Comparison of Metoprolol With Low, Middle and High Doses of Carvedilol in Prevention of Postinfarction Left Ventricular Remodeling in Rats

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SUMMARY

The dose-related beneficial effects of carvedilol on survival in heart failure have been verified, however, the effects on left ventricular remodeling (LVRM) after acute myocardial infarction (AMI) have not been defined. This experiment was designed to compare the effects of low, middle, and high doses of carvedilol (LD-car, MD-car, and HD-car) with metoprolol (Meto) in preventing postinfarction LVRM in rats. After the left coronary artery was ligated, 177 surviving female SD rats were randomized to: (1) AMI ($n = 35$), (2) LD-car ($0.1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, $n = 35$), (3) MD-car ($1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, $n = 35$), (4) HD-car ($10 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, $n = 37$) and (5) Meto ($2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, $n = 35$) groups. A sham-operated group ($n = 16$) was also randomly selected. Gastric gavage therapy lasted for 4 weeks. After hemodynamic studies, the rat hearts were fixed and pathologically analyzed. After exclusion of rats which died or had an infarct size $<35\%$ or $>55\%$, complete data were obtained in 69 rats, comprising AMI ($n = 11$), LD-car ($n = 11$), MD-car ($n = 12$), HD-car ($n = 12$), Meto ($n = 11$) and sham ($n = 12$) groups. There were no significant differences in MI size among the five AMI groups ($44.5\text{--}46.3\%$, all $P > 0.05$). Compared with the sham group, left ventricular (LV) end-diastolic pressure (LVEDP), volume (LVV), weight (LVW) and septal thickness (STh) were all significantly increased, while $\pm \text{dp/dt}$ was significantly decreased in the AMI group (all $P < 0.001$). Compared with the AMI group, heart rate was significantly decreased in all except the LD-car treatment groups ($P < 0.05\text{--}0.01$); LVEDP, LVV, LVW, and STh in the four treatment groups were also significantly decreased ($P < 0.05\text{--}0.001$) except LVW and STh in the Meto group (both $P > 0.05$)(LVEDP: 14.5 ± 4.6 , 12.1 ± 2.4 , 7.7 ± 1.9 and 13.0 ± 6.7 mmHg vs 24.1 ± 5.2 mmHg; LVV: 0.82 ± 0.1 , 0.79 ± 0.1 , 0.72 ± 0.1 and 0.72 ± 0.1 mL vs 0.92 ± 0.1 mL; LVW: 666 ± 57 , 622 ± 70 , 589 ± 57 and 699 ± 78 mg vs 730 ± 79 mg; STh: 1.14 ± 0.12 , 1.18 ± 0.21 , 1.19 ± 0.15 and 1.35 ± 0.20 mm vs 1.33 ± 0.29 mm; $P < 0.05\text{--}0.001$); while $\pm \text{dp/dt}$ was significantly increased in each therapy group ($P < 0.05\text{--}0.001$). There were dose-effect relations in LVEDP and LVV in the carvedilol groups. The results indicate that low, middle and high dose carvedilol has dose-related effects in the prevention of

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postinfarction LVRM with respect to volume expansion and segmental hypertrophy in rats, while metoprolol prevents only LV dilatation but not hypertrophy. (Jpn Heart J 2003; 44: 979-988)

Key words: Carvedilol, Metoprolol, Ventricular remodeling, Acute myocardial infarction, Rats

IT is well known that left ventricular remodeling (LVRM) plays a very important role in developing left ventricular dysfunction and heart failure, and is characterized by infarct expansion, hypertrophy of the noninfarcted myocardium, and alteration of left ventricular geometry. Since Waagstein found that β -blockers had beneficial effects on the hemodynamics and prognosis of patients with heart failure in 1975,¹⁾ clinical trials have proven that β -blockers can improve survival²⁻⁶⁾ and ventricular function,⁴⁾ and prevent LVRM⁶⁾ in patients with heart failure. Carvedilol, a third-generation β -blocker, is a unique multiple action drug with nonselective β -blockade, α_1 -blockade, and antioxidant effects. Recent clinical studies have shown that it has beneficial effects on LVRM attenuation in patients with ischemic heart failure⁶⁾ and acute myocardial infarction.^{7,8)} In experimental studies, however, carvedilol did not show any effects on LVRM attenuation after myocardial infarction induced by permanent coronary occlusion,⁹⁾ or only had beneficial effects with respect to reduced myocardial collagen deposition of non-infarcted myocardium and hypertrophy of the right ventricle.¹⁰⁾ Whether carvedilol does have beneficial effects on postinfarction LVRM is still controversial, and needs further verification. With respect to other β -blockers including metoprolol,⁹⁻¹¹⁾ propranolol,^{12,13)} atenolol¹⁴⁾ and bisoprolol,¹⁵⁾ experimental studies have also showed no beneficial effects on LVRM after AMI. Whether or not metoprolol, a commonly used traditional β_1 -blocker, has beneficial effects on postinfarction LVRM is also uncertain. Therefore, the aim of this study was to evaluate the dose-related effects of carvedilol on attenuating LVRM after AMI in rats and to compare its effects with those of metoprolol.

METHODS

Experimental rats and groups: Acute myocardial infarction (AMI) was induced by ligating the left coronary artery in 394 female Sprague-Dawley (SD) rats (body weight: 200-250 g). Twenty-four hours after the operation, the 177 surviving rats were randomized to the following groups: (1) AMI controls ($n = 35$), (2) Low dose ($n = 35$; $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (3) Middle dose ($n = 35$; $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$), and (4) High dose ($n = 37$; $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) carvedilol, and (5) Metoprolol ($n = 35$; 2

mg·kg⁻¹·d⁻¹) groups. Sham-operated rats ($n = 16$) were randomly selected before AMI.

Methods: AMI in rats was induced using a previously described method.¹⁶⁾ The left coronary artery was ligated using a 6-0 proline suture to induce an anterior myocardial infarction. In the sham-operated rats, a suture was tied loosely around the left coronary artery without ligation.

Twenty-four hours after AMI, carvedilol (donated by Roche Pharmaceutical Company) and metoprolol (donated by ASTRA Pharmaceutical Company) were given by direct gastric gavage twice daily in solutions at concentrations of 125 mg%, 12.5 mg%, 1.25 mg% and 25 mg%, respectively. When the solution was delivered in the same volume of 8 mL·kg⁻¹·d⁻¹, it approximated the targeted low, middle, and high doses of carvedilol and metoprolol of the four treatment groups, respectively. AMI controls as well as the sham-operated controls were given the same amount of drinking water at the same time.

Hemodynamic measurement: Four weeks after drug therapy, hemodynamic studies were performed 2-3 hours after the last administration of drug in each group according to the methods described by Pfeffer.¹⁷⁾ After the rat was weighed and anesthetized, the right carotid artery was separated and cannulated with a 20G sheathed needle. After extracting the needle, the proximal end of the sheath was connected to the energy exchanger of an eight-channel physiological recorder via a heparin saline filled plastic tube. After balancing with the air pressure, the ascending aortic systolic pressure (SBP), diastolic pressure (DBP), and mean pressure (MBP) were recorded. Subsequently, the sheath was retrograded into the left ventricle (LV), and the LV systolic pressure (LVSP), end diastolic pressure (LVEDP), and left ventricular pressure maximal rate of rise and fall ($\pm$ dp/dt) were recorded. The heart rate was also simultaneously recorded.

Pathological analysis: After finishing the hemodynamic studies, the rat hearts were arrested in diastole by intravenous injection of 2-3 mL of 10% KCl through the femoral vein. The rat thorax was then rapidly opened and the aortic arch was ligated with the sheath fixed in the ascending aorta. The proximal end of the sheath was connected to an irrigating bottle of 10% formalin, the coronary arteries were continuously perfused for 20-30 minutes with the fixative, and the right atrium was cut to allow the drainage of blood and fixative. Subsequently, the heart was excised and preserved in 10% formalin after the atria and great vessels were trimmed away.

(1) Weighing of heart. The two ventricles were separated by incising the RV along the septum and weighed with an electronic balance. When the LV and RV weights (LVAW and RVAW) were corrected for body weight, their relative weights were calculated (LVRW and RVRW).

(2) Left ventricular volume (LVV) and length of longitudinal axis (L) measurement. Measurements were performed directly with a cutaneous syringe and Vernier calipers. Each heart sample was measured three times and the mean value was used for further data analysis. The coefficients of variability of 3 measurements by one examiner in LVV and L were both 1% ($0.99 \pm 1.00\%$ and $0.89 \pm 0.64\%$, respectively). The intra- and interobserver variabilities were $1.21 \pm 1.61\%$, $1.28 \pm 1.29\%$ for LVV and $0.96 \pm 1.16\%$, $1.34 \pm 1.62\%$ for L, respectively.

(3) LV transverse diameter (D) and infarction size measurement. Perpendicular to L, the LV was midventricularly cut into two parts. The apex half was embedded in paraffin and a $10\ \mu\text{m}$ transverse section was cut from its bottom and mounted on plastic. The plastic was processed by a BHEC microscope-computer colour imaging processor. The septal thickness (STh), and maximum and minimal transverse diameter of LV (D_{max} and D_{min}) were then measured and their geometric mean value was calculated according to the following formula: $D = \sqrt{D_{\text{max}} \times D_{\text{min}}}$. The epicardial and endocardial circumferences as well as the infarcted circumference were also measured, and MI size was calculated according to the following formula: $\text{MI size\%} = \text{infarcted circumference} / [(\text{epicardial circumference} + \text{endocardial circumference}) / 2] \times 100\%$.^{17,18)}

Statistical analysis: All variables are expressed as the mean $\pm$ SD. Differences among groups were assessed by ANOVA and the differences between two groups were assessed by q test. A value of $P < 0.05$ in a two-tailed distribution was considered statistically significant.

RESULTS

After exclusion of rats which died or had a MI size $<35\%$ or $> 55\%$, complete data were obtained for 69 rats from the AMI control ($n = 11$), LD-car ($n = 11$), MD-car ($n = 12$), HD-car ($n = 12$), Meto ($n = 11$), and sham ($n = 12$) groups. There were no significant differences in MI size among the five AMI groups ($P > 0.05$) (Table I).

1. The effects of low, middle and high doses of carvedilol and metoprolol on hemodynamics (Table I)

In the AMI group, LVEDP was significantly increased ($P < 0.001$), SBP, DBP, MBP, and LVSP were significantly decreased ($P < 0.05$ - 0.01), and HR was not changed ($P > 0.05$) compared with the sham-operated group.

In comparison with the AMI group, HR was significantly decreased in all therapy groups ($P < 0.05$ - 0.01) except LD-car ($P > 0.05$), and the effect on HR of MD-car was equivalent to that in the Meto group ($P > 0.05$); LVEDP was significantly decreased in all therapy groups (all $P < 0.001$), with a dose-dependent

effect being observed in the carvedilol groups (higher dosage, better effect, all $P < 0.05$). The effect on LVEDP in the MD-car group was also equivalent to that in the Meto group.

Effects of low, middle, and high doses of carvedilol and metoprolol on LVRM and LV function (Table II)

In the AMI group, LVV, LVAW, LVRW, STh, RVAW, and RVRW all increased significantly (all $P < 0.001$), while $\pm dp/dt$ and $\pm dp/dt/LVSP$ all decreased significantly (all $P < 0.001$) compared to the sham-operated group.

Table I. The Effects of Low, Middle, and High-dose Carvedilol and Metoprolol on Hemodynamics

	Sham (n = 12)	AMI (n = 11)	Metoprolol (n = 11)	Low (n = 11)	Middle (n = 12)	High (n = 12)
Infarct size (%)	0	46.25 $\pm$ 4.58	46.29 $\pm$ 5.37	44.46 $\pm$ 5.01	46.34 $\pm$ 4.59	45.45 $\pm$ 5.75
HR (bpm)	392.25 $\pm$ 37.30	368.18 $\pm$ 46.23	340.91 $\pm$ 27.84*†	372.64 $\pm$ 32.36†	343.58 $\pm$ 20.52 *†§	322.33 $\pm$ 22.26*†§
SBP (mmHg)	128.27 $\pm$ 12.97	108.92 $\pm$ 15.62*	107.50 $\pm$ 21.59*	115.77 $\pm$ 18.78*	105.77 $\pm$ 15.46*	106.67 $\pm$ 14.26*
DBP (mmHg)	102.50 $\pm$ 17.08	88.96 $\pm$ 18.26*	87.5 $\pm$ 22.69*	88.85 $\pm$ 19.75	81.92 $\pm$ 17.62*	84.47 $\pm$ 14.89*
MBP (mmHg)	110.54 $\pm$ 16.06	97.08 $\pm$ 16.34*	94.32 $\pm$ 21.83*	96.54 $\pm$ 18.27*	92.12 $\pm$ 17.73*	92.33 $\pm$ 13.77*
LVSP (mmHg)	133.27 $\pm$ 16.34	111.88 $\pm$ 16.17*	111.82 $\pm$ 21.16*	117.50 $\pm$ 19.69*	110.96 $\pm$ 16.03*	110.77 $\pm$ 12.16*
LVEDP (mmHg)	2.23 $\pm$ 0.45	24.50 $\pm$ 5.30*	13.00 $\pm$ 6.69*†	14.45 $\pm$ 4.56*†	12.10 $\pm$ 2.03*†§	7.71 $\pm$ 1.86* †‡§#

Compared with sham-operation group, * $P < 0.05$

Compared with AMI group, † $P < 0.05$

Compared with metoprolol group, ‡ $P < 0.05$

Compared with low-dose carvedilol group, § $P < 0.05$

Compared with middle-dose carvedilol group, # $P < 0.05$

Table II. The Effects of Low, Middle, and High-dose Carvedilol and Metoprolol on LVRM and LV Function

	Sham (n = 12)	AMI (n = 11)	Metoprolol (n = 11)	Low (n = 11)	Middle (n = 12)	High (n = 12)
LVV (mL)	0.41 $\pm$ 0.08	0.92 $\pm$ 0.11*	0.72 $\pm$ 0.08*†	0.82 $\pm$ 0.10*†‡	0.79 $\pm$ 0.08*†	0.72 $\pm$ 0.10*†‡§#
STh (mm)	0.81 $\pm$ 0.06	1.33 $\pm$ 0.29*	1.35 $\pm$ 0.20*	1.14 $\pm$ 0.12*†‡	1.18 $\pm$ 0.21*†‡	1.19 $\pm$ 0.15*†‡
LVAW (mg)	530.12 $\pm$ 54.10	730.12 $\pm$ 78.89*	698.94 $\pm$ 78.33*	666.22 $\pm$ 56.60*†	622.03 $\pm$ 69.66*†‡	589.36 $\pm$ 57.20*†§
RVAW (mg)	152.51 $\pm$ 23.60	291.49 $\pm$ 11.35*	238.96 $\pm$ 80.53*	207.17 $\pm$ 36.45*†	217.00 $\pm$ 51.66*†	199.96 $\pm$ 35.06*†
LVRW (mg/g)	1.75 $\pm$ 0.19	2.51 $\pm$ 0.25*	2.36 $\pm$ 0.31*	2.32 $\pm$ 0.19*†	2.16 $\pm$ 0.16*†‡§	2.06 $\pm$ 0.18*†
RVRW (mg/g)	0.51 $\pm$ 0.08	1.00 $\pm$ 0.37*	0.84 $\pm$ 0.29*	0.72 $\pm$ 0.14*†	0.76 $\pm$ 0.18*†	0.70 $\pm$ 0.14*†
dp/dt (mmHg/s)	6880 $\pm$ 984	4070 $\pm$ 863*	4864 $\pm$ 105*	4969 $\pm$ 102*†	4953 $\pm$ 106*†	4673 $\pm$ 789*
-dp/dt (mmHg/s)	5750 $\pm$ 810	2880 $\pm$ 690*	3509 $\pm$ 840*†	3923 $\pm$ 706*†	3654 $\pm$ 658*†	3493 $\pm$ 579*†
dp/dt/LVSP	51.22 $\pm$ 5.56	36.35 $\pm$ 5.45*	44.00 $\pm$ 4.62*†	42.60 $\pm$ 7.15*†	44.48 $\pm$ 5.78*†	42.27 $\pm$ 5.77*†
-dp/dt/LVSP	42.76 $\pm$ 5.37	25.86 $\pm$ 5.14*	31.33 $\pm$ 4.92*†	33.55 $\pm$ 4.49*†	33.06 $\pm$ 4.48*†	31.55 $\pm$ 4.05*†

Compared with sham-operation group, * $P < 0.05$

Compared with AMI group, † $P < 0.05$

Compared with metoprolol group, ‡ $P < 0.05$

Compared with low-dose carvedilol group, § $P < 0.05$

Compared with middle-dose carvedilol group, # $P < 0.05$

In comparison with the AMI group, LVV, LVAW, LVRW, STh, RVAW, and RVRW were all significantly decreased in the three carvedilol groups ($P < 0.05$ - 0.001), with dose-related effects on LVV, LVAW and LVRW (superior in the HD-car group, $P < 0.05$); and $\pm dp/dt$ and $\pm dp/dt/LVSP$ were both significantly increased in all therapy groups ($P < 0.05$ - 0.001). Only LVV but not LVAW, LVRW or STh decreased significantly in the Meto group ($P < 0.001$).

DISCUSSION

It has been elucidated that excessive activation of the sympathetic nervous system is one of the major responses and plays a key role in LVRM initiation and progression after AMI.¹⁹⁾ Therefore, the administration of a β -blocker should have beneficial effects on postinfarction LVRM. Data from clinical studies⁶⁻⁸⁾ show that the third generation β -blocker carvedilol can attenuate the process of LVRM in ischemic heart failure and AMI, though data from experimental studies demonstrate conflicting results with carvedilol⁹⁾ as well as other β -blockers.⁹⁻¹⁵⁾ Whether carvedilol and metoprolol have beneficial effects on LVRM after AMI and the dose-effect relation of carvedilol need to be verified. In this study, the effects of metoprolol with three different dose regimens of carvedilol on postinfarction LVRM were compared. The results were encouraging.

The effects of carvedilol at different doses and metoprolol on hemodynamics:

This study has shown that LVEDP was significantly increased after AMI, which was consistent with the reports of Pfeffer¹⁷⁾ and Litwin,¹⁸⁾ and the elevated LVEDP was significantly decreased after treatment with low, middle and high doses of carvedilol and metoprolol by 41%, 51%, 69%, and 47%, respectively, with dose-related reductions in the carvedilol groups. These results suggest that both carvedilol and metoprolol do have beneficial effects on hemodynamics after AMI and that carvedilol has a dose-related effect. The mechanisms for hemodynamic improvement by β -blockade may be due to the reduction of wall stress and oxygen consumption associated with blockage of excessive sympathetic activation.^{20,21)}

Effects of carvedilol at different doses and metoprolol on LVRM: The present study also showed that LVV, LVW, and STh were significantly increased after AMI, indicating that LVRM occurred, which is similar to the results of Pfeffer¹⁷⁾ and Litwin.¹⁸⁾ The most important findings of this study were that carvedilol at low, middle and high doses and metoprolol were effective in preventing LV dilatation, with carvedilol exhibiting a dose-related effect. LVV was decreased by 12%, 15.2%, 23.9%, and 22.8%, respectively. Carvedilol also had a dose-related effect in attenuating the hypertrophy of noninfarcted myocardium, while metoprolol did not. To the best of our knowledge, this is the first study to show that

carvedilol preferentially attenuates postinfarction LVRM with respect to both LV dilatation and hypertrophy, while metoprolol attenuates only LV dilatation but not hypertrophy. In a similar study to this, Wei, *et al*⁽¹⁰⁾ reported that carvedilol significantly reduced myocardial collagen deposition in the noninfarcted myocardium and cardiac hypertrophy in the right ventricle, whereas metoprolol had no effect on myocardial collagen deposition. In their study, however, they did not demonstrate an antihypertrophic effect of carvedilol on LV and did not evaluate LV volume changes affected by carvedilol and metoprolol. In another study, Yaoita, *et al*⁽⁹⁾ most recently reported that carvedilol at low, middle, and high doses did not attenuate LVRM in AMI rats with permanent coronary occlusion, whereas metoprolol at different doses only tended to attenuate the increase in LV end-diastolic dimension. The reasons for the discrepancy probably result from differences in the MI size determined, the parameters of LV remodeling used and the method with which the parameters were measured, and the time period of treatment (12 weeks vs 4 weeks) between the two studies. In the study by Yaoita, *et al*, MI size, which is well known as one of the most important factors to affect the postinfarction remodeling process was not determined so a comparison of MI size among the AMI control and treatment groups was not confirmed. The parameters of LV remodeling used were only LV dimensions and heart weight instead of exact LV volumes and weight as in our study; and the LV dimension measurements by echocardiography were quite varied (intraobserver, interobserver), which may affect the results. In contrast, in our study, we determined MI size in each rat, and excluded rat hearts with an MI size both < 35% and > 55% in order to decrease the deviation and compare infarct size among multiple groups (44.46-46.34%), which eliminated the most important factor affecting the postinfarction remodeling process. We also weighed the exact LV and RV weights separately when the great vessels and atria were trimmed away, and measured LV volume directly with a cutaneous syringe method with intra- and interobserver variability of only 1.2% and 1.3%, respectively. Therefore, the results of our study were much less affected. Although we still do not know the exact reasons for these conflicting results, the findings in our study are reliable in light of the consistency of hemodynamic improvements with LVRM attenuation by carvedilol and metoprolol, and strongly suggest that both carvedilol and metoprolol do have beneficial effects on postinfarction LVRM in addition to the traditional mechanism of limiting MI size through reduction of myocardial oxygen consumption.

Since LV dilatation after AMI is one of the key characters of LVRM and is the most powerful predictor of a poor prognosis, the prevention of LV dilatation by carvedilol and metoprolol indicates that they not only can be used for treatment of heart failure, but also for prevention of heart failure via attenuating LV dilatation after AMI. The underlying mechanism for LV dilatation prevention by

carvedilol is probably multifactorial, including the vasodilation effect of LV preload and afterload reduction with α 1-blockade, antioxidant effects against catecholamines in myocardium, and a reduction in myocardial oxygen consumption with β -blockade.^{7,22)} The mechanisms for LV dilatation attenuation of metoprolol are due to the beneficial effects of β -blockade associated with inhibition of excessive sympathetic activation after AMI.²³⁾

Because the hypertrophy of noninfarcted myocardium is the main pathologic basis of LVRM, and it in itself can also lead to myocardial dysfunction and heart failure at the end stage due to myocardial fibroblast proliferation, collagen synthesis, and severe fibrosis,²⁴⁾ the attenuation of hypertrophy by carvedilol at different doses is also of clinical significance. The possible mechanisms for hypertrophy attenuation by carvedilol are related to²⁵⁾: 1) reduction of the wall stress associated with α 1-blockade; 2) neurohormonal effects by inhibiting the growth-promoter effects of norepinephrine on cardiomyocytes and attenuating collagen deposition in the noninfarcted zone.¹⁰⁾ Metoprolol seemed to be ineffective in hypertrophy attenuation in our study, which is in agreement with the results of Wei, *et al*¹⁰⁾ and contradict those of Masson, *et al*²⁶⁾ (10 mg·kg⁻¹·d⁻¹), and may be due to the lower dose used in this study.

Effects of carvedilol at different doses and metoprolol on left ventricular function:

The results of this study showed that $\pm$ dp/dt significantly decreased after AMI, indicating that LV function was impaired, and carvedilol at low, middle, and high doses and metoprolol can all improve LV function. Carvedilol improves LV function not only by blockade of adrenergic receptors to have direct protective effects against catecholamines on myocytes and improved regional wall motion, but also by its potent antioxidant and vasodilating effects to protect cardiomyocytes from oxygen free radical injury and reduce the LV preload and afterload, and then further reduce the oxygen consumption of cardiomyocytes.^{4,17)} The improvement of LV function by metoprolol is due to reductions in wall stress and oxygen consumption, and an increase in coronary blood flow.²⁷⁾

Limitations of this study: There are several limitations to our study. First, we did not evaluate the dose-related effect on postinfarction LVRM with metoprolol, only with carvedilol. This may have some unfavorable effects on metoprolol in terms of only preventing LV delatation but not hypertrophy possibly due to just one middle dose (2 mg·kg⁻¹·d⁻¹) used instead of high doses (10 mg·kg⁻¹·d⁻¹). Second, we excluded rats with an infarct size < 35% or > 55% in order to decrease the deviation and maintain comparability in infarct size among the multiple groups since infarct size itself is one of the major factors affecting the LVRM process. The findings from this study may be only suitable for this range of infarct size, not for under or beyond the range. Third, we did not include an additional sham-operated group treated with β -blockers in the study design. Finally, we did

not evaluate the effects of α 1-blockers on LV remodeling attenuation or compare them with carvedilol.

REFERENCES

1. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975; 37: 1022-36.
2. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353: 9-13.
3. 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.
4. Packer M, Colucci WS, Sackner-Bernstein JD, *et al.* Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation* 1996; 94: 2793-9.
5. MERIT-HF Study Group. Effects of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999; 353: 2001-7.
6. Dougherty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *J Am Coll Cardiol* 1997; 29: 1060-6.
7. Senior R, Basu S, Kinsey C, Schaeffer S, Lahiri A. Carvedilol prevents remodeling in patients with left ventricular dysfunction after acute myocardial infarction. *Am Heart J* 1999; 137 (4 Pt 1): 646-52.
8. Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction: a placebo-controlled, randomized trial. *Circulation* 1997; 96: 183-91.
9. Yaoita H, Sakabe A, Maehara K, Maruyama Y. Different effects of carvedilol, metoprolol, and propranolol on left ventricular remodeling after coronary stenosis or after permanent coronary occlusion in rats. *Circulation* 2002; 105: 975-80.
10. Wei S, Chow LT, Sanderson JE. Effects of carvedilol in comparison with metoprolol on myocardial collagen postinfarction. *J Am Coll Cardiol* 2000; 36: 276-81.
11. Jain P, Lillis O, Cohn PF. Effects of metoprolol on early infarct expansion after acute myocardial infarction. *Am Heart J* 1994 Apr; 127(4 Pt 1): 764-73.
12. Fishbein MC, Lei LQ, Rubin SA. Long-term propranolol administration alters myocyte and ventricular geometry in rats hearts with and without infarction. *Circulation* 1988; 78: 369-75.
13. Oh BH, Ono S, Gilpin E, Ross J, *et al.* Altered left ventricular remodeling with beta-adrenergic blockade and exercise after coronary reperfusion in rats. *Circulation* 1993; 87: 608-16.
14. Hochman JS, Wong SC. Effects of atenolol on myocardial infarct expansion in a nonreperfused rat model. *Am Heart J* 1991; 122: 689-94.
15. Hu K, Gaudron P, Ertl G. Long-term effects of beta-adrenergic blocking agent treatment on hemodynamic function and left ventricular remodeling in rats with experimental myocardial infarction. *J Am Coll Cardiol* 1998; 31: 692-700.
16. Olivetti G, Capasso JM, Meggs LG, *et al.* Cellular basis of chronic ventricular remodeling after myocardial infarction in rats. *Circ Res* 1991; 68: 856-69.
17. Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res* 1985; 57: 84-95.
18. Litwin SE, Katz SE, Morgan JP, Douglas PS. Long-term captopril treatment improves diastolic filling more than systolic performance in rats with large myocardial infarction. *J Am Coll Cardiol* 1996; 28: 773-81.
19. Metra M, Nodari S, D'Aloia A, Bontempi L, Boldi E, Cas LD. A rationale for the use of beta-blockers as standard treatment for heart failure. *Am Heart J* 2000; 139: 511-21.
20. Zamchett A, Stella A. Neural control of renin release. *Clin Sci Mol Med* 1975; 48: 215-23.

21. Eichhorn EJ, Heesch CM, Risser RC, Marcoux L, Hatfield B. Predictors of systolic and diastolic improvement in patients with dilated cardiomyopathy treated with metoprolol. *J Am Coll Cardiol* 1995; 25: 154-62.
22. Capomolla S, Febo O, Gnemmi M, *et al.* Beta-blockade therapy in chronic heart failure: diastolic function and mitral regurgitation improvement by carvedilol. *Am Heart J* 2000; 139: 596-608.
23. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. On behalf of the International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000; 35: 569-82.
24. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* 1990; 81: 1161-72.
25. Ruffolo RR, Feuerstein GZ. Pharmacology of carvedilol: rationale for use in hypertension, coronary artery disease, and congestive heart failure. *Cardiovasc Drugs Ther* 1997; 11: 247-56.
26. Masson S, Masseroli M, Fiordaliso F, *et al.* Effects of a DA2/alpha2 agonist and a beta1-blocker in combination with an ACE inhibitor on adrenergic activity and left ventricular remodeling in an experimental model of left ventricular dysfunction after coronary artery occlusion. *J Cardiovasc Pharmacol* 1999; 34: 321-6.
27. Heesch CM, Marcoux L, Hatfield B, Eichhorn EJ. Hemodynamic and energetic comparison of bucindolol and metoprolol for the treatment of congestive heart failure. *Am J Cardiol* 1995; 75: 360-4.