CLINICAL TRIALS WITH CARDIAC SELECTIVE $\beta_1$-ADRENERGIC BLOCKERS (METOPROLOL, BISOPROLOL) AND A NONSELECTIVE $\beta$-ADRENERGIC BLOCKER WITH $\alpha$-ADRENERGIC-BLOCKING ACTIVITY (CARVEDILOL) HAVE DEMONSTRATED CLINICAL BENEFIT AND SIGNIFICANT REDUCTION IN ALL-CAUSE MORTALITY DURING CHRONIC ADMINISTRATION IN PATIENTS WITH HEART FAILURE COMPARED WITH EFFECTS OF PLACEBO.1–4 EXPERIMENTAL AND CLINICAL STUDIES HAVE DEMONSTRATED THAT DIFFERENT PHARMACOLOGICAL CLASSES OF ADRENERGIC RECEPTOR ANTAGONISTS MAY INDUCE DISPARATE EFFECTS ON RESTING PLASMA NOREPINEPHRINE (NE) CONCENTRATION, ADRENERGIC RECEPTOR DENSITY, AND BASAL SYMPATHETIC NERVE ACTIVITY.5–7 HOWEVER, THERE REMAINS UNCERTAINTY AS TO WHETHER THE VARIATIONS IN RECEPTOR AFFINITY PROFILES OF THESE AGENTS ARE ASSOCIATED WITH DIFFERENTIAL HEMODYNAMIC AND CLINICAL EFFECTS IN PATIENTS WITH HEART FAILURE. MOREOVER, THE COMPARATIVE EFFECTS OF THESE AGENTS ON CARDIOVASCULAR AND NEUROHORMONAL RESPONSES TO DIVERSE ADRENERGIC STIMULI HAVE NOT BEEN FULLY CHARACTERIZED.

ACCORDINGLY, THE PRESENT STUDY WAS UNDERTAKEN TO CHARACTERIZE THE COMPARATIVE EFFECTS OF 2 PHARMACOLOGICALLY DISTINCT ADRENERGIC RECEPTOR BLOCKERS, CARVEDILOL AND METOPROLOL, ON ADRENERGICALLY MEDIATED VASOMOTOR RESPONSES IN THE SKELETAL MUSCLE CIRCULATION OF THE FOREARM. WE HYPOTHESIZED THAT THE $\alpha$-ADRENERGIC-BLOCKING EFFECTS OF CARVEDILOL WOULD LIMIT VASOCONSTRICTION IN RESPONSE TO ISOMETRIC HANDGRIFF EXERCISE AND COLD PRESSOR TEST WHEN COMPARED WITH METOPROLOL. THE COMPARATIVE EFFECTS OF METOPROLOL AND CARVEDILOL ON VASOMOTOR AND NEUROHORMONAL RESPONSES TO ADRENERGIC STIMULI WERE INVESTIGATED IN BOTH HEALTHY SUBJECTS AND PATIENTS WITH HEART FAILURE IN PROSPECTIVE RANDOMIZED CLINICAL STUDIES. THE ACUTE EFFECTS OF HIGH DOSES OF THESE AGENTS ON REGIONAL VASCULAR AND NEUROHORMONAL RESPONSES TO ADRENERGIC STIMULI WERE COMPARED WITH PLACEBO IN NORMAL SUBJECTS. THE CHRONIC EFFECTS OF 6 MONTHS OF THERAPY WITH CLINICALLY RECOMMENDED DOSES OF THESE AGENTS ON REGIONAL VASCULAR AND NEUROHORMONAL RESPONSES TO ADRENERGIC STIMULI (WITHOUT PLACEBO CONTROL) WERE COMPARED IN AMBULATORY SUBJECTS WITH CHRONIC HEART FAILURE (CHF).
Methods

Study Population
Fourteen normal subjects (11 men and 3 women; mean age, 35±7 years) and 37 subjects with CHF were studied. Normal subjects were nonsmokers and had no history of cardiovascular or other chronic medical disease. Eligible heart failure subjects had stable NYHA class II or III symptoms for >3 months on a stable medical regimen, no prior exposure to adrenergic receptor antagonists, and left ventricular ejection fraction ≤35%. All protocols were approved by the ethical review committee at Columbia Presbyterian Medical Center. All subjects gave written informed consent before participation.

Study Procedures

Venous Occlusion Plethysmography
Forearm blood flow (milliliters per minute per 100 mL forearm volume) was determined by strain gauge venous occlusion plethysmography as previously described.8 All studies were performed in a temperature-controlled room with the subjects resting supine. All subjects were in a fasting state at the time of study. Forearm blood flow was determined at 15-second intervals at rest and during adrenergic stimuli. Five measurements were averaged for determination of resting forearm blood flow; peak responses to adrenergic stimuli are reported. Coefficient of variance for intraobserver measurement of resting blood flow in our laboratory is <1%. Mean arterial pressure was determined in the contralateral arm with an automated blood pressure device (Dinamap) at 30-second intervals during all forearm blood flow measurements. Forearm vascular resistance was determined in arbitrary units as the ratio of mean arterial pressure and forearm blood flow.

Neurohormonal Measurements
Five milliliters of blood were obtained from an indwelling catheter after 30-minute rest in a supine position and immediately after completion of 2 minutes of isometric handgrip exercise. Plasma was separated by cold centrifugation and stored at −80°C. Plasma brain natriuretic peptide (BNP) was measured with a quantitative fluorescent sandwich immunoassay (Biosite Diagnostics). Plasma NE was measured with a high-performance liquid chromatography method (ESA Inc).

Study Protocols

Normal Subjects
The study protocol in normal subjects was a prospective, double-blind, randomized, crossover design to compare the acute effects of a single dose of 25 mg carvedilol, 100 mg metoprolol tartrate, and placebo on forearm vascular and neurohormonal responses to adrenergic stimuli. Normal healthy subjects were selected to assess the effects of α- and β-adrenergic stimuli. Five measurements were averaged for determination of resting forearm blood flow; peak responses to adrenergic stimuli are reported. Coefficient of variance for within-subjects repeated same-day resting blood flow measurements is <5%. Mean arterial pressure was determined in the contralateral arm with an automated blood pressure device (Dinamap) at 30-second intervals during all forearm blood flow measurements. Forearm vascular resistance was determined in arbitrary units as the ratio of mean arterial pressure and forearm blood flow.

CHF Subjects
The study protocol in CHF subjects was a prospective, randomized, longitudinal parallel group design to compare the effects of 6 months of treatment with metoprolol succinate (extended release formulation with target dose 200 mg daily) and carvedilol (target dose 50 mg daily in 2 divided doses) on forearm vascular and neurohormonal responses to adrenergic stimuli. The formulations and target doses were selected based on published outcomes trials for these agents.3,4 Eligible subjects were randomly assigned in an open-label manner to receive carvedilol (starting dose, 3.125 mg) or metoprolol (starting dose, 25 mg). The dose of adrenergic receptor blocker was increased at 1- to 2-week intervals to achieve target dose or maximally tolerated dose within 8 weeks. Background cardiovascular medications, except adrenergic receptor blockers, were discontinued for at least 12 hours before all forearm vascular measurements. Forearm blood flow, mean arterial pressure, and heart rate were measured at rest and in response to sequential adrenergic stimuli (isometric handgrip exercise and cold pressor test as described above for normal subjects) before initiation of adrenergic receptor blocker therapy and after 6 months of therapy 120 minutes after administration of the assigned adrenergic receptor blocker. Blood samples for neurohormone determination were obtained after 30 minutes of supine rest and after 2 minutes of isometric handgrip exercise.

Data Analysis
All values in text are expressed as mean±SD. The primary end point for both normal subjects and subjects with heart failure was the change in forearm vascular resistance in response to adrenergic stimuli. All end points were assessed by an investigator blinded to treatment assignment (S.D. Katz, MD). The effects of study drug were compared with generalized linear models with adjustment of standard errors for clustered data of the repeated measures study designs. Models adjusting for age and baseline forearm hemodynamics were also analyzed. The sample size was calculated to provide >90% power to detect a 50% difference in α-adrenergic-mediated vasoconstriction between treatment groups assuming baseline SD of 50% of the mean value with 2-tailed α=0.05. A 2-tailed probability value <0.05 was used to infer statistical significance.

Results

Normal Subjects

Resting Hemodynamics
Resting mean arterial pressure, forearm blood flow, forearm vascular resistance, and heart rate after administration of study drug are presented in Table 1. Metoprolol and carvedilol administration significantly decreased resting mean arterial pressure when compared with placebo without significant change in resting heart rate, resting forearm blood flow, or resting forearm vascular resistance.

Hemodynamic Responses to Adrenergic Stimuli
Both carvedilol and metoprolol significantly attenuated the increased heart rate response to isometric handgrip exercise and cold pressor test when compared with effects of placebo (isometric handgrip 2.1±5.0 minutes−1 for carvedilol and 1.2±5.3 minutes−1 for metoprolol versus 4.9±4.0 minutes−1 for placebo, P<0.02; cold pressor test 1.7±5.4 minutes−1 for carvedilol and 1.4±4.5 minutes−1 for metoprolol versus 3.9±3.3 minutes−1 for placebo, P<0.05). Carvedilol attenuated the increased blood pressure response to isometric handgrip exercise when compared with metoprolol and placebo (4.1±3.7 mm Hg for carvedilol versus 8.4±6.0 mm Hg for metoprolol and 6.1±4.1 mm Hg for placebo, P<0.01). Blood pressure responses to cold pressor test did not differ among the 3 treatments. Forearm vascular resistance tended...
to decrease more after carvedilol in response to isometric handgrip exercise when compared with metoprolol and placebo (−3.5 U for carvedilol versus −1.2 U for metoprolol and −2.2 U for placebo, P=0.15) (Figure 1A). In response to cold pressor test, carvedilol significantly attenuated the increase in forearm vascular resistance when compared with that of metoprolol and placebo (3.1±8.9 U for carvedilol versus 9.0±2.7 U for metoprolol and 8.2±5.8 U for placebo, P<0.05) (Figure 1B).

**Neurohormonal Responses to Adrenergic Stimuli**

Neurohormonal responses to isometric handgrip exercise are summarized in Table 2. Plasma NE was higher at rest and in response to isometric handgrip exercise after administration of carvedilol compared with metoprolol and placebo. BNP concentrations did not differ at rest or in response to isometric handgrip exercise after administration of carvedilol, metoprolol, or placebo.

**CHF Subjects**

**Study Population**

Baseline clinical characteristics did not differ among the 37 heart failure subjects randomized to treatment with carvedilol or metoprolol (Table 3). Five subjects in the carvedilol group and 7 subjects in the metoprolol group did not complete the study. Eleven subjects dropped out because of noncompliance with assigned adrenergic receptor blocker therapy (4 subjects assigned to carvedilol, 7 subjects assigned to metoprolol), and 1 subject in the carvedilol group dropped out because of intolerance of adrenergic receptor blockade therapy. The mean daily dose of study drug administered after 6 months was 40±13 mg for carvedilol and 146±44 mg for extended-release metoprolol.

**Resting Hemodynamics**

Resting heart rate, mean arterial pressure, forearm blood flow, and forearm vascular resistance before and after 6 months of therapy with carvedilol and metoprolol are provided in Table 4. After 6 months of therapy, resting heart rate decreased significantly from baseline in both treatment groups, but did not differ between treatment groups. Before administration of adrenergic blockade therapy, resting forearm blood flow was lower and resting forearm vascular resistance was higher in patients assigned to metoprolol compared with subjects assigned to carvedilol. Rest mean arterial pressure, forearm blood flow, and forearm vascular resistance did not change from baseline in either treatment group and did not differ after 6 months of therapy between treatment groups.

**Responses to Adrenergic Stimuli**

Heart rate, blood pressure, and forearm blood flow and forearm vascular resistance response to isometric handgrip and cold pressor test did not change from baseline values in either treatment group and did not differ between treatment groups before or after 6 months of therapy (Table 5 and Figure 2).

**Neurohormonal Responses to Adrenergic Stimuli**

Plasma NE and BNP levels did not change from baseline values at rest or in response to isometric handgrip exercise in either treatment group and did not differ between the 2 treatment groups before or after 6 months of therapy (Table 6).

![Figure 1](https://example.com/figure1.png)
TABLE 2. Plasma NE and BNP Levels at Rest and in Response to Isometric Handgrip Exercise After Administration of Placebo, Carvedilol, and Metoprolol in 14 Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
<td>Rest Exercise</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>213±87</td>
<td>213±89</td>
<td>307±108*</td>
</tr>
<tr>
<td></td>
<td>311±111*</td>
<td>311±111*</td>
<td>220±84</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>11±17</td>
<td>15±24</td>
<td>12±18</td>
</tr>
<tr>
<td></td>
<td>16±23</td>
<td>12±15</td>
<td>15±18</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P<0.05 vs metoprolol and placebo; †P<0.05 vs rest.

Discussion

The current findings demonstrate that acute administration of carvedilol attenuates the regional vasoconstrictor response to adrenergic stimuli compared with that of placebo and metoprolol in the forearm circulation of normal subjects, whereas chronic administration of carvedilol does not attenuate the regional vasoconstrictor response to adrenergic stimuli compared with that of metoprolol in the forearm circulation of subjects with heart failure. Our data indicate that the α-adrenergic receptor blockade effects of carvedilol do not appear to play an important role in regulation of vasomotor stimuli during chronic therapy in subjects with heart failure.

The 2 adrenergic stimuli used in the present study protocol regulate forearm vasomotor tone by distinct signaling pathways. Isometric handgrip exercise induces rapid activation of the sympathetic nervous system via a combination of central command and muscle metaboreceptor neural signaling mechanisms.11,12 Vascular resistance in the contralateral forearm during sustained isometric handgrip exercise is regulated by α-adrenergic–mediated vasoconstriction and concomitant neurogenic vasodilation.13,14 The cold pressor test induces sympathetic activation by a reflex neural pathway that augments α-adrenergic–mediated vasoconstriction in skeletal muscle circulations.15 Our finding in normal subjects that carvedilol but not metoprolol was associated with increased vasodilation during isometric handgrip and decreased vasoconstriction during cold pressor test is consistent with the previously described α-adrenergic receptor blockade activity of carvedilol.16

In contrast to normal subjects, there were no detectable effects of carvedilol or metoprolol on vasomotor response to adrenergic stimuli in our subjects with CHF. Our findings are in accord with a previous study by Kubo et al,17 which demonstrated no difference in the effects of 4 months of therapy with 25 mg BID carvedilol and 50 mg BID short-acting metoprolol tartrate on calf vascular conductance in response to isometric handgrip in 18 patients with heart failure. The present study extends the findings of this previous report as we studied 2 adrenergic stimuli with distinct signaling pathways in both normal subjects and patients with heart failure, studied both acute and chronic effects of these agents, studied doses and formulations of adrenergic-blocking agents used in clinical outcomes trials, and measured neurohormonal responses to adrenergic stimuli. Because metoprolol and carvedilol did not modify sympathetic nerve activity during chronic therapy in the report by Kubo et al,17 and because in the current study neither agent modified plasma NE levels, the most likely explanation for our findings is that the α-adrenergic receptor–blocking activity of carvedilol is subject to the development of pharmacodynamic tolerance, such as previously reported with the α-adrenergic blockers prazosin and doxazosin.18–21 Although the mechanism of tolerance remains uncertain, our findings suggest that α-adrenergic–dependent effects do not likely contribute to the clinical effects of chronic carvedilol therapy in patients with heart failure.

In our study population of compensated ambulatory heart failure subjects, plasma NE levels were moderately elevated

TABLE 3. Baseline Clinical Characteristics of 37 Heart Failure Subjects Randomized to Treatment With Carvedilol and Metoprolol

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (n=19)</th>
<th>Metoprolol (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52±3</td>
<td>54±3</td>
</tr>
<tr>
<td>Sex, men:women</td>
<td>13:6</td>
<td>15:3</td>
</tr>
<tr>
<td>Etiology, ischemic:nonischemic</td>
<td>4:15</td>
<td>3:15</td>
</tr>
<tr>
<td>NYHA class, class 2:class 3</td>
<td>12:7</td>
<td>10:8</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25±2</td>
<td>23±2</td>
</tr>
<tr>
<td>Diuretics, n</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>RAA inhibitors, n</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Digoxin, n</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Rest heart rate, bpm</td>
<td>81±15</td>
<td>77±8</td>
</tr>
<tr>
<td>Rest MAP, mm Hg</td>
<td>86±9</td>
<td>83±9</td>
</tr>
<tr>
<td>Rest FBF, mL·min⁻¹·100 mL⁻¹</td>
<td>4.8±2.5</td>
<td>4.1±2.4</td>
</tr>
<tr>
<td>Rest FVR, resistance units</td>
<td>22.6±10.2</td>
<td>24.3±9.0</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVEF indicates left ventricular ejection fraction; RAA, renin-angiotensin-aldosterone (ACE inhibitors, angiotensin II receptor blockers, and/or spironolactone); MAP, mean arterial pressure; FBF, forearm blood flow; and FVR, forearm vascular resistance.

TABLE 4. Effects of 6 Months of Therapy With Carvedilol and Metoprolol on Regional Hemodynamics at Rest in Subjects With CHF

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (n=14)</th>
<th>Metoprolol (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>81±15</td>
<td>63±7*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>85±8</td>
<td>81±4</td>
</tr>
<tr>
<td>FBF, mL·min⁻¹·100 mL⁻¹</td>
<td>4.9±2.6</td>
<td>4.8±1.9</td>
</tr>
<tr>
<td>FVR, units</td>
<td>23±11</td>
<td>19±6</td>
</tr>
</tbody>
</table>

Values are mean±SD. MAP indicates mean arterial pressure; FBF, forearm blood flow; and FVR, forearm vascular resistance. *P<0.05 vs baseline.
and did not change during treatment with carvedilol or extended-release metoprolol. Our findings are in accord with previous studies in which decreases in plasma NE levels in response to adrenergic receptor blocker therapy have been proportional to the pretreatment levels. BNP levels were also moderately elevated at baseline and did not change during chronic therapy. The lack of change in BNP during adrenergic blockade may indicate that a decrease in stimulus for BNP release in response to decreased left ventricular filling pressures was offset by inhibition of sympathetic-mediated suppression of BNP.

Both carvedilol and extended-release metoprolol reduced mortality when compared with placebo in randomized clinical trials. Clinical studies of the comparative effects of these agents on hemodynamic, exercise, and other surrogate end points have yielded mixed findings.27 These agents have differences in pharmacological properties beyond adrenergic receptor affinity profiles. Our findings suggest that differences in adrenergic receptor affinity profile would not be expected to contribute to long-term differential clinical effects of carvedilol and metoprolol. However, these agents have differences in pharmacological properties beyond adrenergic receptor affinity profile that may contribute to their long-term clinical effects.28 The results of this study may assist in interpretation of the results of an ongoing randomized comparison of the effects of these 2 agents on survival.

Interpretation of the study findings is potentially limited by several factors. Because the effects of adrenergic receptor blockade were determined only during chronic therapy in the present study, it is not known if carvedilol and metoprolol exert differential effects on adrenergic vasoconstriction during initiation of therapy in heart failure subjects. Although study end points were assessed by a blinded investigator, the open-label study design may have introduced bias into the study. The numbers of heart failure subjects studied was small with substantial variability of responses within the study population. The study sample size provided >80% power to detect a 50% difference between treatment groups. Accordingly, a smaller difference in vasomotor responses to adrenergic stimuli between treatment groups cannot be excluded. Age is a potential confounding factor that may have contributed to our findings in heart failure subjects. The possible confounding effects of age do not alter the clinical relevance of our study, because regardless of underlying mechanism, no evidence of α-adrenergic blockade was observed during chronic carvedilol therapy in heart failure subjects. Moreover, adjustment for age did not alter our findings. Differences in baseline forearm blood flow and forearm vascular resistance in heart failure subject treatment groups could also potentially confound interpretation of our findings. The differences in baseline values are not likely related to differences in baseline adrenergic tone as plasma NE levels did not differ in among treatment groups. Adjustment for baseline values did not alter our findings.

In conclusion, our findings demonstrate that the acute α-adrenergic–blocking effects of carvedilol present in normal subjects are absent during chronic therapy in patients with heart failure. α-Adrenergic inhibition does not likely contribute to the beneficial effects of long-term carvedilol therapy.

TABLE 5. Effects of 6 Months of Therapy With Carvedilol and Metoprolol on Regional Hemodynamics in Response to Isometric Handgrip Exercise and Cold Pressor Test in Subjects With CHF

<table>
<thead>
<tr>
<th>Isometric Exercise</th>
<th>Cold Pressor Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carvedilol (n=14)</td>
</tr>
<tr>
<td></td>
<td>Baseline 6 Months</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84±16 66±9*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>93±12 88±11</td>
</tr>
<tr>
<td>FBF, mL·min⁻¹·100 mL⁻¹</td>
<td>5.8±3.2 5.2±2.4</td>
</tr>
<tr>
<td>FVR, units</td>
<td>21±9 20±8</td>
</tr>
</tbody>
</table>

Values are mean±SD. MAP indicates mean arterial pressure; FBF, forearm blood flow; and FVR, forearm vascular resistance. *P<0.05 vs baseline.
### TABLE 6. Effects of 6 Months of Therapy With Carvedilol and Metoprolol on Plasma NE and BNP Levels at Rest and in Response to Isometric Handgrip Exercise in Patients With CHF

<table>
<thead>
<tr>
<th>Carvedilol (n=11)</th>
<th>Metoprolol (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>Rest</td>
</tr>
<tr>
<td>607 ± 377</td>
<td>633 ± 451</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>Rest</td>
</tr>
<tr>
<td>280 ± 402</td>
<td>316 ± 522</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

### Acknowledgments
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Comparative Effects of Carvedilol and Metoprolol on Regional Vascular Responses to Adrenergic Stimuli in Normal Subjects and Patients With Chronic Heart Failure
Katarzyna Hryniewicz, Ana Silvia Androne, Alhakam Hudaihed and Stuart D. Katz

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