Carvedilol but Not Metoprolol Reduces β-Adrenergic Responsiveness After Complete Elimination From Plasma In Vivo

Michael Kindermann, MD*; Christoph Maack, MD*; Susanne Schaller; Nadine Finkler; Kathrin I. Schmidt; Stephanie Läer, MD; Henrike Wuttke, MD; Hans-Joachim Schäfers, MD; Michael Böhm, MD

Background—Carvedilol but not metoprolol exhibits persistent binding to β-adrenergic receptors (β-ARs) even after washout in cell culture experiments. Here, we determined the significance of this phenomenon on human β-ARs in vitro and in vivo.

Methods and Results—Experiments were conducted on human atrial trabeculae (n=8 to 10 per group). In the presence of metoprolol, isoproterenol potency was reduced compared with controls (P<0.001). In the presence of carvedilol, isoproterenol identified 2 distinct binding sites of high (36±6%; –8.8±0.4 log mol/L) and low affinity (–6.5±0.2 log mol/L). After β-blocker washout, isoproterenol potency returned to control values in metoprolol-treated muscles, whereas in carvedilol-treated preparations, isoproterenol potency remained decreased (P<0.001 versus control). In vivo studies were performed in 9 individuals receiving metoprolol succinate (190 mg/d) or carvedilol (50 mg/d) for 11 days in a randomized crossover design. Dobutamine stress echocardiography (5 to 40 μg·kg⁻¹·min⁻¹) was performed before, during, and 44 hours after application of study medication. β-Blocker medication reduced heart rate, heart rate–corrected velocity of circumferential fiber shortening, and cardiac output compared with baseline (P<0.02 to 0.0001). After withdrawal of metoprolol, all parameters returned to baseline values, whereas after carvedilol, all parameters remained reduced (P<0.05 to 0.001) despite complete plasma elimination of carvedilol.

Conclusions—Carvedilol but not metoprolol inhibits the catecholamine response of the human heart beyond its plasma elimination. The persistent β-blockade by carvedilol may be explained by binding of carvedilol to an allosteric site of β-ARs. (Circulation. 2004;109:3182-3190.)

Key Words: beta-antagonists ▪ heart failure ▪ receptors, adrenergic, beta

Carvedilol, metoprolol, and bisoprolol improve left ventricular (LV) function and survival in patients with chronic heart failure.¹ In the recent Carvedilol or Metoprolol European Trial (COMET),² carvedilol was superior to metoprolol in terms of mortality reduction in heart failure. There is an ongoing debate as to whether this difference is due to superiority of the pharmacological profile of carvedilol (combined β₁-, β₂-, and α₁-adrenergic receptor [AR] blockade versus selective β₁-AR blockade by metoprolol) or rather an inappropriate formulation and dosing of metoprolol in COMET.²⁻⁴

Carvedilol and metoprolol differ in terms of their interactions with β-ARs. Sympathetic activation leads to downregulation of myocardial β₁-ARs and uncoupling of β₂-ARs.¹ Metoprolol but not carvedilol upregulates downregulated β-ARs in heart failure,² probably because of differences in inverse agonist activity.⁶,⁷ In cultured chick cardiac myocytes, carvedilol itself did not downregulate β-AR density.⁸ However, affinity of carvedilol to cell membrane–associated β-ARs is high. After carvedilol incubation of cells, the affinity of radioligands to β-ARs remained significantly reduced despite extensive efforts to remove carvedilol from receptors.⁸ In contrast, the binding of metoprolol to β-ARs was reversible under similar in vitro conditions.⁶⁻⁹

The aim of the present study was to investigate the interaction of carvedilol and metoprolol with human β-ARs in vitro and in vivo. In vitro experiments were performed on isolated human myocardial preparations. The inotropic response to β-adrenergic stimulation by isoproterenol was measured in the presence and after extensive washout of carvedilol or metoprolol. In vivo β-adrenergic responsiveness was obtained by dobutamine stress echocardiography (DSE) in healthy volunteers during and 44 hours after 11 days of treatment with either carvedilol or metoprolol succinate.
Methods

The study was approved by the local ethics committee (Arztekammer des Saarlandes No. 131/00 and 177/01). Informed consent was given before participation in the study.

In Vitro Study

Forty-seven right atrial trabeculae were obtained from 12 patients undergoing CABG or aortic valve replacement/reconstruction (n = 5 and 7, respectively; 9 men, 3 women; age, 61±2 years; LV ejection fraction, 65±3%). Medication included ACE inhibitors, diuretics, β-blockers, nitrates, statins, and digitalis. No patient received carvedilol. Experiments were performed as described previously.7,10 In the first protocol of experiments, isoproterenol concentration-response curves (0.1 to 1000 nmol/L) were recorded in all muscles. After repetitive washout of isoproterenol, metoprolol (1 μmol/L; n = 8), carvedilol (10 nmol/L; n = 10), or vehicle (control; n = 8) was added to the organ bath. After 45 minutes of incubation, isoproterenol concentration-response curves (0.1 to 30 000 nmol/L) were determined. After application of the last concentration, all agents were eliminated from the organ bath by extensive rinsing (4 to 5 times). Again, after equilibration of force, isoproterenol concentration-response curves were obtained. In the second protocol, trabeculae were incubated with isoproterenol (100 nmol/L) either alone (control; n = 7) or together with metoprolol (1 μmol/L; n = 7) or carvedilol (10 nmol/L; n = 7).

In Vivo Study

Nine healthy, male individuals (mean±SD age, 26.6±2.6 years) received metoprolol succinate or carvedilol for 11 days in a randomized crossover design with a washout period of 4 weeks in between administrations. β-Blockers were uptitrated within 5 days. On days 5 to 11, carvedilol 25 mg BID or metoprolol succinate 95 mg BID was ingested. DSE was performed before, on day 10, and 44 hours after the last application of study medication (day 13). Complete data sets were obtained for 7 subjects. Two test persons (T.H. and O.A.) terminated the study because of substantial headache during DSE after the last application of study medication (day 13). Complete data was ingested. DSE was performed before, on day 10, and 44 hours after the last application of study medication.

Dobutamine Stress Echocardiography

After equilibration to resting conditions and baseline recordings, continuous intravenous infusion of dobutamine was started at 5 μg·kg⁻¹·min⁻¹ and increased to 10, 20, 30, and 40 μg·kg⁻¹·min⁻¹ at 10-minute intervals. Heart rate (HR) was obtained from simultaneous ECG recordings. Systolic, diastolic, and mean arterial blood pressures were measured by oscillometry (Millennia, In Vivo Research, Inc). For echocardiography, a Vingmed System Five ultrasound system with a 2.5-MHz transducer (GE Medical Systems) was used. Before dobutamine administration and 5 minutes after each dose increase, a 2D M-mode view of the LV parasternal short axis was recorded to obtain LV end-diastolic (EDD) and end-systolic (ESD) diameters, LV ejection time (ET) and LV stroke distance (SD) were measured with pulsed-wave Doppler echocardiography in the LV outflow tract. LV SD is equivalent to LV stroke volume, which was used to calculate minute distance (MD), an equivalent of cardiac output (CO).11 The following formulas were applied: fractional shortening (FS) = (EDD−ESD)/EDD; mean velocity of circumferential fiber shortening (VCF) = FS/ET; HR-corrected VCF (VCFc) = VCF × (60/HR)1/2; minute distance (MD) = HR × stroke distance; and systemic vascular resistance (SVR) = mean arterial blood pressure/MD.

Echocardiographic recordings were performed by the same investigator and evaluated offline in a blinded manner by 2 independent investigators using the EchoPac ultrasound software (GE Medical Systems). All measurements were repeated 5-fold, and the mean values were used for further analysis.

Cytochrome P4502D6 Genotyping

Mutations in the CYP2D6 gene result in the absence of enzyme activity with subsequently higher plasma concentrations of metoprolol.12 Thus, before administration of study medication, CYP2D6 genotype was determined in all participants. Of 10 screened volunteers, 1 individual did not enter the study because of a CYP2D6 genotype that causes a poor metabolizer phenotype (2 null alleles). The remaining had either 1 (n = 4) or 0 (n = 5) null allele.

Metoprolol and Carvedilol Plasma Concentrations

In 5 study participants, metoprolol and carvedilol plasma concentrations were measured during the on-treatment and withdrawal phases as described previously.13,14 Limits of quantification were 1 ng/mL for carvedilol and 3 ng/mL for metoprolol. Terminal half-life was calculated by noncompartmental analysis with KINETICA version 2.0 (Innaphase S. a. r. l.).

Statistical Analysis

Mean±SEM values are given. Nonlinear regression analyses of concentration-response curves (EC₅₀ values, slope factors [nₑₜ]); F-test analysis) were performed with GraphPadPrism (GraphPad Software). For comparison of slope factors, EC₅₀ values (in vitro study), and dobutamine dose-response curves (in vivo study), ANOVA, in conjunction with a post-hoc Duncan test, was used. A value of P<0.05 was considered significant.

Results

In Vitro Experiments

Before administration of β-blockers, isoproterenol potency was identical in all groups, and slope factors (nₑₜ) approached unity (Figure 1A and Table 1). In the presence of β-blockers, isoproterenol potency was significantly decreased compared with control conditions (Figure 1B and Table 1). Isoproterenol efficacy (expressed in percent of maximal force before application of β-blockers) remained unchanged in all groups. Slope factors increased in the presence of metoprolol but decreased in the presence of carvedilol (Table 1). After removal of β-blockers, isoproterenol potency was restored to baseline in metoprolol-incubated trabeculae, whereas it decreased further in carvedilol-treated trabeculae (Figure 1C and Table 1). Isoproterenol efficacy remained unchanged in all groups, and slope factors returned to unity in both β-blocker–incubated groups.

The slope factors of isoproterenol concentration-response curves in the presence of carvedilol (nₑₜ=0.6±0.1) indicate that isoproterenol binds to at least 2 different receptor populations with different affinity. Thus, we determined whether isoproterenol concentration-response curves modeled for 2 binding sites with control conditions. Figure 2B shows representative experiments, and Table 2 verifies that all dose-response curves modeled for 2 binding sites in the presence of carvedilol. The smaller fraction (35.5±5.6%) was a high-affinity binding site with the logEC₅₀ (−8.8±0.4 mol/L) similar to the logEC₅₀ for isoproterenol before the application of carvedilol (−9.0±0.3 mol/L), whereas the low-affinity binding site (−6.5±0.2 log mol/L) was similar to the logEC₅₀ after washout of carvedilol (−6.6±0.2 mol/L). This is in contrast to the uniform rightward shift of the isoproterenol concentration-response curve induced by metoprolol (Figure 2A). To compare the on-kinetics of β-AR blockade by carvedilol and metoprolol, we applied either β-blocker concomitantly with isoproterenol (100 nmol/L) to the organ bath.
Figure 2C and 2D indicates that metoprolol antagonized the positive inotropic effect of isoproterenol within 21±8 minutes, whereas carvedilol did so after 83±18 minutes of coincubation.

**In Vivo Experiment**

Two hours after ingestion of β-blockers on day 10 of treatment (at the time of DSE), metoprolol and carvedilol plasma concentrations were 102±8 and 17±3 ng/mL, respectively. Forty-four hours after the last ingestion of β-blockers, plasma concentrations of either β-blocker were below the limits of quantification (Figure 3A and 3B). In 2 subjects, carvedilol plasma levels were determined 1 to 12 hours after ingestion of carvedilol (25 mg) on day 11 (Figure 3B, inset), with an average terminal elimination half-life of 5.2±1.7 hours.

In Figure 4, representative examples of echocardiographic M-mode images for the maximum dobutamine response (at 40 μg · kg⁻¹ · min⁻¹) before, during, and after withdrawal of β-blockers are illustrated. The cumulative data are summarized in Figure 3C through 3F and Table 3. Before β-blocker administration, dobutamine induced a dose-dependent increase in all parameters. On β-blocker, the increases in HR (Figure 3C and 3D), CO (Figure 3E and 3F), FS, VCF, and VCFc were significantly reduced compared with predrug values (Table 3). Although there were no significant differences between the complete dobutamine dose-response curves during either β-blocker treatment (as indicated in Table 3), the maximum response to dobutamine (at 40 μg · kg⁻¹ · min⁻¹) was significantly higher during metoprolol compared with carvedilol treatment regarding CO (P<0.01) and VCF (P<0.02). Forty-four hours after ingestion of the last metoprolol dose, all parameters returned to baseline values (Figure 3C and 3E and Table 3). In contrast, after carvedilol, HR (Figure 3D), CO (Figure 3F), VCF (P<0.001 for all), VCFc, and FS (P<0.05 for both) remained reduced (Table 3).

**Table 1.** LogEC₅₀ Values and Slope Factors (nH) for Isoproterenol Before, in the Presence of, and After Washout of Vehicle (Control), Metoprolol 1 μmol/L, or Carvedilol 10 nmol/L in Human Atrial Myocardium

<table>
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<tr>
<th>β-Blocker</th>
<th>Control (n=8)</th>
<th>Metoprolol (n=8)</th>
<th>Carvedilol (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
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<tr>
<td>LogEC₅₀, mol/L</td>
<td>8.8±0.4</td>
<td>8.8±0.4</td>
<td>9.0±0.3</td>
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<tr>
<td>nH</td>
<td>1.1±0.2</td>
<td>1.3±0.1</td>
<td>1.1±0.2</td>
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<tr>
<td>In the presence of</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LogEC₅₀, mol/L</td>
<td>8.7±0.4</td>
<td>6.5±0.2*</td>
<td>7.0±0.2*</td>
</tr>
<tr>
<td>nH</td>
<td>1.2±0.2</td>
<td>1.6±0.0†‡</td>
<td>0.6±0.1†</td>
</tr>
<tr>
<td>After washout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LogEC₅₀, mol/L</td>
<td>8.4±0.3</td>
<td>8.2±0.4‡</td>
<td>6.6±0.1*§</td>
</tr>
<tr>
<td>nH</td>
<td>1.1±0.1</td>
<td>1.1±0.1</td>
<td>1.3±0.1‡</td>
</tr>
</tbody>
</table>

*P<0.001 vs control.
†P<0.01 vs control.
‡P<0.01 vs carvedilol.
§P<0.02 vs in the presence of carvedilol.
||P<0.001 vs in the presence of carvedilol.

Figure 1. Isoproterenol-induced increases in force of contraction in human atrial myocardium before (A), in the presence (B), and after washout (C) of vehicle (control, n=8), metoprolol (n=8), or carvedilol (n=10).
Under control conditions, mean arterial blood pressure (MAP) did not increase significantly in response to dobutamine (40 μg · kg⁻¹ · min⁻¹). In contrast, in the presence of carvedilol, MAP increased by 45±4 mm Hg (Figure 5A). To investigate whether different β-blocking profiles account for these differences in MAP, SVR was determined in all groups and compared with an additional group of 5 subjects that underwent DSE after 2 days of treatment with propranolol (160 mg BID), a nonselective β₁-β₂-AR antagonist. In the absence of β-blockers, dobutamine decreased SVR (Figure 5B and 5C). In the presence of metoprolol, the dobutamine-induced decrease of SVR was blunted (P<0.0001 versus control). In contrast, in the presence of carvedilol or propranolol, SVR increased in response to dobutamine (Figure 5B and 5C). Although overall SVR remained decreased in carvedilol- compared with propranolol-treated subjects at higher dobutamine concentrations (Figure 5B), the net increase in SVR was similar in carvedilol- and propranolol-treated subjects (Figure 5C and 5D).

**Discussion**

This is the first study to report that in contrast to metoprolol, the β-AR antagonistic effect of carvedilol outlasts elimination of the drug from the plasma in vivo. This is related to noncompetitive binding of the drug to an allosteric site of human β-ARs. Furthermore, after 11 days of treatment, no α-AR antagonism of carvedilol can be detected in vivo.

**In Vitro Experiments**

In cultured cardiac myocytes, a high affinity of carvedilol to β-ARs was observed. With radioligand binding techniques, it was shown that 12 to 24 hours of incubation with carvedilol apparently reduced maximal β-AR density (Bₘ₉). However, after extensive dialysis of incubated cells, Bₘ₉ of carvedilol-incubated membranes could be restored. Nevertheless, the affinity of the radioligand to β-ARs (expressed by its dissociation constant) remained substantially decreased.

In the present study, we extended these observations to more physiological conditions in intact human myocardium. Despite extensive removal of carvedilol from the organ bath, isoproterenol affinity to human β-ARs remained substantially decreased. However, the fact that isoproterenol efficacy (maximal force) was unchanged both in the presence of and after removal of carvedilol indicates that the maximal accessible number of β-ARs was maintained.

Most β-blockers exert competitive antagonism by binding to “orthosteric” binding sites, ie, the sites to which endogenous (or synthetic) agonists bind. Alternatively, ligands can modulate receptors at sites distinct from the orthosteric site. These nonorthosteric sites are called allosteric receptor sites (Greek for “other site”). We propose that although metoprolol exerts competitive antagonism at the orthosteric site, carvedilol interacts with an allosteric site of β-ARs. This is supported by 3 observations in the in vitro experiments.

First, according to the law of mass action, competitive antagonists induce a monophasic and reversible shift of agonist concentration-response curves. This was observed with metoprolol. In contrast, after incubation with carvedilol, only 64% of β-ARs had a 300-fold-lower affinity to isoproterenol. The fact that the remaining 36% displayed unchanged

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**TABLE 2. Number of Experiments Modeling for 2 Binding Sites, Fraction of High-Affinity Sites, and LogEC₅₀ Values for Isoproterenol at High- and Low-Affinity Sites Before, in the Presence of, and After Washout of Carvedilol 10 nmol/L in Human Atrial Myocardium**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>In the Presence of</th>
<th>After Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Site fits/experiment</td>
<td>0/10</td>
<td>10/10</td>
<td>0/10</td>
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<tr>
<td>Fraction (high), %</td>
<td>100</td>
<td>35.5±5.6</td>
<td>0</td>
</tr>
<tr>
<td>LogEC₅₀ (high), mol/L</td>
<td>-9.0±0.3</td>
<td>-8.8±0.4</td>
<td>…</td>
</tr>
<tr>
<td>LogEC₅₀ (low), mol/L</td>
<td>…</td>
<td>-6.5±0.2</td>
<td>-6.6±0.2</td>
</tr>
</tbody>
</table>
A high affinity for the agonist clearly argues against competitive antagonism of carvedilol at β-ARs.

Second, carvedilol and metoprolol displayed highly different β-AR association kinetics. In radioligand binding studies, the association of agonists and competitive antagonists to β-ARs occurs rapidly, within minutes. Accordingly, in our functional experiments, the maximum inotropic effect of isoproterenol occurred after 6 minutes. At this time, the presence of metoprolol had already reduced the isoproterenol-induced response by 75%, and after 20 minutes, isoproterenol was fully antagonized by metoprolol. In contrast, carvedilol antagonized the isoproterenol effect with at least 4-times-slower kinetics than metoprolol.

Third, dissociation of carvedilol from β-ARs was completely absent, whereas metoprolol effects were fully reversible. Interestingly, after removal of carvedilol from the organ bath, the fraction of β-ARs in the low-affinity state even increased from 64% to 100%. Because carvedilol was present for 45 minutes (preincubation) plus the time required to obtain the isoproterenol concentration-response curves (an-
other \( \approx \) 60 minutes), carvedilol may have established full \( \beta \)-AR blockade at the time of the third isoproterenol concentration-response curve (after washout).

These differences in \( \beta \)-AR interactions of carvedilol and metoprolol cannot be explained by different \( \beta_1 \)-selectivities of these agents. Metoprolol is 35- to 79-fold \( \beta_1 \)-selective, whereas carvedilol is nonselective at human \( \beta \)-ARs.\(^6,7\) Because isoproterenol stimulates \( \beta_1 \) - and \( \beta_2 \)-ARs with similar affinity, it would be predicted that metoprolol rather than carvedilol shifts isoproterenol concentration-response curves biphasically, yielding different affinities for \( \beta_1 \) - and \( \beta_2 \)-ARs. However, the opposite held true. Furthermore, slower association or dissociation kinetics of carvedilol are unlikely due to its higher affinity to \( \beta_2 \)-ARs, because in in vitro experiments, binding of other nonselective antagonists (eg, propranolol or bucindolol) to both \( \beta_1 \) - and \( \beta_2 \)-ARs was completely reversible.\(^5,8\)

Binding of carvedilol to an allosteric rather than the orthosteric site of \( \beta \)-ARs may explain why in radioligand binding experiments neither propranolol\(^6\) nor metoprolol\(^9\) blocked access of carvedilol to \( \beta \)-ARs. In contrast, bucindolol antagonized the inverse agonistic effects of metoprolol\(^7\) or nebivolol,\(^10\) indicating that these agents compete for the same binding site. Because in “competition” experiments carvedilol reduces binding of the radioligand to \( \beta \)-ARs,\(^6,7\) carvedilol apparently induces a conformational change in the receptor that decreases its affinity for other \( \beta \)-AR ligands at the orthosteric site (negative allosteric interaction\(^15\)). The slow kinetics and high lipophilicity of carvedilol suggest that the allosteric site may be located at the transmembrane or intracellular domains of the heptahelix receptor. This, however, needs to be elucidated in future studies.

**In Vivo Experiments**

The primary goal of this study was to determine the functional significance of the atypical binding kinetics of carvedilol in vivo. After 10 days of treatment of healthy volunteers with either \( \beta \)-blocker, dobutamine-induced increases in all contractile and hemodynamic parameters were blunted. Forty-four hours after cessation of treatment, dobutamine-induced responses were completely restored in metoprolol-treated subjects. In contrast, after carvedilol treatment, the dobutamine response remained blunted despite complete plasma elimination of carvedilol. Plasma levels during carvedilol and metoprolol treatment and elimination half-life of carvedilol were in agreement with previously published reports.\(^14,17\) At these concentrations, metoprolol blocks \( \approx 50\% \) of \( \beta_1 \)-ARs but \(<5\% \) of \( \beta_2 \)-ARs, whereas carvedilol blocks \( >90\% \) of both \( \beta_1 \) - and \( \beta_2 \)-ARs.\(^7\) However, because metoprolol displays higher inverse agonist activity than carvedilol,\(^6,7\) these concentrations reduced contractile force in human myocardium by similar extents (43% and 32%, respectively\(^7\)). Accordingly, in our study, HR at rest was reduced similarly by both drugs.
TABLE 3.  Dobutamine 20 and 40 µg·kg⁻¹·min⁻¹-Induced Increase in HR, CO, FS, VCF, and VCF₆

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>20 µg·kg⁻¹·min⁻¹</th>
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<td>HR, min⁻¹</td>
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<tr>
<td>Con</td>
<td>66.4±3.4</td>
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<td>121.2±6.8</td>
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<td>Meto</td>
<td>51.0±2.4</td>
<td>57.3±2.7</td>
<td>74.3±6.6*</td>
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<td>Carv</td>
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<td>127.1±5.2‡</td>
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<td>102.0±8.3§</td>
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<tr>
<td>Con</td>
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<td>31.8±2.1</td>
<td>35.6±1.7</td>
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<td>Meto</td>
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<td>22.3±2.4*</td>
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<tr>
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<td>13.7±0.8</td>
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<tr>
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<tr>
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<td>53.5±1.3</td>
<td>58.2±1.8#</td>
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<td>50.3±1.7</td>
<td>54.5±2.7**</td>
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<td>VCF, s⁻¹</td>
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<tr>
<td>Con</td>
<td>1.38±0.05</td>
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<td>Con</td>
<td>1.32±0.05</td>
<td>2.03±0.09</td>
<td>2.07±0.10</td>
</tr>
<tr>
<td>Meto</td>
<td>1.39±0.06</td>
<td>1.72±0.07</td>
<td>1.98±0.12†</td>
</tr>
<tr>
<td>Carv</td>
<td>1.36±0.06</td>
<td>1.55±0.05</td>
<td>1.68±0.05‡</td>
</tr>
<tr>
<td>Meto&gt;</td>
<td>1.31±0.05</td>
<td>2.01±0.09</td>
<td>2.12±0.12§</td>
</tr>
<tr>
<td>Carv&gt;</td>
<td>1.35±0.04</td>
<td>1.81±0.09</td>
<td>1.89±0.08**</td>
</tr>
</tbody>
</table>

Con indicates control; Meto, metoprolol; Carv, carvedilol; and Meto>, Carv>, withdrawal of the respective β-blocker. Probability values are calculated for complete dose-response curves.

* P<0.0001 Meto vs Con and Meto>.
† P<0.001 Carv vs Con and P<0.01 Carv vs Carv>.
‡ P<0.001 Meto> vs Carv>.
§ P<0.01 Carv> vs Con.
|| P<0.01 Meto vs Con and Meto>.
¶ P<0.01 Carv vs Con.
# P<0.05 Meto> vs Carv>.
** P<0.05 Carv> vs Con.
†† P<0.02 Meto vs Con and Meto>.
‡‡ P<0.01 Carv vs Con.

The persisting β-AR blockade by carvedilol after plasma elimination has important clinical implications. First, carvedilol-treated patients with chronic heart failure in need of inotropic support as a result of acute decompensation may require higher doses of catecholamines up to 44 hours after carvedilol withdrawal. Because phosphodiesterase inhibitors and Ca²⁺ sensitizers act downstream of β-ARs, these agents may be more useful in cardiac decompensated patients on carvedilol medication, whereas metoprolol-treated patients might respond well to catecholamines at higher doses. Second, when dobutamine is used as a diagnostic tool to reveal myocardial ischemia in patients with coronary artery disease, patients are usually advised to withdraw β-blocker medication on the day before DSE. However, to avoid a loss of sensitivity, carvedilol treatment should be interrupted at least 48 hours before the examination.

Third, the profound differences in β-AR dissociation kinetics of carvedilol and metoprolol and their differential effects on β-AR regulation may predispose metoprolol- but not carvedilol-treated patients to experience a “β-blocker rebound phenomenon.” This phenomenon describing increased sensitivity of β-ARs to catecholamines after β-blocker withdrawal is particularly dangerous in patients with coronary artery disease, in whom β-adrenergic stimulation can induce acute ischemia and severe arrhythmia. In addition, in patients with chronic heart failure, withdrawal of metoprolol reduced vagal tone after 24 hours and deteriorated the clinical condition after several weeks. One main concern about COMET is that instead of the extended release succinate formulation, the short-acting metoprolol tartrate was tested against carvedilol. The observation of the present study, ie, that β-adrenergic antagonism of carvedilol persists even longer than that of metoprolol succinate, emphasizes that pharmacokinetic differences between carvedilol and metoprolol may introduce an important confounding factor to the results and conclusions drawn from COMET.

Fourth, in a previous study, we observed adverse effects when switching heart failure patients from chronic carvedilol treatment to metoprolol within 1 day, whereas switching from metoprolol to carvedilol was tolerated well. According to the data of the present study, the reason for increased incidence of bradycardia and hypotension may have been persistent β-AR blockade by carvedilol when metoprolol was initiated. If carvedilol binds to an allosteric and metoprolol to the orthosteric binding site of β-ARs, their effects may be additive rather than competitive.

In the present study, the response to dobutamine was slightly less impaired during metoprolol treatment than during carvedilol. This is in general agreement with other studies on patients with chronic heart failure. Interestingly, in the study of Metra et al, metoprolol treatment had no impact on the dobutamine-induced increase in CO at all. This is in contrast to the blunted dobutamine response during metoprolol treatment in our study. These differences are probably related to differences in study populations. In heart failure patients, chronic metoprolol treatment leads to upregulation of downregulated β-ARs, which probably restored a formerly blunted response to catecholamine stimulation in the patients studied by Metra et al. In the healthy subjects of our study, no further upregulation or sensitization of β-ARs may be expected; thus, the net effect of β-AR blockade by metoprolol was a decrease in β-AR responsiveness. Accordingly, a limitation of the present study is the fact that in vivo data were obtained in a small number of healthy volunteers rather than in patients with heart failure. However, in the latter population, metoprolol withdrawal may be unethical.
because it could lead to hypersensitivity of β-ARs and worsening of heart failure symptoms.21

α-AR Antagonism of Carvedilol

In agreement with previous studies in patients with heart failure, MAP in response to dobutamine increased to a higher degree in carvedilol-treated subjects than in metoprolol-treated individuals. This was associated with a greater increase in SVR. In the absence of β-blockers, dobutamine increases CO predominantly by stimulating myocardial β1-ARs, whereas SVR is decreased by reflex withdrawal of sympathetic tone.24 The additional vasodilating effect of peripheral vascular β2-AR stimulation is largely offset by peripheral postsynaptic α1-AR stimulation.24 In our study, the dobutamine-induced decrease in SVR was blunted in the presence of the β1-selective metoprolol. This effect may be due primarily to less pronounced withdrawal of sympathetic tone. In the presence of the nonselective β1/β2-AR blocker propranolol, the increase in SVR can be explained only by dobutamine-induced α-AR stimulation. The fact that the net increase in SVR was similar in propranolol- and carvedilol-treated subjects clearly indicates a lack of α-AR blockade by carvedilol. Although similar findings have been obtained in patients with chronic heart failure after 4 or 6 months of treatment, this is the first report indicating that tachyphylaxis of α-AR blockade by carvedilol occurs as early as 10 days after initiation of treatment. Because in carvedilol-treated patients pulmonary vascular resistance also increased in response to dobutamine,18 this catecholamine has to be used with caution within the first 2 days after cessation of carvedilol treatment.

Conclusions

Atypical binding of carvedilol to an allosteric site of human β-ARs with substantially slower kinetics compared with the competitive antagonist metoprolol leads to persistent β-AR blockade far beyond its plasma elimination. The substantial pharmacokinetic differences of these widely used β-blockers might be of importance in the treatment of heart failure, coronary artery disease, and hypertension.

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References


Carvedilol but Not Metoprolol Reduces β-Adrenergic Responsiveness After Complete Elimination From Plasma In Vivo

Michael Kindermann, Christoph Maack, Susanne Schaller, Nadine Finkler, Kathrin I. Schmidt, Stephanie Läer, Henrike Wuttke, Hans-Joachim Schäfers and Michael Böhm

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