

Beta-Blocker Therapy Influences the Hemodynamic Response to Inotropic Agents in Patients With Heart Failure

A Randomized Comparison of Dobutamine and Enoximone Before and After Chronic Treatment With Metoprolol or Carvedilol

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OBJECTIVES	We compared the hemodynamic effects of dobutamine and enoximone administration before and after long-term beta-blocker therapy with metoprolol or carvedilol in patients with chronic heart failure (HF).
BACKGROUND	Patients with HF on beta-blocker therapy may need hemodynamic support with inotropic agents, and the hemodynamic response may be influenced by both the inotropic agent and the beta-blocker used.
METHODS	The hemodynamic effects of dobutamine (5 to 20 $\mu\text{g}/\text{kg}/\text{min}$ intravenously) and enoximone (0.5 to 2 mg/kg intravenously) were assessed by pulmonary artery catheterization in 29 patients with chronic HF before and after 9 to 12 months of treatment with metoprolol or carvedilol at standard target maintenance oral doses. Hemodynamic studies were performed after ≥ 12 h of wash-out from all cardiovascular medications, except the beta-blockers that were administered 3 h before the second study.
RESULTS	Compared with before beta-blocker therapy, metoprolol treatment decreased the magnitude of mean pulmonary artery pressure (PAP) and pulmonary wedge pressure (PWP) decline during dobutamine infusion and increased the cardiac index (CI) and stroke volume index (SVI) response to enoximone administration, without any effect on other hemodynamic parameters. Carvedilol treatment abolished the increase in heart rate, SVI, and CI and caused a rise, rather than a decline, in PAP, PWP, systemic vascular resistance, and pulmonary vascular resistance during dobutamine infusion. The hemodynamic response to enoximone, however, was maintained or enhanced in the presence of carvedilol.
CONCLUSIONS	In contrast with its effects on enoximone, carvedilol and, to a lesser extent, metoprolol treatment may significantly inhibit the favorable hemodynamic response to dobutamine. No such beta-blocker-related attenuation of hemodynamic effects occurs with enoximone. (J Am Coll Cardiol 2002;40:1248–58) © 2002 by the American College of Cardiology Foundation

Despite the improvement obtained with the administration of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers, the natural history of chronic heart failure (HF) remains progressive, and many patients eventually develop decompensation. During decompensation, patients with HF are limited by dyspnea and fatigue at rest or with minimal exertion, require frequent hospitalizations, have a higher mortality rate, and both symptoms and prognosis become critically dependent on hemodynamic conditions (1–3). Treatment with inotropic agents may, thus, become necessary (4,5). In addition, beta-blockers, which are indicated for their long-term favorable actions (6–8), may be

less well-tolerated in advanced HF patients because of their initial negative inotropic activity resulting from withdrawal of adrenergic support (9,10). The concomitant administration of an inotropic agent and a beta-blocker, therefore, may be necessary both in patients already on maintenance beta-blocker treatment who have progressed to decompensated HF and in patients with advanced HF who do not tolerate the initiation of beta-blockade (11,12). However, few studies have assessed the hemodynamic effects of different types of inotropic agents in patients on beta-blocker therapy (12–14).

The most common inotropic agents presenting clinical practice are the beta-adrenergic receptor agonist dobutamine and the type III phosphodiesterase (PDE) inhibitors, milrinone and enoximone. These two classes of drugs have important differences (15,16). In human ventricular myocardium, dobutamine is a partial β_1 -receptor agonist (17) but also has action on β_2 - and α_1 -postsynaptic adrenergic receptors. Its inotropic effects are, therefore,

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Abbreviations and Acronyms

ACEI	=	angiotensin-converting enzyme inhibitor
ANOVA	=	analysis of variance
CI	=	cardiac index
HF	=	heart failure
HR	=	heart rate
LVEF	=	left ventricular ejection fraction
MAP	=	mean arterial pressure
NYHA	=	New York Heart Association
PAP	=	mean pulmonary artery pressure
PDE	=	phosphodiesterase
PVR	=	pulmonary vascular resistance
PWP	=	pulmonary wedge pressure
SVI	=	stroke volume index
SVR	=	systemic vascular resistance

dependent on the degree of occupancy of the beta-adrenergic receptors and on the activity of beta-adrenergic signal transduction mechanisms (18,19). The type III PDE inhibitors block the breakdown of cyclic adenosine monophosphate, which in myocardial cells results in activation of protein kinase A, phospholamban, and L-type calcium channel phosphorylation. Phosphorylation of phospholamban results in relief of this regulatory protein's inhibition of calcium adenosine triphosphatase activity, producing positive lusitropic and inotropic effects (15,16). As site of action of the type III PDE inhibitors is distal to beta-adrenergic receptors, their activity is less influenced by the degree of expression and coupling of beta-adrenergic receptors (12,14,19).

The beta-blockers metoprolol and carvedilol have both been shown to favorably affect the prognosis of the patients with HF (6-8). These agents have meaningful pharmacologic differences that might influence the response to inotropic agents (20-22). Metoprolol administration to patients with HF causes the upregulation of beta₁-adrenergic receptors and leaves unoccupied, or may even recouple, beta₂-adrenergic receptors (21,23). In contrast, carvedilol blocks both beta₁- and beta₂-adrenergic receptors, and also has alpha₁-antagonist activity (21). We hypothesized that these differences would influence the hemodynamic responses to inotropic agents that act on adrenergic receptors, but would have less or no effect on agents that act beyond them. The aim of our study was, thus, to compare the hemodynamic effects of dobutamine and enoximone before and after long-term beta-blocker therapy with metoprolol or carvedilol in patients with chronic HF.

METHODS

Patients. We studied patients with chronic HF caused by an ischemic or nonischemic cardiomyopathy who had New York Heart Association (NYHA) functional class II to IV symptoms, a left ventricular ejection fraction (LVEF) \leq 35% by radionuclide ventriculography, and ongoing treatment with furosemide and an ACEI. We excluded patients with an acute ischemic event or a coronary revascularization

procedure within three months; a history of alcohol abuse, primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy (e.g., bronchial asthma sensitive to the administration of beta-agonists); concomitant treatment with other beta-blockers, alpha-antagonists, calcium antagonists, or antiarrhythmic agents (except amiodarone). The protocol was approved by the Ethics Committee of the Hospital of Brescia. Written informed consent was obtained from all study patients.

Protocol. Hemodynamic measurements were obtained using a balloon-tipped, flow-directed pulmonary artery catheter inserted percutaneously into the right internal jugular vein. Cardiac output was assessed by the thermodilution method with the mean of three consecutive measurements with $<$ 15% variations between each other used for data analysis. Derived hemodynamic variables were calculated using standard formulas.

Once a reproducible baseline was obtained, the hemodynamic response to the inotropic agents was assessed. Because of its shorter elimination half-life, dobutamine was infused first, followed by a re-equilibration period of at least 1 h, then by enoximone administration. Dobutamine was infused at the increasing doses of 5, 10, 15, and 20 μ g/kg/min with hemodynamic values measured after 15 min of infusion at each dose level. Dobutamine infusion was then discontinued, and hemodynamic variables were allowed to return to within 10% of the initial baseline values during the re-equilibration period. The second baseline, pre-enoximone measurements were obtained in triplicate, and enoximone was then administered as intravenous bolus injections in increasing increments of 0.5 mg/kg, repeated every 20 min to a maximal final dose of 2.0 mg/kg.

After the initial hemodynamic study, each patient was randomized to metoprolol tartrate or carvedilol, added to the ongoing therapy for HF, according to a protocol described previously (22). A second hemodynamic study that included the assessment of the response to dobutamine and enoximone administration was performed after 9 to 12 months of beta-blocker therapy, using the same protocol of the first study. In order to detect the maximal effects of the beta-blocker treatment on the hemodynamic response to the inotropic agents, the second hemodynamic study was performed 3 h after the last administration of either metoprolol or carvedilol at the standard doses used during chronic maintenance therapy. In contrast, all other cardiovascular medications were withdrawn at least 12 h before both the hemodynamic studies.

In addition to pulmonary artery catheterization, all patients were assessed by the NYHA functional classification and by radionuclide ventriculography, for the assessment of LVEF and volumes, before and after 9 to 12 months of beta-blocker therapy at maintenance doses.

Statistical analysis. Each of the 29 subjects was treated chronically with a beta-blocker (carvedilol or metoprolol) and acutely with two inotropes (dobutamine and enoxi-

mone) before and after beta-blocker treatment. There were no missing values. Using mean and variance data for the patients included in a previous study (14) and assuming a within-subject correlation of +0.50 and two-sided alpha of 0.05, a sample size of 13 carvedilol-treated subjects was calculated to have 90% power to detect a difference from baseline to end of study of 0.05 l/min/m² per $\mu\text{g/kg/min}$ in slope (over dobutamine dose of 0 to 20 $\mu\text{g/kg/min}$) of cardiac index (CI). This difference corresponds to a 45% relative decrease in slope, comparable to the 53% decrease seen in the previous study (14). Comparison of baseline data between the beta-blocker groups was by unpaired *t* test and chi-square test, as appropriate. Effects of chronic treatment were assessed by paired *t* test within-group and by analysis of variance (ANOVA) to compare between-group changes. Effects of acute treatment were assessed as changes from before dobutamine or enoximone administration, separately by each beta-blocker and inotrope. The paired *t* test was used to assess the within-visit effect of dose. Taking the design as that of the split-split-plot experiment (24,25), three-way repeated measures ANOVA was used to assess differences in linear slope of the dose-response curves. The paired *t* test was used to assess the within-dose effect of visit, when the slope differences were significant. A two-tailed *p* value <0.05 was considered significant. Results are expressed as mean \pm SD unless otherwise specified. Reported *p* values are not adjusted for multiple comparisons.

RESULTS

Patient characteristics and response to beta-blocker treatment. We studied 34 patients, 27 males and 7 females, age 58 ± 10 years, with chronic HF caused by idiopathic dilated cardiomyopathy (22 patients) or by previous myocardial infarction (12 patients). Eight patients were NYHA functional class II, 25 were class III, and 1 was class IV. The patients had severe left ventricular dysfunction with a mean LVEF of $18.3 \pm 6.6\%$ and a moderate-severe impairment of maximal functional capacity, with a mean peak oxygen consumption of 13.3 ± 3.5 ml/kg/min. At end of study, all patients were treated with furosemide and an ACEI, 27 were on digoxin, 21 on spironolactone, and 2 patients were receiving amiodarone.

Patients randomized to metoprolol and to carvedilol were similar with respect to all pretreatment characteristics (Table 1). Five patients died before the end of the study, three suddenly (two in the metoprolol and one in the carvedilol group) and two for worsening HF. The remaining 29 patients completed the protocol and were reassessed after 10.4 ± 1.2 months (median time, 10 months) of beta-blocker therapy. Long-term therapy with metoprolol (mean dose, 129 ± 38 mg daily) or carvedilol (mean dose, 43 ± 11 mg daily) was associated with a significant improvement in clinical symptoms, left ventricular function, and hemodynamic parameters, with no significant difference in these parameters between the two study groups (Table 2).

Table 1. Baseline Characteristics of the Patients According to Treatment Group

	Metoprolol (n = 17)	Carvedilol (n = 17)
Age, yrs	60 \pm 8	56 \pm 11
Gender (males/females), n	3/14	4/13
Cause (IDC/CAD), n	11/6	11/6
Atrial fibrillation, n	3	4
NYHA functional class, II/III/IV	5/12/0	3/13/1
LVEF, %	19.5 \pm 7.5	17.0 \pm 5.6
Peak VO ₂ , ml/kg/min	13.7 \pm 4.0	13.0 \pm 3.1
CI, l/min/m ²	2.62 \pm 0.64	2.24 \pm 0.50
PWP, mm Hg	23 \pm 11	29 \pm 11
Concomitant therapy		
Furosemide, n, mg/day	17, 63 \pm 33	17, 74 \pm 72
Captopril, n, mg/day	3, 125 \pm 43	6, 80 \pm 61
Enalapril, n, mg/day	14, 15 \pm 5	11, 20 \pm 8
Digoxin, n, mg/day	15, 0.17 \pm 0.13	12, 0.16 \pm 0.06
Amiodarone, n, mg/day	1, 200	1, 200

There was no significant difference between the two groups with respect to all the pretreatment characteristics.

CAD = coronary artery disease; CI = cardiac index; IDC = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PWP = pulmonary wedge pressure; VO₂ = oxygen consumption.

Hemodynamic response to the inotropic agents. No significant difference in any parameter was detected before dobutamine compared to before enoximone infusion. The changes from baseline in the main hemodynamic parameters caused by dobutamine and enoximone administration, before and after metoprolol or carvedilol treatment, respectively, are shown in Figures 1 to 5. Before beta-blocker administration, CI increased after both dobutamine and enoximone infusions, in both treatment groups. Metoprolol treatment did not change the response to dobutamine, whereas the response to enoximone was augmented. Carvedilol treatment was associated with a significant inhibition of the CI response to dobutamine but not to enoximone administration (Fig. 1). Similarly, metoprolol treatment had no effect on the heart rate (HR) and stroke volume index (SVI) responses to dobutamine and slightly increased them after enoximone; carvedilol significantly inhibited these responses to dobutamine but not to enoximone (Fig. 2).

Before beta-blocker therapy, dobutamine or enoximone administration caused a decline in both the pulmonary wedge pressure (PWP) and mean right atrial pressure. Metoprolol treatment was associated with a reduction in the magnitude of the PWP decline without any change in the direction of this response. Carvedilol treatment had a greater effect than metoprolol on the PWP lowering response of dobutamine as, in its presence, dobutamine infusion was associated with an increase, rather than a decline, in PWP. In contrast, the response to enoximone administration was not influenced by either metoprolol or carvedilol treatment (Fig. 3).

Before either metoprolol or carvedilol treatment, the mean arterial pressure (MAP) was not significantly changed by dobutamine infusion (Fig. 4). After metoprolol treatment MAP slightly, but significantly, increased from pre-

Table 2. Hemodynamic Responses at Rest

	Metoprolol (n = 14)		Carvedilol (n = 15)		p (ANOVA)
	Baseline	EOS	Baseline	EOS	
LVEF (%)	20.4 ± 7.7	30.0 ± 14.0‡	17.0 ± 5.9	27.9 ± 11.1‡	NS
Left ventricular end-diastolic volume (ml/m ²)	174 ± 57	168 ± 100	174 ± 72	145 ± 56*	NS
NYHA functional class, I/II/III/IV	0/5/9/0	3/10/1/0‡	0/3/11/1	4/7/3/1‡	NS
Peak VO ₂ (ml/kg/min)	13.8 ± 4.3	15.7 ± 4.1‡	13.2 ± 3.0	13.8 ± 3.7	NS
Heart rate (beats/min)	87 ± 14	66 ± 8‡	92 ± 17	69 ± 16‡	NS
Mean arterial pressure (mm Hg)	84 ± 9	85 ± 11	92 ± 14	90 ± 9	NS
CI (l/min/m ²)	2.78 ± 0.78	2.74 ± 0.81	2.37 ± 0.53	2.66 ± 0.83	NS
SVI (ml/beat/m ²)	33 ± 11	42 ± 13‡	27 ± 8	41 ± 14‡	NS
Left ventricular stroke work index (g·m/m ²)	29 ± 13	40 ± 18†	24 ± 9	40 ± 15‡	NS
Systemic vascular resistance (dyn·s·cm ⁻⁵)	1,315 ± 501	1,358 ± 375	1,593 ± 537	1,493 ± 575	NS
Mean right atrial pressure (mm Hg)	8 ± 3	6 ± 2*	11 ± 5	8 ± 5*	NS
PAP (mm Hg)	27 ± 10	23 ± 11	34 ± 11	27 ± 10‡	NS
PWP (mm Hg)	22 ± 9	18 ± 9	27 ± 8	20 ± 9‡	NS
PVR (dyn·s·cm ⁻⁵)	107 ± 96	92 ± 51	136 ± 80	124 ± 61	NS

*p < 0.05; †p < 0.01; ‡p < 0.001 for differences between pre- and post-treatment values (within each group). The p (analysis of variance [ANOVA]) denotes significance of differences in the magnitude of change from baseline to end of study between the metoprolol group and the carvedilol group. Values reflect data in patients with paired measurements.

EOS = end of study; SVI = stroke volume index; PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance. Other abbreviations as in Table 1.

infusion values during dobutamine infusions of 15 and 20 μg/kg/min, respectively. This MAP increase was likely related to the increase in the CI, as it was accompanied by a dose-dependent decline in systemic vascular resistance (SVR). In contrast, enoximone caused a dose-dependent decline in MAP and SVR, both before and after metoprolol therapy. The MAP and SVR response to dobutamine was significantly affected by carvedilol treatment. In the presence of carvedilol, dobutamine infusion caused a dose-dependent increase in the MAP, which was accompanied by a similar increase in the SVR, in contrast with the decline observed before carvedilol treatment. In contrast, the MAP and SVR decline during enoximone administration was augmented by carvedilol therapy (Fig. 4).

Compared with effects on MAP and SVR, similar responses were observed with respect to mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) (Fig. 5). Before treatment with beta-blocking agents, these parameters declined during the administration of both inotropic agents. After metoprolol therapy dobutamine produced a directionally similar, but somewhat blunted, PAP and PVR response, while the enoximone PAP and PVR responses were unchanged. In contrast, after carvedilol treatment dobutamine infusion caused a significant, dose-dependent increase in the PAP and PVR, while the response to enoximone was similar to the pre-carvedilol treatment effects (Fig. 5).

DISCUSSION

Potential need of concomitant beta-blocker and inotropic therapy. Because of its beneficial effects on prognosis, beta-blocker therapy is now indicated in all the patients with chronic HF who do not have major contraindications. As a result, the number of patients on beta-blocker therapy who develop decompensated HF and who need inotropic therapy is likely to increase. Second, although the beneficial

effects of beta-blockade have been shown in selected groups of patients with advanced HF (8), beta-blockers may be poorly tolerated, and the initiation of therapy may be particularly difficult in these patients (9,21). Thus, the concomitant administration of the inotropic agents and beta-blockers may become necessary both in the patients who develop decompensated HF while on chronic beta-blocker therapy and in patients who cannot tolerate the initiation of beta-blockers. However, meaningful differences are present among beta-blockers used to treat HF, as well as in inotropic agents. Thus, it is important to know whether these differences account for significant degrees of interaction between individual inotropes and beta-blockers when these two classes of compounds are used in combination. With this aim, we assessed the response to the two inotropic agents dobutamine and enoximone in a group of patients with HF, before and after long-term treatment with metoprolol or carvedilol. We excluded patients with advanced HF and in unstable clinical conditions in whom the initiation of beta-blocker treatment might be difficult and the hemodynamic responses may be affected by the instability of the clinical and hemodynamic conditions. However, we maintain that our results may be extrapolated to patients with advanced HF, whose response to beta-adrenergic agonists may be compromised to an even a greater extent because of even greater impairment of beta-adrenergic signal transduction mechanisms (14,18,19).

Dobutamine-metoprolol interaction. Our study demonstrates that the hemodynamic response to different inotropic agents may be profoundly influenced by the type of ongoing beta-blocker therapy. In particular, the hemodynamic response to the beta-adrenergic agonist dobutamine was affected only slightly by metoprolol, but to a far greater extent by carvedilol therapy. Before beta-blocker therapy, dobutamine infusion was associated with the expected hemodynamic effects, consisting of a dose-dependent in-

Cardiac Index

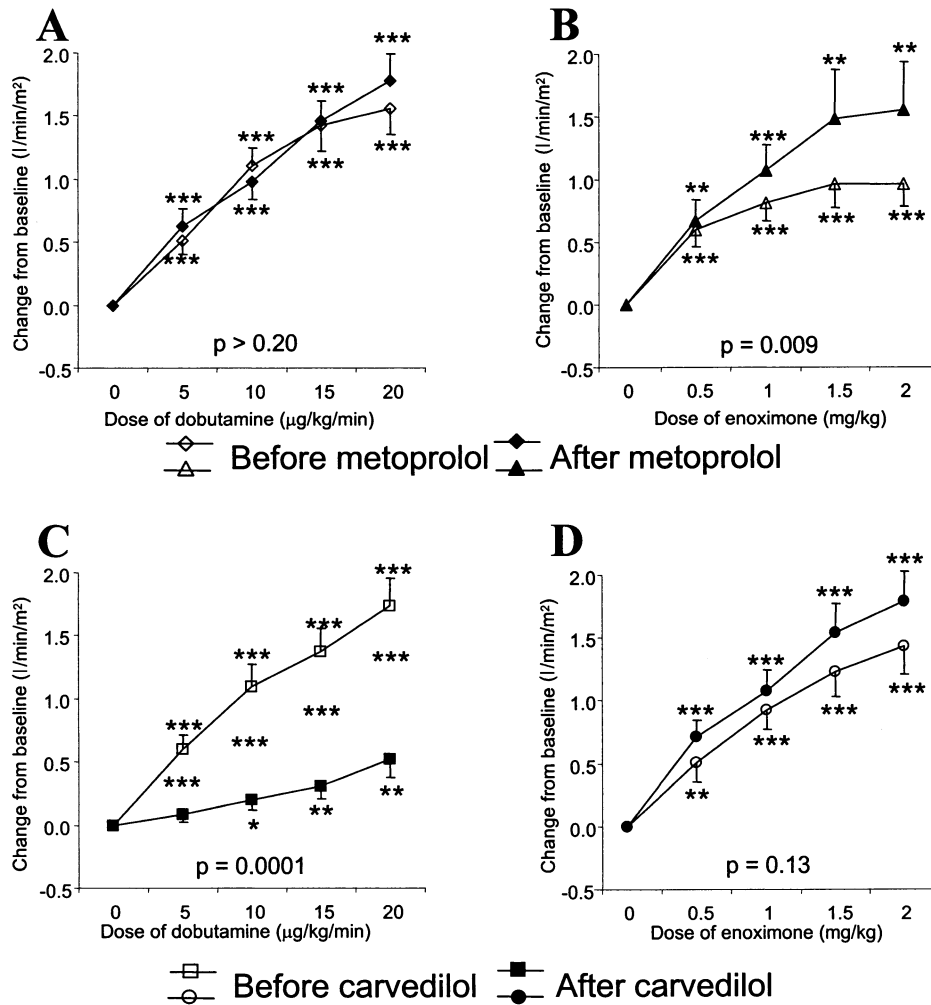


Figure 1. Absolute changes (mean \pm SEM) from baseline in cardiac index after dobutamine (left figures) or enoximone (right figures) administration, before (open symbols) and after (closed symbols) long-term beta-blocker treatment with metoprolol (upper figures) or carvedilol (lower figures). Asterisks immediately above or below the standard error bars indicate significance of dose-specific differences from baseline. Asterisks between the dose-response curves indicate significance of dose-specific differences in the changes from baseline between before and after beta-blocker therapy. Significance values at the bottom of each graph indicate differences between the slopes of the dose response curves before and after metoprolol or carvedilol treatment. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

crease in CI, HR, and SVI and a decrease in ventricular filling pressures (15,16,18). The SVR and PVR also showed a dose-dependent decline, mainly related to the increase in the CI as the α_1 -agonist vasoconstrictive activity of dobutamine is counteracted by its peripheral β_2 -receptor-mediated vasodilating action (16).

Consistent with previous data (14), metoprolol only slightly affected the hemodynamic response to dobutamine infusion. This may be explained by many mechanisms. First, long-term metoprolol therapy may increase the β_1 -adrenergic receptors density and improve beta-adrenergic signal transduction mechanisms, for instance, through the inhibition of the beta-adrenergic receptor kinase or down-regulation in G_{ai} (12,13,18,20). These adjustments may sensitize the heart to β_1 -adrenergic stimulation so that,

when metoprolol is removed from the beta-receptors by mass action, the dobutamine response is preserved or even accentuated. Second, dobutamine has reasonably high affinity for myocardial β_2 -adrenergic receptors (15,16), which have significant inotropic and chronotropic effects and are left unoccupied by the selective β_1 -antagonist metoprolol. In addition, during the chronic administration of β_1 -selective agents such as metoprolol, myocardial β_2 -receptors exhibit improved coupling to intracellular signal transduction mechanisms, through cross-regulation (23). On the other hand, the slight reduction in the response of the PWP and PAP to dobutamine infusion that was observed after metoprolol therapy was likely related to β_1 -receptor occupancy by metoprolol, and is consistent with a slight inhibition of the inotropic response to the β_1 -agonist effects of dobutamine.

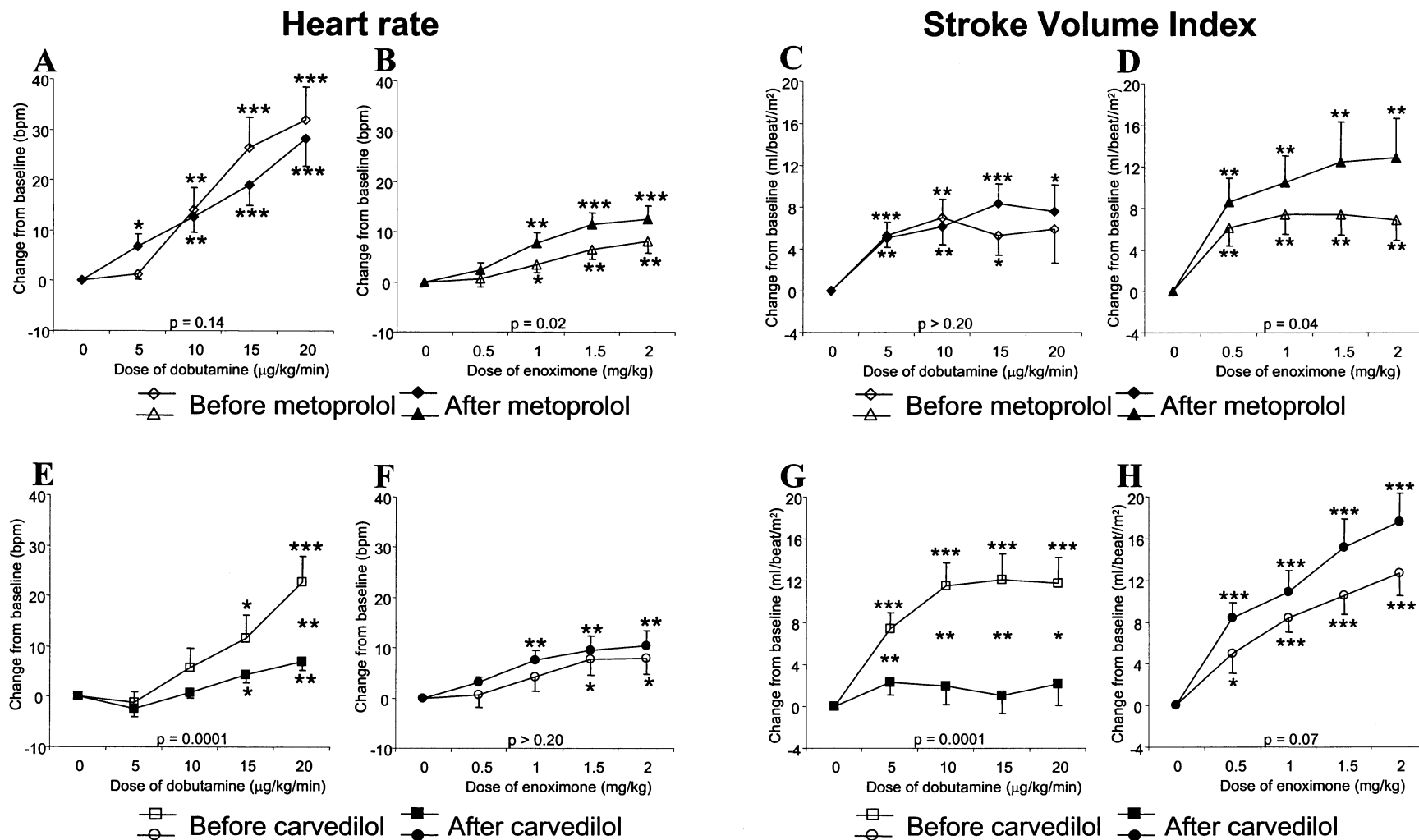


Figure 2. Absolute changes (mean ± SEM) from baseline in heart rate and stroke volume index after dobutamine or enoximone administration, before (open symbols) and after (closed symbols) long-term beta-blocker treatment with metoprolol (upper figures) or carvedilol (lower figures). Significance of symbols as in Figure 1.

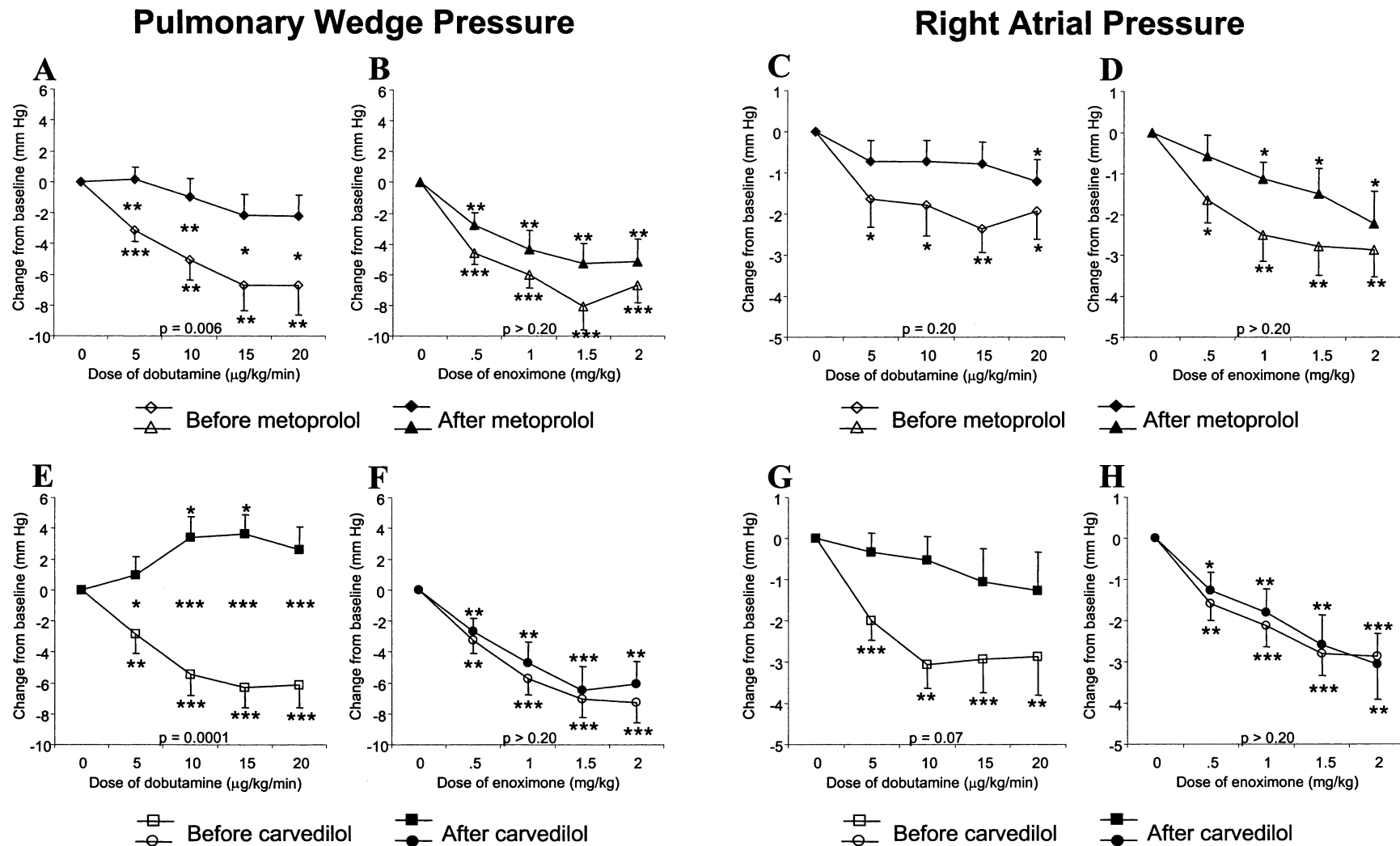


Figure 3. Absolute changes (mean \pm SEM) from baseline in the pulmonary wedge pressure and right atrial pressure after dobutamine or enoximone administration before (open symbols) and after (closed symbols) long-term beta-blocker treatment with metoprolol (upper figures) or carvedilol (lower figures). Significance of symbols as in Figure 1.

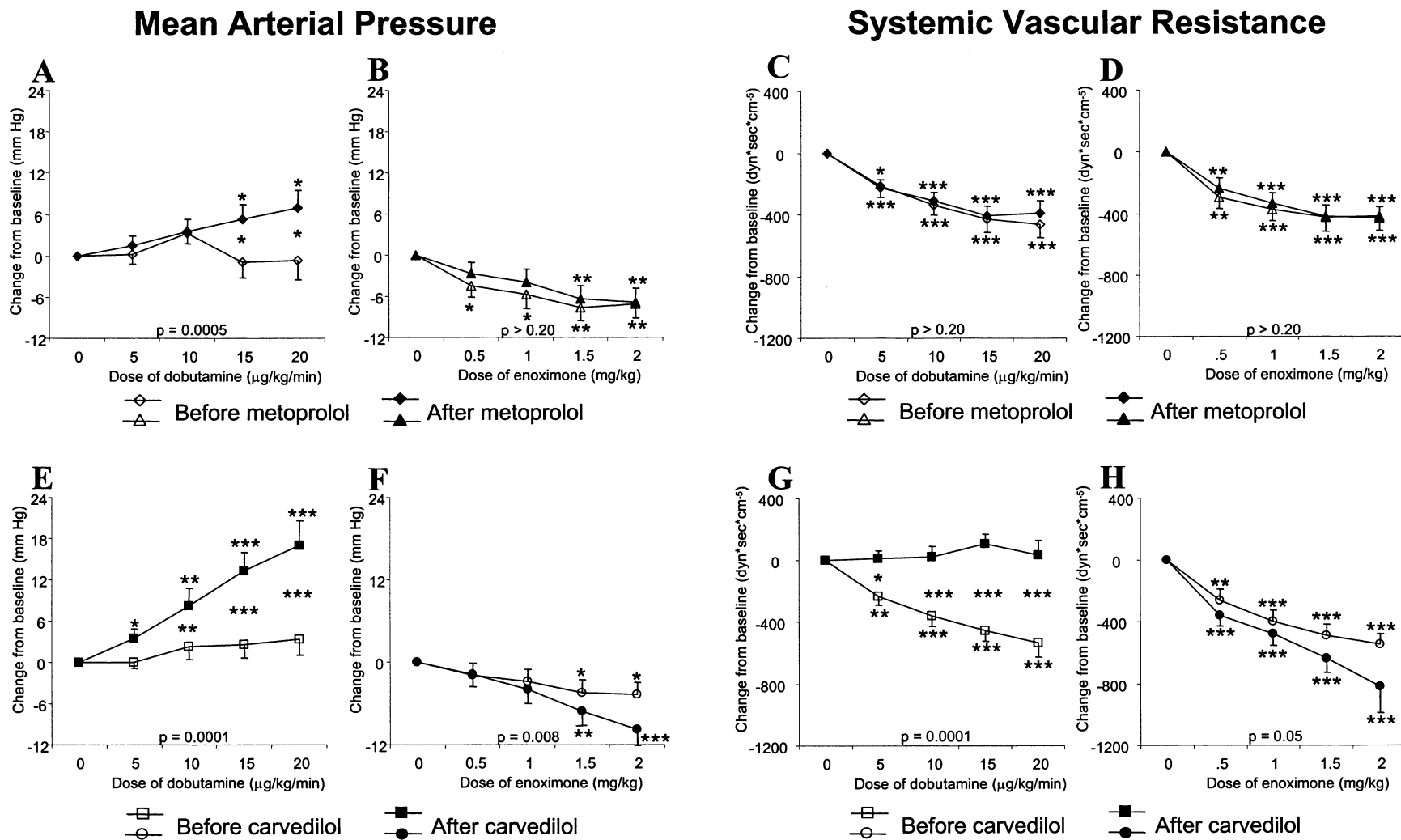


Figure 4. Absolute changes (mean ± SEM) from baseline in the mean arterial pressure and systemic vascular resistance after dobutamine or enoximone administration before (open symbols) and after (closed symbols) long-term beta-blocker treatment with metoprolol (upper figures) or carvedilol (lower figures). Significance of symbols as in Figure 1.

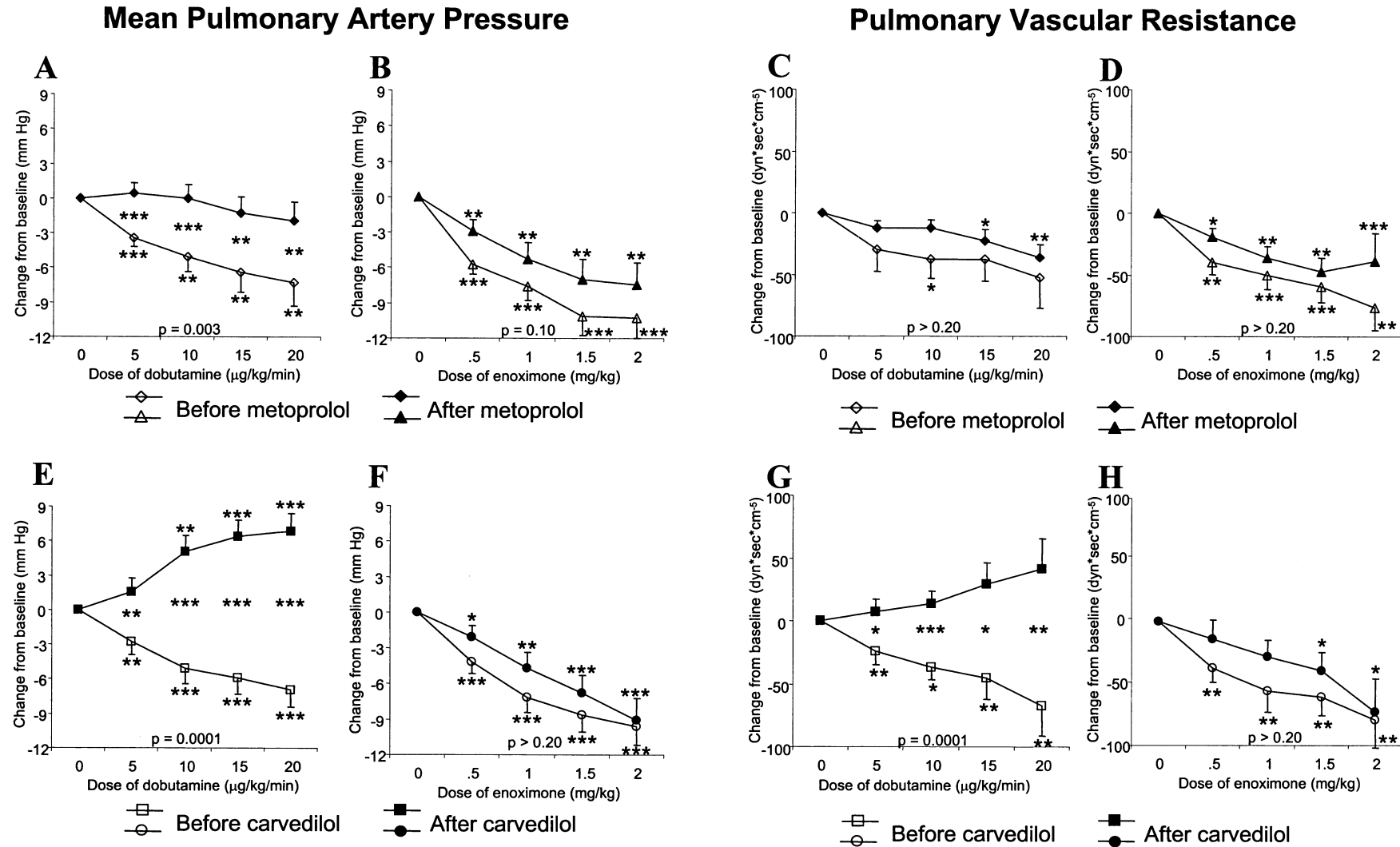


Figure 5. Absolute changes (mean \pm SEM) from baseline in the mean pulmonary artery pressure and pulmonary vascular resistance after dobutamine or enoximone administration before (open symbols) and after (closed symbols) long-term beta-blocker treatment with metoprolol (upper figures) or carvedilol (lower figures). Significance of symbols as in Figure 1.

Dobutamine-carvedilol interaction. Unlike metoprolol, carvedilol profoundly affected the hemodynamic responses to dobutamine. The increases in the CI, HR, and SVI produced by the baseline dobutamine infusion were almost completely inhibited after carvedilol administration. This striking difference between the effects of the two beta-blockers may be ascribed to their different mechanisms of action. Unlike metoprolol, carvedilol does not cause operational beta₁-adrenergic receptor upregulation and also blocks beta₂-adrenergic receptors (21). These properties, although potentially useful in the long-term (22), may cause a greater inhibition of the effects of dobutamine. In addition to its more comprehensive antiadrenergic action, carvedilol also exhibits "tight binding" to beta-adrenergic receptors, making it more difficult for an agonist to displace it (26).

Concomitant carvedilol therapy also affected the dobutamine vascular resistance responses. In contrast with the decreases in SVR and PVR observed in patients treated with metoprolol, dobutamine infusion was associated with a dose-dependent increase in SVR and PVR in carvedilol-treated subjects. This effect has also been described in previous studies (12,14), and may be explained by persistent blockade of vascular beta₂-adrenergic receptors, but not alpha₁-adrenergic receptors, by carvedilol. In fact, carvedilol has a greater dissociation constant for alpha₁- compared with beta₁-adrenergic receptors (21). In addition, the alpha₁-antagonist activity of carvedilol tends to decrease during long-term treatment, similarly to that shown with pure alpha₁-adrenergic antagonists in the patients with HF (27). The persistent blockade of the beta₁- and the beta₂-adrenergic receptors with a concomitant stimulation of the peripheral alpha₁-adrenergic receptors, thus, may explain the increase in the peripheral vascular resistance and PVR caused by dobutamine after long-term carvedilol administration.

Enoximone-beta-blocker interactions. In contrast with dobutamine, the hemodynamic responses to enoximone were less affected and, in the case of some parameters, even enhanced after long-term beta-blockade with either metoprolol or carvedilol. These data are in accordance with previous studies showing the favorable hemodynamic effects of milrinone administration during concomitant carvedilol treatment (12,14). The maintenance of the effects of the PDE inhibitors during carvedilol therapy is consistent with their mechanism of action, which is distal to and independent of occupancy of the beta-adrenergic receptors (15,16,19). These results also support the potential utility of combined therapy with a beta-blocker and a PDE inhibitor when it is necessary to improve hemodynamics while maintaining the long-term beneficial effects of beta-blockade in patients with advanced HF (28-30).

Conclusions. In conclusion, our study shows that the hemodynamic response to dobutamine may be influenced by the type of concomitant beta-blocker therapy. Prior and ongoing metoprolol therapy was only associated with an attenuation of the decrease in PWP and PAP produced by

dobutamine infusion. In contrast with carvedilol treatment, the administration of dobutamine was associated with an almost complete inhibition of the increases in CI, HR, and SVI, and a tendency to a increase, rather than decrease, in MAP, SVR, PWP, PAP, and PVR. In marked contrast with dobutamine, the hemodynamic response to enoximone was not significantly inhibited by either concomitantly administered beta-blocking agent, and some responses were enhanced. These data favor the use of a PDE inhibitor over dobutamine when it is necessary to administer an inotropic agent to a patient on beta-blockade, particularly carvedilol.

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REFERENCES

1. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or nonischemic dilated cardiomyopathy. *Am J Cardiol* 1990;66:1348-54.
2. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med* 2000;343:246-53.
3. Slawsky MT, Colucci WS, Gottlieb SS, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. *Circulation* 2000;102:2222-7.
4. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. *Am Heart J* 1998;135:S293-309.
5. Bristow MR. Management of heart failure. In: Braunwald E, Zipes DP, Libby P, editors. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA: W.B. Saunders Company, 2001:635-51.
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-55.
7. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
8. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
9. Macdonald PS, Keogh AM, Aboyoun CL, Lund M, Amor R, McCaffrey DJ. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. *J Am Coll Cardiol* 1999;33:924-31.
10. Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. *J Am Coll Cardiol* 2000;35:45-50.
11. De Marco T, Chatterjee K. Phosphodiesterase inhibitors in refractory heart failure: bridge to beta-blockade? *J Am Coll Cardiol* 1998;31:1341-3.
12. Lowes BD, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. *Clin Cardiol* 2000;23 Suppl 3:III11-6.
13. Bohm M, Deutsch HJ, Hartmann D, Rosee KL, Stablein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. *J Am Coll Cardiol* 1997;30:992-6.
14. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone vs. dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol* 2001;81:141-9.
15. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure: mechanisms of action and recent clinical developments. *N Engl J Med* 1986;314:290-9.
16. Leier CV, Binkley PF. Parenteral inotropic support for advanced congestive heart failure. *Prog Cardiovasc Dis* 1998;41:207-24.
17. Wollmering MM, Wiechmann RJ, Port JD, Hershberger RE, Focaccio A, Bristow MR. Dobutamine is a partial agonist with an intrinsic

- activity of 0.5 in human myocardium (abstr). *J Am Coll Cardiol* 1991;17:283A.
18. Fowles MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Assessment of the beta-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and sub-sensitivity to agonist response. *Circulation* 1986;74:1290-302.
 19. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation* 1986;73 Suppl III:III175-83.
 20. Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation* 1996;94:2817-25.
 21. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101:558-69.
 22. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation* 2000;102:546-51.
 23. Hall JA, Kaumann AJ, Brown MJ. Selective beta₁-adrenoceptor blockade enhances positive inotropic responses to endogenous catecholamines mediated through beta₂-adrenoceptors in human atrial myocardium. *Circ Res* 1990;66:1610-23.
 24. Winer BJ. Design and analysis of factorial experiments. In: *Statistical Principles in Experimental Design*. 2nd ed. New York, NY: McGraw-Hill, 1971:366-71.
 25. Neter J, Wasserman W, Kutner MH. Repeated measures and related designs. In: *Applied Linear Statistical Models*. 3rd ed. Burr Ridge, IL: Irwin, 1990:1066-72.
 26. Asano K, Zisman LS, Yoshikawa T, Headley V, Bristow MR, Port JD. Bucindolol, a nonselective beta₁- and beta₂-adrenergic receptor antagonist, decreases beta-adrenergic receptor density in cultured embryonic chick cardiac myocyte membranes. *J Cardiovasc Pharmacol* 2001;37:678-91.
 27. Metra M, Nardi M, Giubbini R, Dei Cas L. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1994;24:1678-87.
 28. Shaker SF, Abraham WT, Gilbert EM, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol* 1998;31:1336-40.
 29. Yoshikawa T, Baba A, Suzuki M, et al. Effectiveness of carvedilol alone versus carvedilol + pimobendan for severe congestive heart failure. *Am J Cardiol* 2000;85:1495-7.
 30. Kumar A, Choudhary G, Antonio C, et al. Carvedilol titration in patients with congestive heart failure receiving inotropic therapy. *Am Heart J* 2001;142:512-5.