EXPERIMENTAL STUDIES

Effect of Carvedilol in Comparison With Metoprolol on Myocardial Collagen Postinfarction

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OBJECTIVES	We sought to compare the effects of two different beta-blockers, carvedilol and metoprolol, to an angiotensin-converting enzyme (ACE) inhibitor (captopril) on myocardial collagen deposition during healing and ventricular remodeling after myocardial infarction (MI).
BACKGROUND	Beta-adrenergic blockade has been shown to be beneficial post-MI and in chronic heart failure. Carvedilol is a new-generation vasodilating beta-blocker with additional alpha1-adrenoceptor antagonism and an antiproliferative action, but it is not known if it is more beneficial than standard selective beta-blockers.
METHODS	Using a rat model of MI, induced by left coronary ligation, we studied the effects of 11 weeks of therapy with oral carvedilol, metoprolol or captopril on hemodynamics, tissue weights, collagen volume fraction and hydroxyproline content.
RESULTS	Both beta-blockers caused similar decreases in heart rate and LVEDP compared with untreated post-MI rats. At equivalent beta-adrenoceptor blocking doses, however, carvedilol, but not metoprolol, attenuated the increase in collagen content in noninfarcted regions and prevented the increase in right ventricular weight/body weight (all $p < 0.05$), and its effect was similar to captopril. Metoprolol treatment tended to increase right ventricular weight and heart weight ($p < 0.05$). There were no differences in infarct size between the groups.
CONCLUSIONS	Long-term treatment with both beta-blockers, as well as an ACE inhibitor, benefited the healing process in rats post-MI. At equivalent myocardial beta-adrenoceptor blocking doses, however, carvedilol significantly reduced myocardial collagen in the noninfarcted myocardium and cardiac hypertrophy in the right ventricle, whereas metoprolol had no effect on myocardial collagen deposition. (J Am Coll Cardiol 2000;36:276–81) © 2000 by the American College of Cardiology

Since the early study in Sweden in 1975 (1), the possibility that long-term therapy with beta-blockers might produce hemodynamic and clinical benefit has been increasingly recognized (2–4). The most commonly used beta-blocker has been metoprolol, a traditional beta1-selective adrenoceptor agent (1–5). Carvedilol is a new-generation vasodilating beta-adrenergic antagonist with additional alpha1-adrenoceptor antagonist activity introduced for the treatment of mild to moderate hypertension, and it is currently being evaluated in clinical trials in patients with heart failure (6,7). However, there is debate whether the nonselective beta- and alpha-blockade and ancillary antiproliferative properties of carvedilol offer advantages over traditional beta1-selective agents (8).

The amount of myocardial collagen deposition in infarcted and noninfarcted regions during healing after myocardial infarction (MI) influences and is integral to the process of ventricular remodeling (9). Excessive accumulation of myocardial collagen may result in rigidity of the myocardium and severely impair relaxation (10,11). In animal studies, carvedilol has been shown to have many additional properties, including vasodilation mediated by alpha1-adrenoceptor antagonism, antioxidant, antiproliferative activities and reduction of infarct size in hearts with acute MI (12–14). However, there is little information concerning the effects of long-term beta-blockade by carvedilol on myocardial collagen deposition post-MI. In this study, we have investigated the effect of long-term treatment with carvedilol and metoprolol on myocardial collagen deposition, in comparison with ACE inhibitor therapy during healing and ventricular remodeling after coronary ligation in rats.

METHODS

Experimental infarction. Left ventricular (LV) infarction was induced by the method of Selye et al. (15). Male Sprague-Dawley rats weighing 200 to 250 g were anesthetized with sodium pentobarbital (30 mg/kg, i.p.), and ventilated by positive pressure through an animal respirator (Phipps and Bird, Inc., Richmond, Virginia). A left thoracotomy was performed in the fifth or sixth intercostal space, and the left coronary artery was ligated near its origin. The chest was closed and the rat was allowed to recover. We experienced a 45% mortality rate within 48 h after this procedure.

Abbreviations and Acronyms

CVF = collagen volume fraction
DMSO = dimethy sulphoxide
IA = infarcted area
LV = left ventricular
LVEDP = left ventricular end-diastolic pressure
MAP = mean arterial pressure
MI = myocardial infarction
NIA = noninfarcted area
RV = right ventricular

Drug administration. Carvedilol was provided by Boehringer Mannheim (Mannheim, Germany), and was dissolved in a small volume of dimethy sulphoxide (DMSO) and diluted with 1% acetic acid in drinking water. The final concentration of DMSO was less than 1%. The ACE inhibitor used in the present study was captopril. Metoprolol and captopril were purchased from Sigma Chemical Co. (St. Louis, Missouri), and were dissolved in drinking water. In pilot studies, we demonstrated that the rats with MI treated with carvedilol at a dose of 1.2 g/liter in drinking water containing 1% DMSO and 1% acetic acid (approximate dose of 150 mg/kg/day) for four weeks demonstrated a 22-fold rightward shift of the isoprenaline pressure-response curve (log EC_{50} -6.0 ± 0.1 $\mu g/kg$ in carvedilol-treated rats, n = 4, vs. -7.4 ± 0.2 in untreated rats with MI, n = 4 p < 0.05), and 18% reduction on baseline heart rate (325 ± 10 in carvedilol-treated rats, n = 4 vs. 397 ± 8 beats/min in untreated rats with MI, n = 4, p < 0.05). We also confirmed that a similar overall beta-blockade was achieved by metoprolol at a dose of 2 g/liter in drinking water (approximate dose of 250 mg/kg/day), producing an identical reduction of 17% in baseline heart rate (335 ± 6 beats/min in metoprolol-treated rats, n = 4). In the present study, therefore, the doses of drugs were 1.2 g/liter carvedilol, and 2 g/liter metoprolol in drinking water. The dose of captopril was 2 g/liter in drinking water, as used by Pfeffer et al. (11).

Treatment protocol. Seven days after coronary ligation, the surviving rats with MI were randomized into four groups. The first group (10 rats) received carvedilol (MI-carv). The second group (10 rats) received metoprolol (MI-met). The third group (10 rats) received captopril (MI-cap). In the fourth group (18 rats), 12 rats received tap water and 6 rats received tap water contained 1% DMSO and 1% acetic acid (MI-V). Ten sham-operated rats received tap water as a control group (sham-V). To avoid the early risk induced by beta-blockers on the rats with MI, the two beta-blockers were administrated gradually as follows: a quarter of the full dosage within the first week, a half within the second week, and from the third week full dosage as described above was given. The treatment was continued for 11 weeks (12 weeks after operation) in all groups. All rats were housed under identical conditions in a 12-h light/dark cycle and given food and water ad libitum.

Hemodynamic studies. At 12 weeks after coronary ligation, rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and the mean arterial pressure (MAP) was measured via a cannula (a saline-filled PE 50 tubing), which was inserted into the right carotid artery and connected to a pressure transducer (model DX-60; Nihon Kohden, Tokyo, Japan). The heart rate measurement was triggered by the change in systemic pressure (model AT-601G; Nihon Kohden). After MAP and heart rate were monitored, the cannula was briefly advanced to the left ventricle for evaluation of the left ventricular end-diastolic pressure (LVEDP).

Infarct size measurement. After completion of the hemodynamic measurements, the hearts were arrested in diastole with intravenous 30 mM potassium chloride. The hearts were then removed, submersed in saline and the ventricles were divided from apex to base into four transverse sections (2.0 to 2.2 mm thick), identified as levels 1, 2, 3, and 4, respectively, and the right and the left ventricle of each level were separated. Levels 1 and 3 were fixed in 10% formalin and embedded in paraffin for the determination of infarct size and collagen volume fraction (CVF). Level 2 was immediately frozen for the measurement of hydroxyproline content.

Paraffin sections (10 μm) from levels 1 and 3 of the left ventricle were stained with hematoxyline and eosin, and projected into a color imaging analysis system (Q500MC; Leica Cambridge Ltd., Cambridge, England) at a magnification of approximately ×10 and traced, and the extent of the infarcted area (IA) was marked. A planimeter was used to obtain the mean of scar endocardial and epicardial circumferences of the two slices, the two were summed and infarct size was expressed as a percentage of means left ventricular (LV) circumference.

Determination of CVF. Paraffin sections (4 μm) of level 1 from the left and the right ventricle were stained with the collagen-specific dye Sirius red F3BA (0.5% in saturated aqueous picric acid) according to the method of Junqueira et al. (16). Three sections per animal and 16 fields per section were scanned and computerized with a Leica Q500MC digital image analyzer at a magnification of ×40. The sections from all groups were simultaneously stained in one batch. Collagen volume fraction was obtained from the ratio of the connective tissue areas divided by the total tissue area within the same microscopic field. The interstitial CVF in the noninfarcted area (NIA) of the left ventricle, as well as in the right ventricle, was estimated using the central part of the myocardium, excluding the subendocardium and epicardium, because the profuse collagen tissue in the subendocardium and epicardial coronary vessels interfered with the accurate quantitation of myocardial interstitial collagen content. The CVF was expressed as the mean $\pm$ SE of all measurements from three sections per animal. The collagen-positive areas from all sections were determined by a single investigator who was unaware of the experimental groups.

Table 1. Effects of Long-Term Treatment With Carvedilol, Metoprolol and Captopril on Infarct Size and Cardiac Tissue Weights in Rats With MI

Parameters	Sham-V	MI-V	MI-carvedilol	MI-metoprolol	MI-captopril
N	10	16	7	9	7
Infarct size (%)	0	40 ± 6%	38 ± 4%	41 ± 4%	39 ± 3%
BW (g)	425 ± 20	436 ± 14	450 ± 14	441 ± 14	411 ± 10
HW (g)	1.62 ± 0.06	1.77 ± 0.13	1.84 ± 0.08	2.28 ± 0.12*	1.61 ± 0.08
LV wt (g)	1.02 ± 0.04	1.16 ± 0.07	1.26 ± 0.06	1.32 ± 0.05	1.0 ± 0.03
RV wt (g)	0.25 ± 0.01*	0.47 ± 0.04	0.31 ± 0.02*	0.43 ± 0.05	0.28 ± 0.02*
HW/BW (g/kg)	3.79 ± 0.16	4.05 ± 0.25	4.31 ± 0.24	4.40 ± 0.17	3.44 ± 0.21
LV/BW (g/kg)	2.40 ± 0.07	2.67 ± 0.17	2.73 ± 0.13	2.71 ± 0.08	2.41 ± 0.12
RV/BW (g/kg)	0.59 ± 0.02*	1.07 ± 0.10	0.67 ± 0.04*	0.92 ± 0.08	0.67 ± 0.04*

Values are mean ± SE. *$p < 0.05$ versus the untreated rats with MI.
BW = body weight; HW = heart weight; LV wt = left ventricular weight; MI = myocardial infarction; N = number of animals; RV wt = right ventricular weight; V = vehicle only. Rat groups are as in text.

Quantification of hydroxyproline content. The right ventricle, the IA of the left ventricle and the interventricular septum were analyzed separately. Tissue samples (25 to 50 mg) were lyophilized for 8 h to a constant weight. Tissue dry weights were determined and the samples were flushed with nitrogen and sealed under vacuum with 6N HCl (1 ml/10 mg dry tissue weight) before boiling for 24 h at 130°C. The samples were then filtered, vacuum dried and dissolved in 500 μm water. After the pH was raised to 6, the hydroxyproline content was determined according to the method of Woessnser (17). The data are expressed as milligrams hydroxyproline per gram dry tissue weight.

Statistical analysis. All grouped data are expressed as mean ± SE. Comparison between groups was performed by one-way analysis of variance followed by Bonferroni/Dunnett's test. Differences were considered significant at $p < 0.05$.

RESULTS

None of the animals died during the 11-week treatment protocol. The rats with measured infarct sizes less than 20% of LV circumference were excluded from the study (two rats in MI-V, three rats in MI-carv, one rat in MI-met and three rats in MI-cap). One percent DMSO and 1% acetic acid in tap water did not influent tissue weight, hemodynamic parameters or collagen content in rats with MI.

Tissue weight and infarct size. EFFECT OF MI. The right ventricular (RV) weight and the ratio of RV weight/body weight were markedly increased in the rats with MI compared with the sham-operated rats (Table 1). The total heart weight and LV weight in the rats with MI were not different from the sham-operated rats. The mean infarct size in the rats with MI was 40% of LV circumference.

EFFECT OF TREATMENT. Carvedilol, as well as captopril, significantly attenuated the increase in RV weight and the ratio of RV weight/body weight in the rats with MI, whereas metoprolol did not. There were 7% and 10% increases in LV weight in carvedilol- and metoprolol-treated groups, respectively. However, these increases were not statistically significant. There were no differences in the ratio of LV weight/body weight between beta-blocker-treated groups and other groups. Treatment with metoprolol showed a significant increase in heart weight, although the ratio of heart weight/body weight did not reach a significant difference.

Hemodynamic parameters. EFFECT OF MI. The rats with MI had evidence of chronic compensated heart failure, including a lower MAP, and a higher LVEDP compared with the sham-operated rats (Table 2). There is no difference in heart rate between the sham-operated rats and the rats with MI.

EFFECT OF TREATMENT. Carvedilol, metoprolol and captopril prevented the increase of LVEDP observed in the untreated rats with MI, but had no effect on MAP. Carvedilol and metoprolol caused a similar decline in heart rate, whereas captopril had no effect.

CVF. EFFECT OF MI. In the rats with MI, a ninefold increase in CVF (2.7 ± 0.1 in sham-V vs. 34 ± 4% in MI-V, $p < 0.01$) was found in the IA. A 2.0-fold and a

Table 2. Effects of Long-Term Treatment With Carvedilol, Metoprolol and Captopril on Hemodynamic Parameters in Rats with MI

Parameters	Sham-V	MI-V	MI-carvedilol	MI-metoprolol	MI-captopril
N	10	16	7	9	7
MAP (mm Hg)	131 ± 3*	108 ± 3	105 ± 10	117 ± 5	92 ± 8
LVEDP (mm Hg)	1.6 ± 0.8*	15 ± 3.9	4.0 ± 0.7*	3.9 ± 0.7*	3.6 ± 0.8
Heart rate (beats/min)	401 ± 8	395 ± 9	328 ± 17*	331 ± 11*	403 ± 23

Values are mean ± SE. *$p < 0.05$ versus the untreated rats with MI.
LVEDP = ventricular end-diastolic pressure; MAP = mean arterial pressure; N = indicates number of rats; V = vehicle only. Rat groups are as in text.
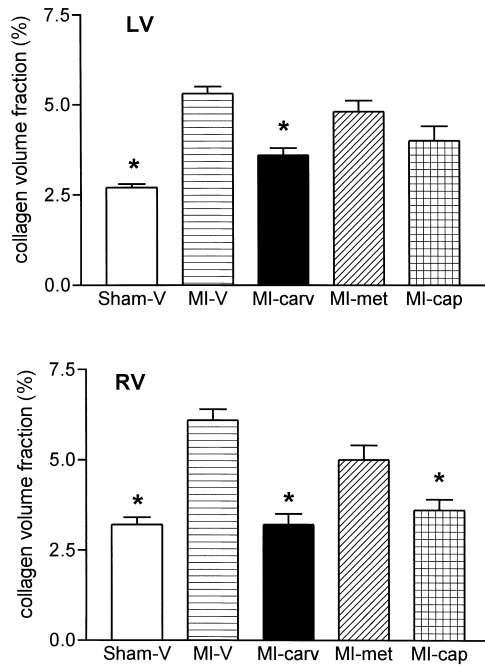
Figure 1. Effects of long-term treatment with carvedilol (Carv), metoprolol (Met) and captopril (Cap) on collagen volume fraction in the noninfarcted area of the left ventricle **(top)** and the right ventricle **(bottom)** post-MI compared with untreated rats with MI taking vehicle (V) and sham-operated rats. Values are mean ± SE. *p < 0.05 versus untreated rats with MI. Rat groups are as in text. Numbers of animals in each group are as in Table 1.
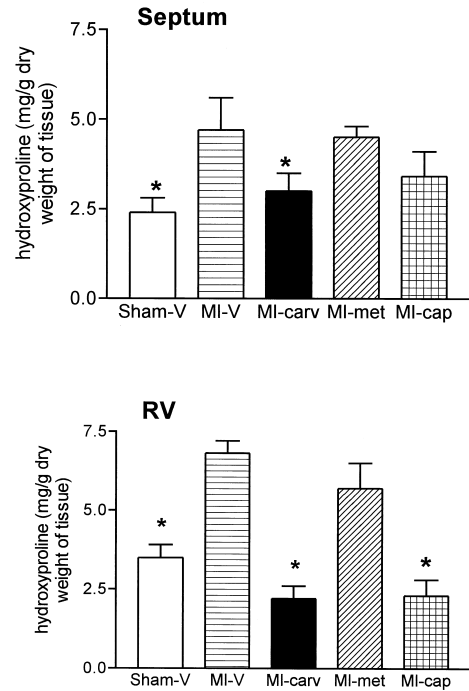

Figure 2. Effects of long-term treatment with carvedilol (Carv), metoprolol (Met) and captopril (Cap) on hydroxyproline contents in the interventricular septum **(top)** and the right ventricle **(bottom)** post-MI compared with untreated rats with MI taking vehicle (V) and sham-operated rats. Values are mean ± SE. *p < 0.05 versus untreated rats with MI. Rat groups are as in text. Numbers of animals in each group are as in Table 1.

2.2-fold elevation in CVF were found in the NIA of the left ventricle and the RV of the rats with MI, respectively (Fig. 1).

EFFECT OF TREATMENT. Carvedilol, metoprolol and captopril had no effect on CVF of the IA (36 ± 4 in MI-carv, 37 ± 5 in MI-met, 32 ± 5% in MI-cap, p = NS). Carvedilol completely inhibited the increased CVF in the RV and partly inhibited the increased CVF in the NIA, whereas metoprolol had no effect on CVF in both the NIA and the RV (Fig. 1). Captopril completely prevented the increase in CVF in the RV and slightly reduced the increased CVF in the NIA.

Hydroxyproline content. EFFECT OF MI. In the rats with MI, an 11-fold increase in hydroxyproline content (2.4 ± 0.4 in sham-V vs. 18 ± 8 mg/g dry tissue in MI-V, p < 0.01) was found in the IA compared with the sham-operated rats. Two-fold increases in hydroxyproline content were found in the interventricular septum and the RV.

EFFECT OF TREATMENT. Neither carvedilol, metoprolol nor captopril had any effect on the hydroxyproline content in the IA (26 ± 7 in MI-carv, 33 ± 9 in MI-met, 32 ± 6 mg/g dry tissue in MI-cap, p = NS). Carvedilol significantly reduced the hydroxyproline content in the interventricular septum and the RV, whereas metoprolol had no effect on the hydroxyproline content in both the interventricular septum and the RV (Fig. 2). Captopril reduced the

hydroxyproline content in the RV, but not in the interventricular septum.

DISCUSSION

The hemodynamic effects of long-term treatment with beta-blockers in patients with chronic heart failure are a lower heart rate, a drop in systolic blood pressure, a reduction of LVEDP and an increase in ejection fraction (18–20). In a canine (21) and rat (22) model of chronic heart failure, metoprolol produced a decrease in LVEDP and an increase in left atrial shortening. To our knowledge, to date, there are no data on the effect of long-term treatment with carvedilol on animal models of heart failure. Our data indicated that in rats with chronic heart failure after MI, hemodynamic performance was preserved during long-term treatment with both cavedilol and metoprolol, which are consistent with previous studies in patients with chronic heart failure.

The major finding of the present study is that at comparable beta-adrenoceptor blocking doses, there was a marked difference between the two beta-blockers with respect to their effect on myocardial collagen deposition. The present study is the first report demonstrating a different effect of carvedilol and metoprolol on myocardial collagen.

Mechanism of carvedilol's effect on collagen. The exact mechanisms that account for the marked discrepancy between the two beta-blockers on myocardial collagen are

likely to be complex. It is unlikely that this difference is due to their different beta1-blocking potencies, or any regulator factors that come into play by hemodynamic changes induced by beta-blocker treatment, because treatment with carvedilol decreased heart rate and LVEDP to the same extent as treatment with metoprolol. In the myocardium, growth-promoting mechanisms include adrenoceptors (beta1, beta2, alpha1), angiotensin II receptor and endothelin 1 (ET1) receptor pathways. Bristow and coworkers' work indicates that there are differences in adrenoceptor subtype distribution in failing human heart as compared with that in nonfailing human heart (23,24). The nonfailing myocardium is dominated by the beta1-adrenoceptor subtype, whereas failing myocardium exhibits a mixture of receptor subtypes, with beta2- and alpha1-adrenoceptor comprising approximately 50% of the total population. It has been suggested that synthesis of myocardial collagen type I is also regulated by norepinephrine via an indirect effect (25). In the heart, carvedilol in the doses used in clinical practice (50 to 100 mg/day), blocks all three adrenoceptor subtypes (24). The dose of carvedilol used in our study (150 mg/kg/day) was high enough to block all adrenoceptor subtypes. Thus, the alpha1-adrenoceptor blocking activity of carvedilol may provide additional protection beyond that produced by beta-blockade by limiting myocardial collagen formation post-MI. In contrast to our findings, Latini et al. (22) reported that beta-blockade by metoprolol limited myocardial collagen deposition in the same model of heart failure. In their study, however, metoprolol treatment was started two months after coronary ligation, and treatment continued for only one month. The conflicting results may in part be explained by the different treatment regimens. Our data support the hypothesis that carvedilol exerts a vasodilator effect that could enhance its efficacy and reduce the risks of worsening heart failure during initiation of therapy, in a fashion similar to that seen with angiotensin-converting enzyme inhibitors.

Effect on RV hypertrophy. Despite the reduction of LVEDP in rats with MI after metoprolol treatment, the increased RV weight was not reduced by metoprolol in contrast to carvedilol and captopril. This finding suggests that the mechanisms underlying RV myocardial hypertrophy in untreated rats with MI and metoprolol-treated rats are different. When LV filling pressure is elevated after MI, RV systolic pressure increases to maintain the pressure gradient across the pulmonary bed. Hence, the elevation of LVEDP produced by extensive infarction would appear to be the cause of the RV hypertrophy (26). In the metoprolol-treated rats, however, the increased RV weight/body weight appeared to be independent of any pressor effects and probably was due to the increased adrenergic stimulation found in the failing heart (27) operating through beta2, and alpha1-adrenoceptor pathways. In addition, the increase in myocardial beta1-adrenoceptor density during long-term metoprolol therapy may be relevant (28). In contrast to metoprolol, carvedilol does not upregulate downregulated

beta1-receptors (29). A similar finding was reported in a rat model using beta-blockade with propranolol, which also resulted in an increased LV weight/body weight, but did not normalize the increase in the ratio of RV weight/body weight (30).

Effect on LV hypertrophy. In our experiment, a slight increase in LV weight was seen in both carvedilol- (7%) and metoprolol-treated rats (10%), compared with that in captopril-treated and untreated rats. After MI, the LV responds to loss of myocardial tissue and function with hypertrophy of the remaining viable myocardium, remodeling and increasing ventricular volume so that stroke volume can be maintained. The fact that in our study LV weight remained unchanged despite loss of myocardium from infarction and development of a thin scar in captopril-treated and untreated rats, compared with that in sham-operated rats, suggests that hypertrophy had occurred in the LV. The further increases in LV weight in both carvedilol- and metoprolol-treated rats probably were caused by the decrease in heart rate by beta-blockade. In our study, we did not examine ventricular volume systematically. However, the decrease in heart rate enhances diastolic filling, which would increase diastolic wall stress and in turn act as a stimulus to increase end-diastolic volume (31). This increase in volume would increase systolic wall stress, which would provide the stimulus to increase cardiac mass, as a means to normalize systolic wall stress (30,32). Because the heart rate changes were similar with the two drugs, this effect is likely to be common to both drugs. But the more complete blockade of adrenergic stimulation by carvedilol may be associated with a greater negative inotropic effect and hence higher ventricular volumes and wall stress. Alternatively, there may be less loss of myocardial cells through apoptosis or ischemia in the carvedilol group, and this may explain the apparent anomaly that LV weight increased while collagen is less with carvedilol treatment.

Other actions of carvedilol. The benefits of carvedilol in the present study may not be entirely explained by its adrenergic blocking properties. Carvedilol also exerts antioxidant effects (12) and acts to reduce the proliferation of vascular smooth muscle in vitro (13). Such effects are potentially of therapeutic value, because heart failure is characterized both by increased formation of oxygen free radicals in the failing heart and by peripheral vascular remodeling.

In summary, we have demonstrated the beneficial effects of long-term treatment with both carvedilol, a new nonselective beta-adrenergic with additional alpha1-adrenergic receptor antagonist activity, and metoprolol, a traditional beta1-selective agent, post-MI in rats. However, at equivalent beta1-adrenoceptor blocking doses, only carvedilol reduced the associated increase in collagen content in the noninfarcted myocardium, and limited the cardiac hypertrophy in infarcted hearts in contrast to metoprolol. These effects appeared to be influenced by specific changes independent of changes in hemodynamics in response to the

long-term beta-blocker treatment, and the mechanism may be related to the inherent difference between the two beta-blockers, such as the alpha1-adrenoceptor antagonism or antioxidant actions of carvedilol. Indeed, we found that carvedilol had favorable effects on preserving heart function after MI, in a manner similar to that seen with standard angiotensin-converting enzyme inhibitor therapy in rats. Our results therefore support the concept that combined beta- and alpha-adrenoreceptor blockade may have more favorable cardioprotective effects on infarcted hearts than selective beta-blockade alone.

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