Mechanisms of Carvedilol Action in Human Congestive Heart Failure

David M. Kaye, Leonie Johnston, Gautam Vaddadi, Hanspeter Brunner-LaRocca, Garry L. Jennings, Murray D. Esler

Abstract—The precise mechanism by which β-adrenoceptor blockers exert their beneficial actions in patients with heart failure remains unclear. Several possibilities have been proposed, including heart rate reduction, β2-adrenoceptor–mediated modulation of catecholamine release, antagonism of the receptor-mediated toxic actions of norepinephrine on the myocardium, and favorable effects on myocardial energetics. In the present study we evaluated the effect of 3 months of carvedilol therapy on hemodynamics, total systemic and cardiac norepinephrine spillover (isotope dilution method), and myocardial metabolism (myocardial oxygen consumption and carbon dioxide release) in 10 patients with severe congestive heart failure. Although carvedilol treatment was associated with a significant improvement in left ventricular ejection fraction (17±1% to 28±3%; P<0.01) and left ventricular stroke work (87±13 to 119±21 g m per beat; P<0.05), this effect was unrelated to changes in total systemic or cardiac norepinephrine spillover. The rise in left ventricular stroke work was accompanied by a modest rise in myocardial oxygen consumption per beat (0.33±0.04 to 0.42±0.04; P=0.05), although contractile efficiency was unchanged. The favorable effects of carvedilol on ventricular function in the failing heart are not explained by alterations in norepinephrine release or by changes in myocardial contractile efficiency. (Hypertension. 2001;37:1216-1221.)

Key Words: heart failure ■ norepinephrine ■ beta-antagonists ■ myocardium ■ energy metabolism

Congestive heart failure has been extensively characterized as a disorder arising from a complex interaction between impaired ventricular performance and neurohormonal activation. Over the past decade, clinical trials have highlighted the beneficial actions of pharmacological approaches to modulating the renin-angiotensin system in congestive heart failure, and more recently the value of antagonizing the effects of sympathetic overactivity has emerged.

While the precise mechanism of the beneficial clinical and hemodynamic actions of β-adrenoceptor blockers remains unclear, several possibilities have been proposed, including heart rate reduction, modulation of systemic neurohormonal activity, antagonism of the toxic actions of norepinephrine on the myocardium, and favorable effects on myocardial energetics. Although it had been proposed that nonselective β-antagonists may be more beneficial in the management of heart failure because of potential presynaptic modulation of catecholamine release,1 recent reports of the use of bisoprolol and metoprolol have clouded this issue.2,3

In the present study we sought to evaluate whether the beneficial hemodynamic actions of carvedilol in patients with congestive heart failure could be explained by alterations in sympathetic nervous tone or myocardial metabolism.

Methods
The study population consisted of 10 consecutive patients (all male; mean age, 55±3 years) with stable congestive heart failure who were commencing carvedilol therapy. In 6 patients heart failure was due to a nonischemic dilated cardiomyopathy, and in the remaining 4 it was due to ischemic heart disease. All patients were treated with an angiotensin-converting enzyme inhibitor and a diuretic, and all but 1 patient were on digoxin. The mean left and right ventricular ejection fractions, assessed by radionuclide ventriculography, were 17±1% and 45±5%, respectively. Before the commencement of carvedilol therapy, patients underwent invasive hemodynamic evaluation, biochemical assessment of myocardial energetics. After baseline catheterization studies, carvedilol therapy was commenced and up-titrated to 50 mg/d as tolerated, according to previously published guidelines.4 After 3 months of stable carvedilol therapy, repeated radionuclide ventriculography and cardiac catheterization were performed. All patients gave written informed consent, and the study was performed with the approval of the Alfred Hospital Ethics Review Committee.

Study Outline and Catheterization Protocol
All studies were performed in the morning, and medications were continued in all cases to avoid hemodynamic instability. A balloon-tipped thermomil dilated catheter (7F Arrow, Arrow International) was inserted via an introducer sheath placed in the right internal jugular vein for the determination of pulmonary arterial pressures, wedge
pressure, and cardiac output. A right radial arterial line was placed for arterial blood pressure measurement and blood sampling.

After the hemodynamic assessment, a coronary sinus thermodilution catheter (Webster Laboratories) was positioned in the coronary sinus under fluoroscopic control. The tip of the catheter was positioned at least 2 cm proximal to the orifice of the coronary sinus, as confirmed by injection of radiographic contrast. Coronary sinus blood flow was estimated by thermodilution, and an average was determined from at least 2 measurements.

**Radiotracer Determination of Adrenergic Activity**
Cardiac and total systemic norepinephrine and epinephrine kinetics were determined by isotope dilution, as originally reported by our group. In brief, radioactively labeled 1-[^3]H]norepinephrine and 1-[N-methyl-^3]H]epinephrine were continuously infused (0.5 to 1 μCi/min) into a peripheral vein to achieve a steady state plasma concentration. The total systemic spillover rate for norepinephrine and epinephrine was calculated as the ratio of the radiotracer infusion rate to the plasma specific activity of norepinephrine and epinephrine in plasma, respectively. The rate of clearance of norepinephrine and epinephrine from the circulation was calculated as the ratio of the infusion rate of each radiotracer to the concentration of norepinephrine and epinephrine, respectively, in arterial plasma. The rate of norepinephrine (or epinephrine) spillover from the heart was calculated by the modified Fick equation

Cardiac Norepinephrine or Epinephrine Spillover Rate

\[
\text{Spillover Rate} = \left(\frac{[C_{CS}-C_{A}]}{[C_{CS}] \times F_{IS}}\right) \times \text{CSFP}
\]

where \(C_{A}\) and \(C_{CS}\) are the arterial and coronary sinus plasma norepinephrine (or epinephrine) concentrations, \(F_{IS}\) is the fractional extraction of [^3]H]norepinephrine (or [^3]H]epinephrine) across the heart, and CSFP is the coronary sinus plasma flow.

**Measurement of Left Ventricular Energetics**
Myocardial oxygen consumption (MVO\(_{2}\)) and carbon dioxide production (MVCO\(_{2}\)) were calculated as the product of the coronary sinus blood flow and the coronary sinus–arterial concentration difference for each gas. The concentration of oxygen and carbon dioxide in blood was calculated by standard methods.

Left ventricular work (LVW) was determined from the following formula:\(5\)

\[
\text{LVW} = \text{Cardiac Output} \times (\text{Arterial Systolic Pressure} - \text{Wedge Pressure}) \times 0.0136.
\]

Ventricular mechanical efficiency (MEF) was calculated as the ratio of LVW to the myocardial energy expenditure (MEE). MEE was calculated as the ratio of LVW to the increase in left ventricular potential energy. The myocardial respiratory quotient (RQ) was calculated as RQ = MVCO\(_{2}\)/MVO\(_{2}\).

**Biochemical Assays**
Blood samples collected for catecholamine assay were immediately transferred to ice-chilled tubes containing EGTA and reduced glutathione. Samples were stored on ice, and plasma was subsequently separated by centrifugation at 4°C. Plasma samples were stored at −70°C until assay. Plasma norepinephrine and epinephrine concentrations were determined by high-performance liquid chromatography, as previously described. The plasma specific activity of tritiated norepinephrine and epinephrine was determined by performing timed fraction collections of the eluant leaving the detector cell. Cross contamination of the tritiated fractions was minimal (typically <0.1%). Radioactivity was subsequently determined by liquid scintillation spectroscopy.

**Statistical Methods**
Data are presented as mean±SEM. When normally distributed, paired data analysis was performed by a paired t test. Paired analysis of data that was not normally distributed was conducted with the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>123±6</td>
<td>125±9</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>82±4</td>
<td>82±6</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>80±6</td>
<td>64±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>14±3</td>
<td>14±3</td>
<td>NS</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>5±1</td>
<td>5±1</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary output, L/min</td>
<td>4.4±0.5</td>
<td>4.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVW, kg · m/min⁻¹</td>
<td>7.0±1.1</td>
<td>7.7±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>17±1</td>
<td>28±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>45±5</td>
<td>56±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CSBF, ml/min</td>
<td>168±20</td>
<td>178±22</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial O(_{2}) saturation, %</td>
<td>97±1</td>
<td>98±1</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; and CSBF, coronary sinus blood flow.

Wilcoxon signed rank test. A P value <0.05 was considered statistically significant.

**Results**
After 3 months of enrollment in the study, the average total daily dose of carvedilol was 42.5 mg/d. Carvedilol therapy was individually titrated according to heart rate, blood pressure, and features of congestive heart failure. Carvedilol therapy was associated with an improvement in New York Heart Association class from 2.9±0.1 to 2.1±0.2 (P<0.01).

**Hemodynamic Response to Carvedilol**
As outlined in Table 1, 3 months of carvedilol therapy was associated with a significant reduction in the resting heart rate, consistent with adrenergic blockade. No significant changes in systemic or pulmonary arterial pressures were evident. The study group demonstrated a significant improvement in both left and right ventricular ejection fraction. While the resting cardiac output was unchanged by carvedilol therapy, a substantial rise in stroke volume was evident (57±6 to 75±7 mL; P<0.05). Although the resting left ventricular work was not significantly altered by carvedilol therapy, this was achieved at a lower heart rate in the presence of carvedilol. Accordingly, calculation of the left ventricular stroke work demonstrated a significant improvement from 87±13 to 119±21 g · m per beat (P<0.05) with carvedilol therapy.

**Adrenergic Response to Carvedilol Therapy**
Consistent with the diagnosis of heart failure, the baseline plasma norepinephrine and epinephrine concentrations were elevated, at 2.5±0.3 nmol/L and 456±121 pmol/L respectively. After 3 months carvedilol therapy, we were unable to detect any change in the plasma concentrations of norepinephrine or epinephrine. In conjunction, we did not detect any change in the total systemic spillover rate or clearance for either norepinephrine or epinephrine (Figures 1 and 2). Although patients had symptomatically and hemodynamically only moderate heart failure, measurement of the cardiac norepinephrine spillover rate at baseline revealed marked sympathetic nervous...
activation (Figure 3). At the end of the 3-month treatment period, no evidence of an effect on the cardiac spillover rate for either norepinephrine or epinephrine or the respective transcardiac extraction was apparent (Figure 3).

Ventricular Mechanics and Oxygen Consumption
To evaluate the influence of carvedilol on the myocardial metabolism and mechanical efficiency on the failing heart, we also performed simultaneous arterial and coronary sinus blood gas analysis. In conjunction with the rise in left ventricular stroke work, carvedilol therapy was associated with an increase in myocardial oxygen consumption, when indexed to heart rate (Table 2). No changes in the myocardial efficiency or respiratory quotient were apparent. Although the myocardial energy expenditure remained unchanged overall, there was a trend toward higher energy expenditure per beat (Table 2).

Discussion
The adverse influence of sustained sympathetic nervous overactivity on both myocardial function and survival is now well recognized both experimentally and clinically.\(^{13-17}\) In combination with these findings, recent reports describe favorable effects of \(\beta\)-adrenoceptor antagonists on symptomatic status and mortality in patients with congestive heart failure.\(^{2,4,18,19}\) Together, these observations highlight the importance of the sympathetic nervous system as a therapeutic target in heart failure.

The exact mechanism responsible for the favorable hemodynamic actions of \(\beta\)-adrenoceptor blockers remains unclear. For carvedilol specifically, \(\beta_1\)-adrenoceptors could yield ben-

**TABLE 2. Influence of Carvedilol on Myocardial Metabolism**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 Months</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVO(_2), mL/min</td>
<td>27 ± 4</td>
<td>26 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>MVO(_2), per beat</td>
<td>0.33 ± 0.04</td>
<td>0.42 ± 0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>MVCO(_2), mL/min</td>
<td>27 ± 5</td>
<td>26 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>MVCO(_2), per beat</td>
<td>0.32 ± 0.05</td>
<td>0.41 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>RQ</td>
<td>0.96 ± 0.05</td>
<td>0.98 ± 0.07</td>
<td>NS</td>
</tr>
<tr>
<td>MEP, J/min</td>
<td>585 ± 103</td>
<td>567 ± 71</td>
<td>NS</td>
</tr>
<tr>
<td>MEP, per beat</td>
<td>7.0 ± 1.0</td>
<td>8.9 ± 0.8</td>
<td>0.06</td>
</tr>
<tr>
<td>MEF</td>
<td>0.16 ± 0.04</td>
<td>0.15 ± 0.03</td>
<td>NS</td>
</tr>
</tbody>
</table>

MEP indicates myocardial energy production.
ficial actions via heart rate reduction, antagonism of the toxic actions of norepinephrine on the myocardium, and favorable effects on myocardial energetics.\textsuperscript{20,21} The presence of $\beta_2$-adrenoceptor antagonism may also be of importance because of a potential role in the presynaptic modulation of catecholamine release.\textsuperscript{1} Finally, carvedilol also displays antioxidant actions, although the relevance of this property remains uncertain.

While the beneficial effects of $\beta$-adrenoceptor blockade are increasingly appreciated, controversy continues to surround the relative merits of nonselective compared with $\beta_2$-selective adrenoceptor antagonists.\textsuperscript{19,22} On the basis of these differences, it has been proposed that the additional $\beta_2$-adrenoceptor antagonism provided by agents such as carvedilol may be of clinical relevance. In this context, it has been reported that activation of myocardial $\beta_2$-adrenoceptors increases contractility and under certain circumstances may facilitate the development of ventricular arrhythmias.\textsuperscript{23–25} The potential clinical importance of the myocardial $\beta_2$-adrenoceptor in the failing heart has been highlighted by observations that it does not undergo downregulation, as displayed by the $\beta_1$-adrenoceptor. The $\beta_2$-adrenoceptor has also been identified both experimentally and clinically in sympathetic ganglia and in postganglionic sympathetic nerve terminals,\textsuperscript{1,26–30} where it appears to facilitate the release of norepinephrine.

While the reported beneficial actions of long-term administration of nonselective $\beta$-adrenoceptor antagonists, such as carvedilol, could potentially be explained by multiple actions, the precise mechanism remains unclear. Accordingly, the aim of this study was to evaluate the influence of long-term carvedilol therapy on systemic and cardiac adrenergic state, measured by the isotope dilution method, and ventricular function and metabolism.

In agreement with previous reports, carvedilol therapy in the present study was associated with a significant improvement in left ventricular ejection fraction.\textsuperscript{19,31,32} As with other studies,\textsuperscript{31} no change in cardiac output was evident. The pulmonary capillary wedge pressure did not fall in our study, being only modestly elevated compared with some other studies. As such, the results of our study may differ from those of others on the basis of a relatively milder degree of hemodynamic impairment. Resting heart rate was significantly reduced by carvedilol, consistent with a significant degree of $\beta$-adrenoceptor blockade, although it did not correlate with the improvement in left ventricular ejection fraction. In the present study we did not include a control group because the principal aim of the study was to examine the relationship between the apparent improvement in $\beta$-adrenoceptor blockade–mediated improvement in ejection fraction and potential candidate mechanisms.

In the present study we could not demonstrate any effect of carvedilol on either plasma norepinephrine or epinephrine or their respective rates of spillover to plasma from the heart or total circulation. In previous studies, we and others\textsuperscript{12,33,34} have shown that the elevation of plasma norepinephrine represents the combined influence of reduced clearance and increased spillover from the sympathetic nervous system to plasma. The lack of change of the total clearance rate of norepinephrine from plasma is readily explained by the absence of a change in cardiac output after therapy. Previous work demonstrates that norepinephrine clearance is particularly dependent on cardiac output.\textsuperscript{5,35} The total systemic spillover rate of norepinephrine to plasma in patients with heart failure, as an integrated index of sympathetic nervous activity, is particularly influenced acutely by arterial hypotension.\textsuperscript{35} The lack of change of the total norepinephrine spillover rate is consistent with the absence of a change in arterial blood pressure and, furthermore, contradicts the notion that the lipophilic $\beta$-adrenoceptor blocking agents might exert some of their actions via actions in the central nervous regulation of sympathetic outflow.\textsuperscript{36}

Despite the introduction of carvedilol, the average cardiac norepinephrine spillover rate of our study group remained approximately 3 times that of previously described healthy subjects.\textsuperscript{12} Although recent observations by Newton and colleagues\textsuperscript{1,34} suggest that acute alterations in the release or norepinephrine from cardiac sympathetic nerve terminals can be effected by pharmacological manipulation of presynaptic $\beta_2$-adrenoceptors, the present study does not support this notion. Unlike our study, in their acute studies significant changes in ventricular contractility and coronary sinus blood flow were possible confounding factors. Previously, Gilbert and colleagues\textsuperscript{31} reported that carvedilol, unlike metoprolol, was associated with a reduction in the transcardiac norepinephrine concentration gradient, although coronary sinus blood flow and norepinephrine extraction were not accounted for. Unlike our study, carvedilol treatment was associated with a significant fall in pulmonary capillary wedge pressure, and accordingly the fall in cardiac norepinephrine release may have been due in part to hemodynamic factors per se.\textsuperscript{35} Alternatively, Cousineau et al,\textsuperscript{37} using a multiple indicator methodology, showed that although an apparent reduction in the local release rate for norepinephrine was apparent after $\beta$-blockade, this phenomenon was the result of altered local permeability rather than a true change in the release rate. In the present study we also observed net release of epinephrine from the failing heart, as previously reported by us,\textsuperscript{7} and carvedilol did not appreciably alter the rate of release.

In the present study we also tested the proposed notion that one of the favorable effects of $\beta$-adrenoceptor blockade in heart failure was due to a reduction in oxygen consumption, as proposed by Eichhorn et al.\textsuperscript{38} In the present study carvedilol therapy was associated with no overall change in myocardial oxygen consumption, although when heart rate changes are considered, a significant rise in oxygen consumption per beat was detected. This rise may be explained by the increase in stroke work, while mechanical efficiency was unchanged. Of interest, Yamakawa and coworkers\textsuperscript{31} showed that acute $\beta$-blockade in patients with heart failure was not accompanied by a fall in total myocardial oxygen consumption, but rather by a selective reduction in the oxygen consumed for nonmechanical work. Furthermore, this study did not demonstrate...
any beneficial effects on mechanical efficiency. The anti-
oxidant properties of carvedilol could also potentially
explain the beneficial actions of the drug. In an attempt
to examine this possibility, we sought to determine the
cardiac transduction concentration gradient of the lipid peroxy-
dation product malondialdehyde. However, we could not
detect a net malondialdehyde gradient, making this mea-
surement unsuitable for further exploration of the anti-
oxidant property of carvedilol (data not shown).

In summary, the present study confirms the favorable
effects of carvedilol on left ventricular ejection fraction
and stroke work in patients with congestive heart failure.
Despite these improvements, no significant alterations in
global or cardiac adrenergic drive were evident, suggesting
that modulation of catecholamine release does not explain
the beneficial effect of carvedilol. Furthermore, although
carvedilol treatment was associated with a rise in oxygen
consumption, it did not substantially alter mechanical
efficiency. These findings therefore suggest that the
principal mode of action of β-blockade in heart failure is
probably via protection against the toxic effect of cate-
cholamines on the heart.

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