The Effects of Combined Versus Selective Adrenergic Blockade on Left Ventricular and Systemic Hemodynamics, Myocardial Substrate Preference, and Regional Perfusion in Conscious Dogs With Dilated Cardiomyopathy

Lazaros A. Nikolaidis, MD, Indu Poornima, MD, Pratik Parikh, MD, Megan Magovern, You-Tang Shen, MD, Richard P. Shannon, MD, FACC

Pittsburgh, Pennsylvania

OBJECTIVES
Given that adverse effects of chronic sympathetic activation are mediated by all three adrenergic receptor subtypes ($\beta_1$, $\beta_2$, $\alpha_1$), we examined the effects of standard doses of carvedilol and metoprolol succinate (metoprolol controlled release/extended release [CR/XL]) on hemodynamics, myocardial metabolism, and regional organ perfusion.

BACKGROUND
Both $\beta_1$ selective and combined adrenergic blockade reduce morbidity and mortality in heart failure. Whether there are advantages of one class over the other remains controversial, even in the wake of the Carvedilol Or Metoprolol European Trial (COMET). Similarly, the mechanistic basis for the relative differences is incompletely understood.

METHODS
Thirty-three conscious, chronically instrumented dogs with pacing-induced (240 min−1 for 4 weeks) dilated cardiomyopathy (DCM) were randomized to carvedilol (25 mg twice daily, Coreg, Glaxo Smith Kline, Research Triangle, North Carolina) or metoprolol succinate (100 mg qd, Toprol XL, AstraZeneca, Wilmington, Delaware). Left ventricular and systemic hemodynamics, myocardial substrate uptake, and norepinephrine spillover were measured before and after three days of treatment. Regional (renal, hepatic, skeletal muscle) blood flows were measured using neutron-activated microspheres.

RESULTS
Both agents had comparable heart rate effects. However, carvedilol-treated dogs showed significantly greater increases in stroke volume and cardiac output and decreases in left ventricular end-diastolic pressure and systemic vascular resistance. Carvedilol increased renal, hepatic, and skeletal muscle blood flow. Carvedilol increased myocardial glucose uptake and suppressed norepinephrine and glucagon. Carvedilol antagonized the response to exogenous norepinephrine to a greater extent than metoprolol CR/XL.

CONCLUSIONS
At doses inducing comparable heart rate reductions, short-term treatment with carvedilol had superior hemodynamic and metabolic effects compared with metoprolol CR/XL. These data suggest important advantages of blocking all three adrenergic receptor subtypes in DCM. (J Am Coll Cardiol 2006;47:1871–81) © 2006 by the American College of Cardiology Foundation

There is convincing evidence showing that the addition of $\beta$-adrenergic blocking agents to angiotensin-converting enzyme inhibitors in patients with left ventricular (LV) systolic dysfunction is associated with significant improvements in morbidity and mortality (1–6). However, there are potentially important differences in the pharmacological profile of the agents studied and approved for clinical use. Whether there are important clinical differences between selective $\beta_1$-adrenergic receptor antagonists such as metoprolol or combined $\beta_1$, $\beta_2$, $\alpha_1$-adrenergic receptor antagonists, such as carvedilol, remains controversial. Recently, the Carvedilol Or Metoprolol European Trial (COMET) (6) showed that carvedilol was superior to metoprolol tartrate in reducing all-cause mortality, although the mechanisms of the benefit remain uncertain. Rather than reconciling the controversy, the COMET study has served to rekindle the debate regarding the importance of other adrenergic-blocking properties over and above $\beta_1$-adrenergic antagonism as well as the formulation and dose of the $\beta_1$-antagonists (7–9). In theory, combined adrenergic blockade would be more efficacious because it would antagonize the effects of the endogenous neurotransmitter norepinephrine (NE) at all three post-synaptic receptor targets. However, there is little direct evidence regarding whether the $\beta_2$- or $\alpha_1$-blocking properties of carvedilol are important or enduring (8).

Therefore, the purpose of this study was to examine in detail the hemodynamic effects of combined versus selective $\beta_1$-adrenergic blockade in conscious, chronically instrumented dogs with pacing-induced dilated cardiomyopathy (DCM). We chose to compare metoprolol succinate controlled release/extended release (CR/XL) with carvedilol to show the respective hemodynamic effects of the two classes of $\beta$-adrenergic blockers that have been shown to reduce
were subjected to rapid right ventricular pacing (240 min sampling before initiation of pacing. Subsequently, all dogs modynamic recordings and arterial and coronary sinus blood General Hospital. Institutional Animal Care and Use Committee at Allegheny Health, Department of Health and Human Services Pub-

Laboratory Animal Resources” (National Institutes for accordance with the “Guide for the Care and Use of

quietly on their right side. Animals were maintained in quiet lying on the experimental table in a conscious, unrestrained state. Hemodynamic measurements were made with the dogs fully awake, lying quietly on their right side. Animals were maintained in accordance with the “Guide for the Care and Use of Laboratory Animal Resources” (National Institutes for Health, Department of Health and Human Services Publication No. 86-23, revised 1996) and the guidelines of the Institutional Animal Care and Use Committee at Allegheny General Hospital.

Experimental protocol. All dogs underwent baseline hemodynamic recordings and arterial and coronary sinus blood sampling before initiation of pacing. Subsequently, all dogs were subjected to rapid right ventricular pacing (240 min$^{-1}$) to induce DCM. All hemodynamic and metabolic measurements were repeated once severe DCM developed (10–12). When there was evidence of severe DCM characterized by left ventricular end-diastolic pressure (LVEDP) $>$30 mm Hg, LV derivative of pressure with time (dP/dt) $<$1,500 mm Hg, left ventricular end-diastolic diameter $>$36 mm, and cardiac output $<$1.8 l/min, dogs were randomized to receive either combined adrenergic blockade with carvedilol (Coreg [Glaxo Smith Kline, Research Triangle, North Carolina] 25 mg orally twice daily, n = 10) or selective $\beta_1$-blockade with metoprolol succinate CR/XL (Toprol XL [Astra Zeneca, Wilmington, Delaware] 100 mg orally every day, n = 8). The dosing was chosen based on preliminary studies in conscious dogs with pacing-induced DCM that showed comparable reductions in heart rate. Treatment was continued for three days, during which time pacing was suspended. A separate group (n = 5) of dogs instrumented as described above and with a similar degree of severe DCM served as controls to account for the effects of discontinuing pacing on spontaneous hemodynamic recovery. Follow-up hemodynamic measurements were made on the fourth day after the final dose. Myocardial oxygen consumption ($\text{MVO}_2$), LV stroke work, and myocardial mechanical efficiency were calculated as previously described (13).

Regional blood flow. Regional organ perfusion was measured in DCM before and at the end of the third day of treatment using neutron-activated microspheres (BioPal, Worcester, Massachusetts). Microspheres were administered via the left atrial catheter under steady-state conditions. Renal, hepatic, and skeletal (gracilis) muscle blood flows were also determined before and after respective treatments from respective tissue samples obtained at the time of euthanasia. Neutron-activated microsphere flows were calculated by BioPal (10).

Response to challenge with adrenergic agonists. To determine that comparable levels of $\beta_1$-adrenergic blockade were achieved with the doses of carvedilol and metoprolol used, an additional 10 dogs were instrumented as described above. We examined the heart rate response to a graded intravenous infusion of isoproterenol (0.05 to 0.4 $\mu$g/kg/min) at baseline, after the development of DCM, and on the morning of the fourth day of treatment. The heart rate responses were measured in steady state at the highest dose of isoproterenol (0.4 $\mu$g/kg/min) in five dogs receiving carvedilol, five receiving metoprolol CR/XL, and the five control dogs.

To examine the ability of the two classes of adrenergic antagonists to block the respective effects of $\beta_2$ and $\alpha_1$ agonists, we challenged each dog with a graded infusion of the endogenous neurotransmitter, NE (0.05 to 0.4 $\mu$g/kg/min) before and at the end of the third day of treatment with the respective antagonists. Hemodynamic measurements were made during steady-state infusion at the highest dose (0.04 $\mu$g/kg/min), and the response was compared between the metoprolol CR/XL (n = 8) and carvedilol (n = 8) groups.

Metabolic determinations. Transmyocardial glucose, NE, nonesterified fatty acids (NEFA), and plasma insulin and glucagon levels were obtained before and after the final dose of the respective treatments (12). The NE was measured by high-phase liquid chromatography (HPLC) analysis using a kit purchased from Chromsystems Instruments and Chemicals, Inc. (catalog number CS000, Munich, Germany).
Plasma insulin and glucagon levels were measured using the Human Insulin Specific RIA Kit (catalog number HI-14K) and the Glucagon RIA Kit (catalog number GL-32K) from Linco Research, Inc. (St. Charles, Missouri), and NEFAs were measured using the NEFA C test kit from Wako Diagnostics (catalog number 994-75409E, Richmond, Virginia). Plasma glucose was measured using a Beckman Glucose Analyzer-2 (Beckman Instruments, Fullerton, California). Myocardial substrate uptake was calculated as the product of the transmyocardial substrate difference and coronary blood flow.

To determine the effects of $\beta_2$-adrenergic receptor stimulation on the observed responses, we challenged each dog with the $\beta_1/\beta_2$ agonist, isoproterenol (0.2 $\mu$g/kg/min) before and on the morning of the fourth day of treatment with the respective antagonists. In the presence of $\beta_1$-adrenergic blockade, the effects of intravenous isoproterenol are mediated through $\beta_2$ receptors. Because the myocardial effects of $\beta_2$-adrenergic stimulation are modest in conscious dogs with DCM (14), we used myocardial substrate uptake as the measure of response to $\beta_2$-adrenergic stimulation (15).

**Sarcolemmal membrane preparations.** After the experiments on the morning of the fourth day of treatment, dogs were euthanized with pentobarbital, the heart removed, and sarcolemmal membrane preparations generated as described previously (16). The adenylyl cyclase activity was determined by measuring cyclic adenine monophosphate (cAMP) generation in response to guanine triphosphate/isoproterenol (GTP/Iso) (0.15 mmol GTP; 0.3 nmol isoproterenol/µg tissue), a $\beta_1$-adrenergic receptor mediated mechanism, and sodium fluoride (NaF; 0.03 µmol/µg tissue) a non-$\beta_1$-adrenergic receptor mediated mechanism (16).

**Statistical analysis.** Data are expressed as the mean value ± SEM. Differences between hemodynamic, regional flow, and metabolic parameters among the groups were determined by repeated-measures analysis of variance (ANOVA). The Student Newman-Keuls post-hoc test was further used for pairwise comparisons after ANOVA showed a significant difference among groups. Parameters derived from the same animal at different conditions (i.e., before vs. during treatment) were compared by two-tailed paired Student t tests. A p value of <0.05 was considered statistically significant.

**RESULTS**

**Efficacy of $\beta_1$-adrenergic blockade.** Both carvedilol and metoprolol CR/XL were associated with significant and comparable decreases in resting heart rate ($44\pm5$ min$^{-1}$) (Fig. 1). To confirm that the doses of the respective agents had comparable $\beta_1$-adrenergic blocking properties, we examined the dose response to isoproterenol administration in vivo and in vitro. Figure 2A shows that the heart rate...
response to isoproterenol infusion (0.05 to 0.4 μg/kg/min) was attenuated to a similar extent in dogs treated with carvedilol compared with metoprolol CR/XL. The response was attenuated significantly compared with the response in control dogs. Figure 2B illustrates the effects of β1-adrenergic receptor blockade on adenylyl cyclase activity in vitro. The basal, GTP/Iso, and NaF responses were attenuated in DCM, consistent with heterologous desensitization. The adenylyl cyclase responses to GTP/Iso in sarcolemmal membrane preparations from dogs treated with either carvedilol or metoprolol were depressed compared with the response in DCM. In contrast, the response to the non–β1-receptor–mediated stimulus, NaF, was not affected by β1-adrenergic receptor blockade.

**Hemodynamic effects.** Table 1 shows the LV and systemic hemodynamics at baseline and after 28 ± 2 days of rapid pacing when severe dilated cardiomyopathy had developed. Both groups manifested comparable and significant increases in LVEDP, heart rate, systemic vascular resistance (SVR), and progressive declines in LV contractile perfor-

![Figure 2](image_url)

**Figure 2.** The heart rate response to isoproterenol infusion in dilated cardiomyopathy (DCM) before (A) and during carvedilol (n = 5) or metoprolol controlled release/extended release (CR/XL) (n = 5) treatment (B) and in five control dogs with cessation of pacing alone. *p < 0.05 compared with carvedilol and metoprolol. (C) The adenylyl cyclase response to guanine triphosphate/isoproterenol (GTP/Iso) and sodium fluoride in sarcolemmal membrane preparations from these same dogs obtained after euthanasia. *p < 0.05 compared with baseline. †p < 0.05 compared with DCM. Carv = carvedilol; Con = control subjects; Iso = isoproterenol; Met = metoprolol.

**Table 1.** Baseline Hemodynamics Before Treatment

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 5)</th>
<th>Carvedilol (n = 10)</th>
<th>Metoprolol CR/XL (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>DCM</td>
<td>Baseline</td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>118 ± 3</td>
<td>108 ± 2*</td>
<td>123 ± 4</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10 ± 1</td>
<td>30 ± 1*</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>LV dp/dt (mm Hg/s)</td>
<td>2,744 ± 72</td>
<td>1,424 ± 100*</td>
<td>2,841 ± 168</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>77 ± 4</td>
<td>104 ± 7*</td>
<td>87 ± 6</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>92 ± 3</td>
<td>88 ± 2*</td>
<td>101 ± 3</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>2.1 ± 0.4</td>
<td>1.5 ± 0.3*</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>28 ± 1</td>
<td>30 ± 2</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>34 ± 1</td>
<td>38 ± 1*</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>29 ± 1</td>
<td>35 ± 1*</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>SVR (dyne·cm⁻⁵·s⁻¹)</td>
<td>3,627 ± 214</td>
<td>5,523 ± 313*</td>
<td>3,500 ± 288</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with baseline.

CBF = coronary blood flow; DCM = dilated cardiomyopathy; LV dp/dt = maximal rate of left ventricular systolic pressure development; LVP = left ventricular pressure; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; metoprolol CR/XL = metoprolol controlled release/extended release; SVR = systemic vascular resistance.
mance, stroke volume, cardiac output, and mean arterial pressure during the evolution of advanced DCM.

Figure 1 illustrates the effects of the respective treatments on LV and systemic hemodynamics in DCM. Both treatments were associated with modest increases in LV dP/dtmax but significant decreases in LVEDP, the magnitude of which was significantly greater (p < 0.05) with carvedilol. Both carvedilol and metoprolol CR/XL increased stroke volume and cardiac output, but the magnitude of the benefit was greater (p < 0.01) with carvedilol. These beneficial effects were associated with greater reductions in mean arterial pressure and SVR seen with carvedilol compared with metoprolol CR/XL (p < 0.05). Neither carvedilol nor metoprolol CR/XL were associated with significant changes in LV systolic pressure or LV end diastolic dimensions. Importantly, the differences between the carvedilol and metoprolol CR/XL responses were not explained by spontaneous recovery after cessation of rapid pacing.

Figure 3 illustrates the effects of the respective treatments on stroke work, MVo2, and LV mechanical efficiency. Although both treatments had comparable effects on MVo2, carvedilol was associated with greater increases in stroke work and mechanical efficiency. Cessation of pacing alone had no effect. The indicated p values represent the differences in the carvedilol response and metoprolol response. *p < 0.05 compared with before treatment. Open bars = before treatment; solid bars = after treatment. Carv = carvedilol; Con = control subjects; Met = metoprolol.

Hemodynamic response to NE challenge. Table 2 shows the hemodynamic response to NE administration in dogs studied before pacing and after the development of DCM. There was the expected desensitization to the LV and systemic effects of NE in DCM. Figure 5 shows the response to the endogenous neurotransmitter before and after 3 days of treatment with the β1 selective versus the combined adrenergic antagonist. Norepinephrine (0.4 μg/kg/min) caused comparable increases in LV and mean arterial pressures as well as LV dP/dtmax in both groups. However, metoprolol CR/XL treatment accentuated whereas carvedilol attenuated the pressor response to NE. In the presence of metoprolol treatment, NE accentuated the systemic pressor response to NE, including both the peripheral resistance and the aortic impedance (Fig. 6). Both treatments blunted the effects of NE on cardiac output and stroke volume comparably.

Metabolic effects. Table 3 shows the alterations in metabolic parameters during the evolution of DCM. Advanced DCM was characterized by increases in plasma insulin,
glucagon, and NEFA while plasma glucose levels remained unchanged. Figure 7 shows the effects of the two treatments on metabolic parameters. Carvedilol was associated with a significant increase in plasma insulin levels (64 ± 9 pmol/l to 151 ± 38 pmol/l, p < 0.05) and suppression of NEFA (476 ± 56 mol/l to 275 ± 41 mol/l, p < 0.05), whereas metoprolol CR/XL had no effect. Neither treatment altered plasma glucose levels. Carvedilol also decreased plasma glucagon levels (40 ± 4 pg/ml to 30 ± 2 pg/ml, p < 0.05), whereas metoprolol CR/XL had no effect (37 ± 5 pg/ml to 40 ± 5 pg/ml). As a consequence, myocardial glucose uptake was significantly (p < 0.05) increased after carvedilol (3.5 ± 0.4 μmol/min to 16.8 ± 3.5 μmol/min) compared with metoprolol CR/XL (3.2 ± 0.7 μmol/min to 2.8 ± 0.7 μmol/min). The effects observed with combined adrenergic blockade were not attributable to cessation of pacing.

To explore further the adrenergic mechanisms involved in the observed substrate preferences, we conducted additional experiments in the respective groups in response to acute blockade were not attributable to cessation of pacing. The indicated p values represent the differences in the carvedilol responses and the metoprolol responses by analysis of variance. Open bars = before treatment; solid bars = after treatment.

Table 2. The Effects of Exogenous Norepinephrine Administration in Conscious Dogs in the Control and DCM Groups

<table>
<thead>
<tr>
<th></th>
<th>Pre-Pacing (n = 10)</th>
<th>DCM (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL→NE (0.4 μg/kg/min)</td>
<td>BL→NE (0.4 μg/kg/min)</td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>119 ± 3→204 ± 5 (+73 ± 7%)</td>
<td>106 ± 3→155 ± 5 (+47 ± 4%)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>12 ± 1→24 ± 2 (+39 ± 11%)</td>
<td>31 ± 1→43 ± 1 (+41 ± 5%)</td>
</tr>
<tr>
<td>LV Δp/dt (mm Hg/s)</td>
<td>2,489 ± 82→6,315 ± 312 (+157 ± 16%)</td>
<td>1,405 ± 70→2,909 ± 223 (+107 ± 15%)</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>88 ± 4→95 ± 10 (+8 ± 10%)</td>
<td>115 ± 4→109 ± 5 (+4 ± 4%)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95 ± 2→155 ± 6 (+65 ± 7%)</td>
<td>88 ± 2→123 ± 4 (+39 ± 5%)</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>2.4 ± 0.2→2.9 ± 0.2 (+27 ± 11%)</td>
<td>1.7 ± 0.1→2.2 ± 0.2 (+26 ± 7%)</td>
</tr>
<tr>
<td>SVR (dyn·cm⁻¹·s⁻¹)</td>
<td>3,549 ± 300→4,768 ± 468 (+39 ± 9%)</td>
<td>4,438 ± 389→5,156 ± 719 (+17 ± 9%)</td>
</tr>
<tr>
<td>AoZ (mm Hg/l/min)</td>
<td>18 ± 2→29 ± 2 (+66 ± 12%)</td>
<td>16 ± 1→24 ± 2 (+51 ± 10%)</td>
</tr>
</tbody>
</table>

AoZ = aortic impedance; BL = baseline; CO = cardiac output; DCM = dilated cardiomyopathy; NE = norepinephrine; other abbreviations as in Table 1.

DISCUSSION

In the present investigation, we showed that carvedilol had greater acute LV and systemic hemodynamic benefits compared with metoprolol CR/XL in conscious dogs with dilated NEFA uptake was decreased in DCM. However, β₁/β₂ stimulation with isoproterenol in DCM markedly enhanced myocardial NEFA uptake and was associated with an increase in V̇O₂ (2.32 ± 0.4 ml O₂/min to 3.42 ± 0.4 ml O₂/min, p < 0.05). The effects were mediated principally by β₂-adrenergic receptors, because the effects of isoproterenol were comparable in the presence of β₁ blockade with metoprolol CR/XL. However, the effects were completely abolished by combined β₁/β₂ blockade with carvedilol. Figure 8B shows the effects of β₁/β₂ stimulation with isoproterenol on myocardial glucose uptake. Isoproterenol suppressed myocardial glucose uptake. The effect was unaltered by metoprolol CR/XL. However, carvedilol antagonized the effects of isoproterenol and increased myocardial glucose uptake. Again, these effects were not attributable to cessation of pacing.
severe DCM. These hemodynamic effects were associated with increased end-organ perfusion in renal, hepatic, and skeletal muscle beds. Carvedilol suppressed plasma NE levels and myocardial NE spillover to a greater extent than metoprolol CR/XL. In addition, carvedilol increased plasma insulin levels and suppressed plasma NEFA and glucagon levels, leading to increased myocardial glucose uptake in advanced DCM. This shift in metabolic preference was attributable to the β2-blocking properties of carvedilol. Carvedilol also attenuated the pressor responses to exogenously administered NE by a greater extent than metoprolol CR/XL. Importantly, we confirmed that the doses used had similar β1-adrenergic blocking properties by showing a comparable impairment in heart rate responses to isoproterenol infusion in vivo and an attenuated cAMP response to Iso/GTP in vitro. It is important to note that isoproterenol is a combined β1/β2 agonist and that signaling through β2/Gi-coupled pathways may attenuate β1/Gs-stimulated cAMP production. Thus, combined as opposed to more selective β1-adrenergic blockade was associated with greater hemodynamic, neurohormonal, and metabolic benefit in advanced DCM.

Both carvedilol (1,4) and metoprolol CR/XL (2) as well as bisoprolol (3) have been shown to reduce mortality in patients with mild to moderate heart failure. In addition, carvedilol has also been shown to be efficacious in severe (5) heart failure. However, considerable controversy exists regarding whether combined (β1, β2, α1) is superior to selective (β1) adrenergic blockade (8,9). To date, this controversy has focused on the pharmacokinetics of controlled- versus immediate-release formulations of metoprolol and the doses required to show a mortality benefit with β1-selective adrenergic blockade (9). In light of the controversy, it is surprising that most hemodynamic

![Figure 5](image-url).

The left ventricular (LV) and mean arterial pressure (MAP) response to exogenously administered norepinephrine (0.4 µg/kg/min) before (dilated cardiomyopathy [DCM]) and after 3 days of treatment with carvedilol (DCM+C) or metoprolol controlled release/extended release (DCM+M). The indicated p values represent the differences in the carvedilol responses and metoprolol responses by analysis of variance. LV dP/dt = maximal rate of left ventricular systolic pressure development; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular pressure.
studies in humans (17–24) have compared carvedilol with short-acting metoprolol tartrate without reaching a consensus regarding a consistent benefit of one class over another. The controversy was recently rekindled with the publication of the COMET study (6), in which the use of combined adrenergic blockade with carvedilol was found to be superior to metoprolol tartrate. Although pharmacokinetic differences have been implicated as the basis for the differences in mortality (8,9), our data suggest that there may be important pharmacodynamic differences that lead to additional hemodynamic and metabolic benefits over and above \( \beta_1 \) blockade alone. In the present investigation, we used doses of carvedilol and metoprolol designed to have comparable \( \beta_1 \) effects at rest and after isoproterenol stimulation. At these doses over three days, carvedilol was associated with greater LV and systemic hemodynamic effects and increased organ perfusion. The major effects were attributable to the significant declines in SVR seen with carvedilol but not metoprolol CR/XL. The associated reductions in ventricular loading led to significantly greater improvements in LVEDP, stroke volume, and cardiac output.

**Table 3.** Metabolic Parameters Before Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group (n = 5)</th>
<th>Carvedilol (n = 6)</th>
<th>Metoprolol CR/XL (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma glucose (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.6 ± 0.7</td>
<td>5.4 ± 0.1</td>
<td>4.8 ± 0.2</td>
</tr>
<tr>
<td>DCM</td>
<td>4.9 ± 0.6</td>
<td>5.2 ± 0.3</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td><strong>Nonesterified fatty acids (NEFA) (µmol/l)</strong></td>
<td>276 ± 76</td>
<td>601 ± 66*</td>
<td>202 ± 21</td>
</tr>
<tr>
<td><strong>Plasma insulin (pmol/l)</strong></td>
<td>30 ± 1</td>
<td>30 ± 6</td>
<td>27 ± 9</td>
</tr>
<tr>
<td><strong>Plasma glucagon (pg/ml)</strong></td>
<td>20 ± 3</td>
<td>19 ± 4</td>
<td>17 ± 5</td>
</tr>
<tr>
<td><strong>Myocardial NEFA uptake (µmol/min)</strong></td>
<td>6.2 ± 0.8</td>
<td>5.1 ± 1.0</td>
<td>4.6 ± 1.4</td>
</tr>
<tr>
<td><strong>Myocardial glucose uptake (µmol/min)</strong></td>
<td>5.0 ± 0.7</td>
<td>4.2 ± 0.3*</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td><strong>Plasma NE (nmol/l)</strong></td>
<td>0.47 ± 0.04</td>
<td>0.75 ± 0.12</td>
<td>0.68 ± 0.05</td>
</tr>
<tr>
<td><strong>Myocardial NE spillover (pmol/min)</strong></td>
<td>−0.51 ± 0.16</td>
<td>1.15 ± 0.09*</td>
<td>−0.78 ± 0.15</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with baseline.

NEFA = nonesterified fatty acid; other abbreviations as in Table 2.
output. We confirmed that these observed effects on ventricular loading conditions were likely attributable to α1-adrenergic blockade by showing that carvedilol attenuated whereas metoprolol CR/XL accentuated the pressor response to exogenously administered NE. Prior studies in experimental rodent models have shown that carvedilol antagonized the hemodynamic response to NE to a greater extent than metoprolol (25). Similarly, carvedilol has been shown to improve arterial elastance for up to 12 months in patients with stable heart failure (26). However, it should be noted that chronic treatment with α-blockade alone has not been associated with improved clinical outcomes in heart failure (27) or hypertension (28), supporting the notion that combined adrenergic blockade also has advantages over selective α1 blockade alone.

Carvedilol reduced plasma NE levels and suppressed myocardial NE spillover to a greater extent than β1-adrenergic blockade alone. These findings are similar to those of Azevedo et al. (29), who examined cardiac NE turnover in 36 patients with heart failure, and showed that carvedilol was associated with decreased cardiac NE spillover.

We showed significant improvement in renal, hepatic, and skeletal muscle blood flow with carvedilol. Prior studies have suggested favorable effects of carvedilol on renal perfusion in hypertension (30), but this is the first comparative study in a canine model of severe heart failure to directly assess end-organ perfusion in multiple beds after adrenergic blockade.

We also found that carvedilol treatment was associated with significant increases in plasma insulin levels and associated suppression of plasma NEFA. Carvedilol also suppressed glucagon and NE, which are known to exert counterregulatory effects to the action of insulin. The result was greater increases in myocardial glucose uptake by the failing heart compared with the metoprolol CR/XL treated group. Prior studies have shown maintenance of myocardial glucose uptake after carvedilol using positron emission tomography scanning (31), but did not provide a comparison to metoprolol. Podbregar and Voga (32) showed that although both β1 selective bisoprolol and combined adrenergic blockade with carvedilol reduced total body energy production rate, carvedilol shifted substrate preference from NEFA to glucose. Our study is the first to show that carvedilol increases plasma insulin and reduces NEFA in conscious dogs with severe heart failure. Furthermore, we showed that β1/β2-adrenergic stimulation with isoproterenol in the presence of β1 blockade markedly enhanced myocardial NEFA uptake and increased MVO2, whereas carvedilol suppressed NEFA uptake during isoproterenol challenge. These data underscore an important role for myocardial β2 receptors in determining substrate prefer-
ence. $\beta_2$-adrenergic stimulation is known to inhibit acetyl coenzyme A carboxylase, thereby decreasing malonyl coenzyme A and stimulating carnitine-palmitoyl transferase-1, the rate-limiting step in NEFA oxidation. Furthermore, $\beta_2$-adrenergic stimulation decreases fructose 2,6 phosphate, inhibiting glycolysis (15). Also, $\beta_2$-adrenergic receptors have been shown to be up-regulated in heart failure (33). Taken together, our data show that $\beta_2$ stimulation in conscious dogs with DCM favor NEFA as opposed to glucose uptake and that carvedilol but not metoprolol CR/XL shifts the preference toward glucose uptake and oxidation. Our data also provide a plausible mechanism for explaining the clinical observation that carvedilol treatment reduces the incidence of type 2 diabetes mellitus in patients with DCM (6). Finally, defining an important role for myocardial $\beta_2$-adrenergic responses in substrate regulation in DCM may explain why higher as opposed to lower doses of metoprolol are particularly beneficial, because the $\beta_1$ selectivity is attenuated at higher doses.

In the present investigation, it was our goal to identify possible non-$\beta_1$-mediated effects of two classes of adrenergic antagonists that might explain the clinical and mortality benefits of carvedilol versus metoprolol observed in the COMET study (6). We sought to go beyond the pharmacokinetic arguments surrounding the use of short-acting metoprolol and used long-acting metoprolol succinate at doses that had comparable heart rate effects. It is important to note that we used only two doses over a three-day period in a commonly studied model of DCM in conscious dogs.

Further studies in other chronic animal models of heart failure and in humans are required to prove whether the non-$\beta_1$-mediated benefits of carvedilol are enduring.

Reprint requests and correspondence: Dr. Richard P. Shannon, Department of Medicine, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, Pennsylvania 15212. E-mail: rshannon@wpahs.org.

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