into 33 msec segments. Each cardiac image in the cycle underwent light pen digitization by a blinded observer. Left ventricular volumes, including end-diastolic, end-systolic, and stroke volume, were determined by a standard angiographic area-length method. End diastole applied to the largest ventricular volume (near the peak of the R wave), and end systole was taken as the smallest volume in each cardiac cycle. Simultaneous left ventricular pressure recordings were interfaced directly onto the digital volume assessment at each data point in the cardiac cycle. The ADAC digital computer plotted simultaneous pressure and volume for all data points in the cardiac cycle (Figure 1).

Intraobserver and interobserver variability of our digital ventriculogram measurements has been tested by repeated analysis of 21 digital left ventricular volumes. The SEE for intraobserver measurements was 4.5 ml (n=21, r=0.99, y=0.86x+25.8, p=0.0001), and the SEE for interobserver measurements was 4.8 ml (n=21, r=0.99, y=0.97x−3.7, p=0.0001).

Assessment of Systolic Performance

Left ventricular systolic performance was assessed at matched paced heart rates by comparing changes in the following relations before therapy with that at 3 months of therapy: 1) end-systolic elastance (Esv) derived from the end-systolic pressure-volume relation16,17 (slope of the relation of left ventricular end-systolic pressure versus left ventricular end-systolic volume before and after loading conditions are altered), 2) peak +dP/dtmax-end-diastolic volume relation,18 and 3) the left ventricular stroke work index versus left ventricular end-diastolic pressure relationship.19 Left ventricular stroke work index (LVSWI) was determined by the formula19:

LVSWI=(MSBP−PCW)×SI×0.0136

where MSBP=mean systolic blood pressure, PCW= mean pulmonary capillary wedge pressure, and SI=stroke index by thermodilution (cardiac index/heart rate).

Assessment of Diastolic Performance

Isovolumic relaxation. Left ventricular relaxation was assessed by analyzing changes in −dP/dtmax20 and the time constant of exponential isovolumic pressure fall, τ,21–23 both before and after long-term β-adrenergic blockade.

τ was determined using a program developed at the University of Arizona. The micromanometer analog signal from the strip-chart recorder was interfaced with an IBM AT computer equipped with an analog/digital converter. Approximately 50 beats of the pressure signal was digitized on-line and stored at 200 Hz. The digitized study was subsequently recalled for analysis, and a five-point moving average smoothing routine was then applied. Thus, each cardiac cycle was digitized at a rate of roughly 150–200 points per cardiac cycle, depending on the cycle length. The program automatically identifies end systole, end diastole, peak positive dP/dt, and negative dP/dt for each beat of the acquisition. The decay of left ventricular pressure with time can be closely approximated by the exponential relation21,24:

P=Poe−a(t)+Pb

where P is left ventricular pressure, Poe is pressure at peak negative dP/dt, t is the time (msec) after peak negative dP/dt, Pb is left ventricular asymptote pressure (assuming a nonzero asymptote and assuming that left ventricular pressure decays to infinity), and a is the constant of the exponential relation. The first derivative of this equation with respect to t is:

dP/dt=−aPoe−a(t)

If P from the first equation is then substituted to eliminate Poe−a(t):

dP/dt=−a(P−Pb)

Thus, τ was calculated using a linear regression of dP/dt versus (P−Pb) from maximum negative dP/dt to left ventricular end-diastolic pressure: τ=−1/a (the inverse of the slope of the regression). Beats with an r value of less than 0.95 for this linear regression were discarded, and 20–30 beats were analyzed and averaged.

Because τ is sensitive to changes in heart rate and afterload,22 the relation of τ to aortic end-systolic pressure at matched paced heart rates was examined.
FIGURE 1. Plots of end-systolic pressure-volume relation for one patient with left ventricular volume on abscissa and pressure on ordinate. There is an increase in slope of relation from baseline (top panel) to post-therapy state (bottom panel). This demonstrates increased systolic elastance reflecting improved myocardial contractility.

Chamber stiffness. Alterations in chamber stiffness were assessed by changes in the constant (k), determined as the slope of the relation of the natural logarithm of the left ventricular end-diastolic pressure to the end-diastolic volume index. The relaxation rate constant (k) was defined by the equation:

\[ P = b e^{kV} \]

where \( P \) is left ventricular end-diastolic pressure, \( b \) is the left ventricular end-diastolic pressure at zero volume, and \( V \) is simultaneous left ventricular end-diastolic volume. This equation can be rewritten as:

\[ \ln P = kV + \ln b \]

Thus, \( k \) was determined from a regression analysis of the natural logarithm of the left ventricular end-diastolic pressure compared with the end-diastolic volume at each of the three data points during each study. The \( \ln P \) versus \( V \), at several different end-diastolic volumes, was assumed to be linear in these patients, and the slope of this relationship (k) is highest in patients with noncompliant ventricles. Thus, a reduction in \( k \) would represent an index of reduced chamber stiffness.

Myocardial Oxygen Consumption, Efficiency, and Coronary Flow

Coronary blood flow was determined with the thermodilution methods of Ganz et al. Myocardial oxygen consumption was determined by the formula (myocardial oxygen consumption [ml O$_2$/min]) equals
(coronary blood flow [ml/min]) times (aortocoronary sinus oxygen difference [vol %]) divided by 100.

Myocardial efficiency was determined by a derivation of the formula of Bing (see References 13 and 14):

\[
\text{Efficiency (\%)} = \frac{\text{Stroke work (kg-m) } \times \text{Heart rate (min}^{-1}\text{)}}{\text{Myocardial oxygen consumption (ml O}_2\text{/min) } \times k}
\]

where \( k \) is 2.059 (kg-m/ml \( O_2 \) consumed).

Myocardial oxygen extraction (\%) was defined as the ratio of aortocoronary sinus oxygen difference to arterial oxygen content.26

Statistics

Changes in left ventricular volumes, hemodynamic variables, isovolumic indexes of contractility and relaxation, and myocardial oxygen consumption were analyzed by a paired Student's \( t \) test.

Because peak +dP/dt is sensitive to changes in heart rate and preload,18 peak +dP/dt was compared at identical heart rates. To correct for changes in end-diastolic volume, a two-way (bucindolol and nitroprusside effects) analysis of variance was performed with subjects treated as blocks and end-diastolic volume treated as a covariate.

Previous studies have shown a linear relation for \( E_v \) (slope of the left ventricular end-systolic pressure–volume relation),16,17 for the relation of \( \tau \) to aortic end-systolic pressure,22 and for the relation relating the natural logarithm of the left ventricular end-diastolic pressure to ventricular volume.25 For each patient, the data points for these relations were subjected to regression analysis, and an equation that best described each line was determined, both before and after \( \beta \)-adrenergic blocker therapy. The slope of each line, before and after intervention, was compared by paired Student's \( t \) test to determine significance. A \( p \) value of 0.05 or less was sufficient to reject the null hypothesis that \( \beta \)-blockade does not improve ventricular function. All values are given as mean±SD unless otherwise indicated.

Results

The clinical characteristics of the 15 patients are summarized in Table 1. Twelve of the patients had nonischemic etiology for cardiomyopathy, whereas three had significant coronary artery disease to account for their left ventricular dysfunction. Fourteen of the patients were taking angiotensin converting enzyme inhibitors during the trial. None of the patients had a change in angiotensin converting enzyme inhibitor dosage during the trial period or for 2 months before entering the trial. Two of the patients had their diuretic dosage increased nominally during the 3-month trial period (from 80 to 120 mg orally twice daily).

All patients tolerated the titration of bucindolol well. Only three patients, two of whom had ejection fractions of less than 0.10, were unable to tolerate the maximal dose of 100 mg twice daily due to mild lightheadedness. One of the three patients was intolerant to even low doses of angiotensin converting enzyme inhibitors due to symptomatic hypotension. A bucindolol dose of 75 mg twice daily was well tolerated in all three of these patients. No other side effects were noted among the 15 patients.

Effect of Bucindolol on Hemodynamics in Absence of Pacing

The changes in hemodynamics can be seen in Table 2. Heart rates were mildly reduced with bucindolol therapy, but this did not reach statistical significance (82±20 versus 73±11 min\(^{-1}\), \( p=0.059 \)). There was an increase in cardiac outputs from 5.0±1.5 to 5.8±1.6 l/min (\( p=0.0043 \)), which can be accounted for by an increase in stroke volumes from 64±25 to 82±28 ml (\( p=0.0009 \)). The increase in stroke volumes was accompanied by an increase in stroke work (from 34±13 to 47±19 g-m/m\(^2\), \( p=0.0059 \)) and minute work (from 5.5±2.2 to 7.0±2.6 kg-m/min). This occurred despite a decrease in left ventricular end-diastolic pressures from 19±8 to 15±5 mm Hg (\( p=0.021 \)) (Figure 2).

Mean pulmonary artery pressures fell with chronic \( \beta \)-adrenergic blocker therapy with bucindolol (30±12 to 21±9 mm Hg (\( p=0.0029 \)). The fall in pulmonary artery pressures was primarily due to a fall in left ventricular end-diastolic pressures and pulmonary vascular resistances (from 196±176 to 131±103 dyne-sec-cm\(^{-5}\), \( p=0.034 \)).

Both peak systolic pressures (109±17 to 120±26 mm Hg, \( p=0.023 \)) and aortic end-systolic (dicrotic notch) pressures (90±12 to 98±18 mm Hg, \( p=0.049 \)) were increased with therapy. Systemic

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<td>M</td>
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I, ischemic etiology; NI, nonischemic etiology; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
vascular resistances were unchanged by β-blockade with bucindolol (from 1,318±406 to 1,183±290 dyne-sec-cm⁻², p=NS).

**Myocardial Oxygen Consumption and Efficiency**

Coronary sinus blood flow did not change after bucindolol therapy (109±44 to 116±53 ml/min, p=NS) (Table 2). Neither myocardial aortocoronary sinus oxygen difference (11.9±1.2 versus 11.6±1.6 vol %, p=NS) nor oxygen extraction changed (68±6% to 65±6%, p=NS). Despite an increase in stroke work and minute work, myocardial oxygen consumption did not increase (11.6±4.4 to 12.3±4.9 ml O₂/min, p=NS). Myocardial efficiency was unchanged after therapy (28±18% versus 30±14%, p=NS). Thus, the increase in mechanical stroke work did not occur at the expense of either oxygen extraction or myocardial efficiency.

**Systolic Assessment**

**Left ventricular volumes.** Fourteen of the 15 patients had interpretable ventriculograms, which were obtained during atrial pacing (Table 3). One patient had ventricular ectopy with each ventriculogram and was excluded from volume and elastance analyses. A significant increase in left ventricular ejection fractions (from 0.23±0.12 to 0.29±0.14, p=0.0071; Figure 3) with chronic β-adrenergic blocker therapy was due to a decrease in left ventricular end-systolic volumes from 100±51 to 84±51 ml/m² (p=0.0047) with a smaller decrease in left ventricular end-diastolic volumes from 125±48 to 111±52 ml/m² (p=0.041). The decrease in left ventricular end-systolic volumes and increase in ejection fractions occurred despite decreased left ventricular end-diastolic pressures and volumes (preload) and increased aortic end-systolic pressures (afterload). This suggests increased myocardial contractility. Ejection fractions in the patients without (n=11) coronary heart disease also increased significantly (p<0.025) (Figure 3).

**Isovolumic indexes of contractility.** At matched paced heart rates without correction for end-diastolic volume, peak +dP/dt increased from 895±172 to 1,055±265 mm Hg/sec (p=0.014) after bucindolol therapy. To correct for changes in end-diastolic volumes, we examined the relation of peak +dP/dt to left ventricular end-diastolic volume at matched paced heart rates. This relatively load-independent index of contractility exhibited a significant upward shift of the relation between +dP/dt and preload with bucindolol therapy.

**Table 3. Volumetric and Contractility Changes After 3 Months of Therapy With Oral Bucindolol at Matched Paced Heart Rates**

<table>
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<th>Heart rate (min⁻¹)</th>
<th>Pretreatment pacing</th>
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<td>Aortic end-systolic pressure (mm Hg)</td>
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<td>Peak +dP/dt (mm Hg/sec)</td>
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<td>LVEDV (ml)</td>
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<td>LVESV (ml)</td>
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<tr>
<td>LVEF</td>
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<td>Ees (mm Hg/ml)</td>
<td>0.60±0.40</td>
<td>1.11±0.45</td>
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Values are given as mean±SD.

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; Ees, end-systolic elastance.

**Figure 2. Plot of stroke work increased after β-blocker therapy despite a reduction in preload as reflected by left ventricular end-diastolic pressure (mean±SEM). As afterload, reflected by aortic end-systolic pressure, increased, increase in stroke work is most likely accounted for by increased contractility.**
Eichhorn et al. Hemodynamic Effects of Bucindolol in CHF

Diastolic Assessment

Left ventricular isovolumic relaxation. At the pre-pacing heart rate, there was no difference in $\tau$ after bucindolol therapy (96±17 versus 99±19 msec, $p=0.67$), despite an increase in end-systolic pressure. However, at a higher paced heart rate, there was a significant reduction in $\tau$ (92±17 versus 73±11 msec, $p=0.0013$; Figure 5), suggesting improved relaxation with bucindolol therapy. To correct for the effects of end-systolic pressure and heart rate on $\tau$, the relation of $\tau$ to left ventricular end-systolic pressure at matched heart rates, before and after bucindolol therapy, was examined (Figure 5). There was a significant downward shift in this relation after bucindolol ($p=0.014$), suggesting improved myocardial relaxation.

Maximum $-dP/dt$ increased from 946±193 to 1,125±373 mm Hg/sec at matched paced heart rates ($p=0.027$). This increase in maximum $-dP/dt$ occurred despite a decrease in preload. This also suggests improved myocardial relaxation.

Left ventricular pressure-volume relation. The relation of the left ventricular end-diastolic pressure to volume and the changes in chamber stiffness constant ($k$) are shown in Figure 6. As is evident, there was no significant alteration in the left ventricular pressure-volume relation after bucindolol therapy. Both pressure and volume were decreased along a common curve rather than shifting curves (Figure 6a). The slope ($k$) of the logarithm of left ventricular end-diastolic pressure–left ventricular end-diastolic volume relation was 0.020±0.026 ml$^{-1}$ before therapy and 0.013±0.010 ml$^{-1}$ ($p=0.51$) after bucindolol (Figure 6b). As the intercept of this relation was also unchanged after therapy, this does not represent a parallel shift of this relation.
Discussion

Hemodynamic Benefit

In this study, \( \beta \)-adrenergic blockade with bucindolol improved two relatively load-independent indexes of contractility—the end-systolic pressure-volume relation and the peak \( +dP/dt \)-end-diastolic volume relation. In addition, stroke work increased at a lower left ventricular end-systolic pressure, and left ventricular end-systolic volume was reduced at a similar end-systolic pressure. An increase in left ventricular ejection fraction with \( \beta \)-adrenergic blockade in patients with chronic congestive heart failure has been shown previously.\(^1\)\(^4\)\(^7\) However, ejection fraction is sensitive to loading conditions and does not necessarily reflect myocardial contractility. The present study suggests that chronic \( \beta \)-blockade may improve myocardial contractility in patients with congestive heart failure.

Myocardial relaxation also appeared to improve after long-term bucindolol therapy as evidenced by an increase in \( -dP/dt \) at matched heart rates but lower preloads. The reduction in \( \tau \) at matched heart rates and afterload cannot be accounted for by a decrease in preload, to which \( \tau \) is relatively insensitive.\(^23\) The lack of a decrease in \( \tau \) at the baseline heart rate may reflect unmatched afterload and heart rate. Previous investigators have shown that \( \beta \)-agonists given acutely will shift the \( \tau \)-end-systolic pressure relation downward in both normal and failing hearts, whereas \( \beta \)-blockers shift the relation upward.\(^22\)\(^27\) The ability of chronic administration of \( \beta \)-adrenergic blockade to produce the opposite effect in congestive heart failure (i.e., to improve relaxation) is unexpected.

Because there was no shift in the pressure-volume relation and no shift in \( k \) (the slope of the logarithm left ventricular end-diastolic pressure–end-diastolic volume relation), no change in left ventricular chamber stiffness can be inferred.\(^25\) The present finding differs from an acute decrease in chamber stiffness

FIGURE 5. Plot of improvements in isovolumic relaxation as manifested by a reduction in \( \tau \) at matched heart rates (\( p=0.0013 \)) (left panel). There are some missing cases due to either computer malfunction or lack of linearity in the regression analysis prohibiting proper assessment of \( \tau \) (tau). Right panel: Linear relation of \( \tau \) to aortic end-systolic pressure at matched paced heart rate (HR). Each line represents mean slope and intercept of this relation before and after therapy with bucindolol. There was a downward shift in this relation after therapy with a \( \beta \)-adrenergic blocker (\( p<0.02 \)) demonstrating improved myocardial relaxation.

FIGURE 6. Plots demonstrating no significant change in chamber stiffness after therapy with bucindolol in the 10 patients in whom \( k \) was measurable. Left panel: Relation of left ventricular end-diastolic pressure to its covariate left ventricular end-diastolic volume. There was no significant alteration in the left ventricular pressure–volume relation after bucindolol therapy. Both pressure and volume were concomitantly decreased after \( \beta \)-adrenergic blockade along a common curve rather than shifting curves. Right panel: Change in the chamber stiffness constant (\( k \)) with \( \beta \)-adrenergic blockade. As can be seen, \( k \) was unchanged after bucindolol therapy. Because the intercept of this relation was also unchanged after therapy, this does not represent a parallel shift of this relation.
seen with β-blocker administration in congestive heart failure in one previous study.28 Possible explanations for these differences between acute and chronic β-adrenergic blockade include presence of chamber remodeling and collagen production over time, which could offset reductions in myocardial elastic stiffness; an increase in coronary vascular volume, which could offset a decrement in myocardial stiffness; or transient alterations in myocardial elastic stiffness, which are not found with longer administration.

**Energetic considerations.** There is evidence in both patients and animal models of heart failure that the failing heart is in an energy-depleted state.29—33 Although the unexpected improvement in both contractility and relaxation after chronic administration of bucindolol could have arisen from favorable effects on myocardial energetics, direct measurements of myocardial high-energy phosphate reserves would be needed to establish such a mechanism. Nevertheless, bucindolol increased stroke work without a significant increase in oxygen consumption or decrease in afterload. The absence of an increase in oxygen consumption despite increased stroke work and minute work may be due to effects of bucindolol on substrate utilization because β-adrenergic agonists stimulate both glycolysis and lipolysis in the heart.34 Because increased fatty acid use is associated with increased myocardial oxygen consumption without a concomitant increase in mechanical performance,35 suppression of fatty acid oxidation by β-blockade in the setting of high catecholamine levels could permit more efficient use of oxygen. Additionally, systolic wall stress, a major determinant of myocardial oxygen consumption,36 may have decreased with therapy, although this was not measured.

**Limitations**

This study, which was designed to assess the hemodynamic and energetic effects of β-adrenergic blocker therapy for the treatment of congestive heart failure, was not a survival or therapeutic efficacy trial. Thus, a major limitation of the present study was the lack of a placebo group for comparison; every patient served as his own control. However, a recently completed placebo-controlled, double-blind, randomized study of bucindolol in idiopathic dilated cardiomyopathy has demonstrated therapeutic efficacy of the drug.5

There are several difficulties with using the measurement of Ees in patients with congestive heart failure. Because the end-systolic pressure–volume relation may be curvilinear in artificially loaded canine hearts,37 reduction of preload by itself could increase Ees. However, in humans with congestive heart failure, this relation has been found to be linear in the physiological range.17

These assessments of diastolic chamber stiffness had significant limitations.38 Ideally, measurement of multiple pressure-volume points permits normalization of chamber volumes and calculation of Vdp/dV at common pressures. Due to technical considerations, we were able to retrieve enough points along the diastolic pressure-volume curve to examine Vdp/dV before and after therapy in only seven of 15 patients. The relation of Vdp/dV to pressure is linear, with a slope of kN. This normalized slope did not change with therapy (4.96±2.58 to 3.45±2.12, p=0.14), although a weak trend may be present. Furthermore, pericardial restraints may have played an important role in the determination of chamber diastolic properties because the hearts we studied were large. Several considerations suggest that myocardial stiffness did not increase with a concomitant and equal decrease in pericardial restraints. Visual interpretation of the pressure-volume loops during diastole, which showed a large decrease in volume for a smaller decrement in pressure during nitroprusside infusion, suggests that these hearts were not on the steep portion of the end-diastolic pressure–volume relation. Furthermore, as end-diastolic volume did not decrease markedly with therapy, the effect of the pericardium should not have changed dramatically.

The use of a β-adrenergic blocker with mild intrinsic sympathomimetic activity in some in situ model systems9,10 raises the possibility that inotropic stimulation, rather than β-blockade, increased contractility in the present study. However, no intrinsic sympathomimetic activity in humans has been demonstrated.5,8,11 Furthermore, evidence that bucindolol has β-blocking properties equipotent to those of propanolol5'9,11 and that bucindolol reduced heart rate by about 10% in these patients suggests that the predominant effect of bucindolol is β-blockade and not β stimulation.

Although bucindolol has weak α1-antagonist properties (the affinity of bucindolol for myocardial α1-receptors is approximately 30-fold less than that for β-adrenergic receptors) and some direct vasodilating effects,11 this cannot be considered its primary mode of action. There was a small decrease in systemic vascular resistance in our study, but this was not statistically significant. The increase in systolic elastance and load-corrected peak +dP/dt suggests the major effect is on contractility and not afterload reduction.

**Theoretical considerations.** The present study suggests that myocardial contractility and relaxation improve with chronic β-adrenergic blocker therapy and that mechanical work increases without concomitant increases in oxygen consumption. These data imply that bucindolol is energetically favorable. The mechanism by which bucindolol improves myocardial contractility and relaxation is uncertain and beyond the scope of this hemodynamic study. However, several mechanisms have been postulated.4—6,39,40 Animal and human data suggest that high concentrations of systemic catecholamines induce myocardial necrosis and dysfunction,41—43 leading to progressive myocardial degeneration, a process that may be attenuated by β-blockade, thereby allowing reparative processes to occur. Blockade of the β-adrenergic receptors may increase myocardial energy available
for these synthetic and reparative processes. Although blockade of the sympathetic nervous system up-regulates myocardial β1-receptors and may alter β-receptor–adenylate cyclase coupling, the physiological and prognostic consequences of β1 up-regulation are only now being elucidated. It has been suggested that up-regulation permits increased sensitivity to endogenous catecholamines. This may be particularly important during exercise when increased neurotransmitter norepinephrine levels may displace β-adrenergic blockers from cardiac receptors, thereby improving exercise tolerance. However, our hemodynamic measurements were made at rest, not during exercise. Because the resting heart rate in this study tended to decrease with therapy, the predominant effect was that of β-adrenergic blockade rather than β-stimulation from circulating catecholamines. Although elevated intracellular adenylate cyclase activity could explain improved contractility and relaxation, there has yet to be a proven mechanism by which this could occur. Thus, it seems unlikely that the improvement in resting left ventricular contractility seen in this study can be attributed to β1 up-regulation.

While bucindolol appears likely to have improved myocardial contractility and relaxation without a concomitant increase in myocardial oxygen consumption, additional studies to elucidate the mechanisms by which β-adrenergic blockade effects these beneficial changes in the hypertrophied failing myocardium are warranted.

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