



Comparing the Effects of Carvedilol Enantiomers on Regression of Established Cardiac Hypertrophy Induced by Pressure Overload

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Pressure overload diseases such as valvular stenosis and systemic hypertension morphologically manifest in patients as cardiac concentric hypertrophy. Preventing cardiac remodeling due to increased pressure overload is important to reduce the morbidity and mortality. A recent clinical study has shown that carvedilol has beneficial effects on the survival rate of patients with heart failure. This may be due to the actions of carvedilol such as β -adrenoceptor blockade and the α_1 -adrenergic receptor blockade effects. Therefore, we investigated whether carvedilol can reverse preexisting cardiac hypertrophy and we compared the effects of racemic carvedilol and the carvedilol enantiomers. Cardiac hypertrophy was induced in rats by suprarenal transverse abdominal aortic constriction (AC). Fifteen weeks after AC surgery, concentric hypertrophy was identified in the AC group by performing echocardiography. Low dose *S*- and *SR*-carvedilol (2 mg/kg/day), which were orally administered for three weeks, caused significant regression of the cardiac hypertrophy, and this most significantly occurred in the rats that received *S*-carvedilol. However, *R*-carvedilol did not reduce cardiac hypertrophy. Regression of cardiac hypertrophy by carvedilol was confirmed on the echocardiograms and electrocardiograms. These results suggest that carvedilol could reverse the development of leftventricular concentric hypertrophy that is induced by pressure overload. *S*-carvedilol is proposed to be superior to *SR*- and *R*-carvedilol as a beneficial treatment for cardiac hypertrophy.

Key words: Established cardiac hypertrophy, carvedilol, enantiomers, pressure overload

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Increased cardiovascular mortality is a serious problem in modern societies. Minimizing the risk of cardiac disease and alleviating the complications of cardiovascular dysfunction are the main therapeutic aims in modern medicine. Most heart diseases, regardless of etiology or pathogenesis, progress to congestive heart failure causing mortality (Mosterd *et al.*, 1999). The prognosis for patients with heart failure depends on the severity of cardiac dysfunction and the presence of complications and generally varies from guarded to poor. The single most powerful predictor for the development of heart failure is the presence of cardiac hypertrophy (Murray and Lopez, 1997).

Cardiac concentric hypertrophy is a homeostatic response to elevated afterload that develops due to pressure overload (e.g. systemic hypertension or valvular stenosis). Although cardiac hypertrophy is the initial compensatory response to increased wall stress, it is followed by decompensating hypertrophy and ultimately leads to heart failure if the stimulus is sufficiently intense and prolonged.

Catecholamines have been implicated in the pathogenesis of myocardial hypertrophy, and adrenergic blockade is at the center of neurohormonal antagonism in heart failure. Multiple clinical trials demonstrate the benefit of β -adrenergic receptor antagonism on heart failure morbidity and mortality (Longet *et al.*, 1992). Moreover, α_1 -adrenergic receptor stimulation produces vasoconstriction, and myocyte hypertrophy, suggesting a potential therapeutic role for α_1 -adrenergic receptor antagonists to reduce cardiac workload and myocardial hypertrophy.

Carvedilol is a nonselective third-generation β -adrenergic receptor antagonist with additional antagonist activity at the

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α_1 -adrenergic receptor, and has been shown to more effectively improve symptoms and left ventricular ejection fraction and to reduce mortality in patients with heart failure in comparison with selective β_1 -antagonist, metoprolol (Cohn *et al.*, 1997). Carvedilol is used as a racemic mixture clinically. *S*-carvedilol has greater affinity for β -adrenergic receptor than *R*-carvedilol, although *S*- and *R*-carvedilols have equal affinity for α_1 -adrenergic receptor (Bartsch *et al.*, 1990; Watanabe *et al.*, 2000).

Therefore, the purpose of this study is to investigate whether chronic administration of an oral daily dose of carvedilol can regress established cardiac hypertrophy, which might be of greater clinical significance because the patient would most likely already have hypertrophy at the initiation of treatment. Furthermore, we also compared the effects of racemic carvedilol and enantiomers on the cardiac hypertrophy.

Materials and Methods

In vivo hypertrophy model

Male Sprague-Dawley rats (7 weeks old, 200-220 g) were purchased from Koatech (Pyeongtaek, Korea). The experimental protocol was approved by the Chungbuk National University Medical School Research Institutional Animal Care and Use Committee. All surgical procedures were performed on animals anesthetized with ketamine (80 mg/kg, IP) and xylazine (5 mg/kg, IP). Abdominal aortic constriction (AC) on animals was performed by using a 4-0 suture tied around the suprarenal aorta and a 21-gauge needle. The needle was then removed by yielding a 0.8 mm internal diameter. Rats were randomly assigned to AC or sham-operated groups and the sham-operated rats underwent the same procedure, with the exception that the aorta was not constricted. Establishment of cardiac hypertrophy was confirmed by echocardiography by measuring left ventricular (LV) wall thickness and dimensions. After identification of cardiac hypertrophy at 15 weeks of aortic constriction, racemic carvedilol and enantiomers (kindly provided by Ahngook Pharmaceuticals Co., Seoul, Korea) were dissolved in 0.5% methylcellulose and orally administered (1 mL/kg), using an animal-feeding needle (Zonde, Natsume, Japan) every day over a period of 21 consecutive days. Whereas control animals were supplied with vehicle lacking carvedilol (Figure 1). Dietary administration was chosen to establish clinical relevance to human dietary habits. Regression of cardiac hypertrophy was evaluated by heart weight (HW)/body weight (BW) ratio and by echocardiogram.

Experimental design

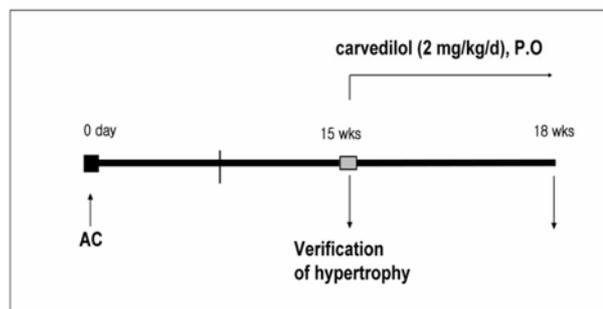


Figure 1. Experimental design. Cardiac hypertrophy were confirmed at 15 weeks after abdominal aortic constriction (AC) using echocardiography. Carvedilol was dissolved in 0.5% methylcellulose and oral administered (1 mL/kg) for 3 weeks. Cardiac function, cardiac hypertrophy and electrocardiogram were performed after 18 weeks of abdominal AC.

Determination of the activities of serum enzymes

In order to evaluate the extent of heart and liver injury induced by pressure overload, the activities of lactate dehydrogenase (LDH), creatine kinase (CK) and aspartate transaminase (AST)/alanine transaminase (GPT) in serum of rats were measured. When animals were killed, blood sample was collected and centrifuged at 800 rpm for 5 min, and then the serum was collected. Serum LDH, CK and AST/ALT levels were assayed, using commercial kits (Asan Pharmaceuticals Co., Seoul, Korea) and all operations followed the instructions of the kits.

Echocardiography (EcCG)

After 18 weeks of AC, rats were anesthetized with ketamine (80 mg/kg, IP) and xylazine (5 mg/kg, IP), and cardiac dimension and function were analyzed by 10-MHz pulse-wave doppler echocardiography (SONOACE 8800; Medison, Seoul, Korea). Two dimensionally guided M-mode of LV at the papillary level was obtained from the parasternal long-axis view. For each rat, measurements were made from at least 4 beats. LV cavity dimension and wall thickness were measured, and percent change in LV dimension (fractional shortening, FS) and relative wall thickness (RWT) were calculated as follows: $FS = [(LVDd - LVSD) / LVDd] \times 100$, where LVDd is LV dimension at end-diastole and LVSD is LV dimension at end-systole. $RWT = (\text{posterior wall thickness at end diastole} / LVDd) \times 2$.

Electrocardiograms (ECG)

Anesthetized rats were kept in the supine position with spontaneous breathing for ECG recording. The electrodes

Table 1. Echocardiographic changes after pressure overload

	15 weeks		18 weeks				
	Control	AC	Control	AC	Treatment (2 mg/kg/day)		
					R-Carvedilol	SR-Carvedilol	S-Carvedilol
IVSd (mm)	1.22±0.04	1.85±0.06 [†]	1.75±0.05	2.00±0.15 [†]	1.73±0.12*	1.78±0.06*	1.70±0.09*
LVIDd (mm)	8.22±0.50	7.21±0.40 [†]	7.82±0.60	7.40±0.1 [†]	7.40±0.20	7.15±0.35	8.53±0.13*
PWTd (mm)	1.42±0.13	2.22±0.12 [†]	1.98±0.10	3.08±0.20 [†]	2.55±0.19*	2.43±0.12*	2.22±0.10*
RWT(mm/mm)	0.34±0.01	0.62±0.05 [†]	0.51±0.01	0.84±0.09 [†]	0.68±0.06	0.67±0.08	0.51±0.02*
FS (%)	30.6±2.11	39.72±3.85	43.30±3.00	31.2±0.40 [†]	37.5±3.72*	33.8±5.28	34.4±1.69*

Data are means±SE; n≥6. AC, aortic constriction; IVSd, interventricular septum thickness in diastole; LVIDd, left ventricular internal dimension in diastole; PWTd, posterior wall thickness of the left ventricle in diastole, respectively; RWT, relative wall thickness; FS, fractional shortening. [†]P<0.05 compared with normal control group; *P<0.05 compared to the AC group.

were connected to the data acquisition system (ML132 bioamp and ML870; AD Instrument, Bella Vista NSW, Australia) and all ECG signal processing was performed with the use of customized software written in the Powerlab chart 6 program (AD Instrument).

Statistical analysis

Results are presented as mean±SE. Data obtained were compared using the unpaired Students *t*-test or one-way ANOVA. Statistical significance was defined as a value of *P*<0.05.

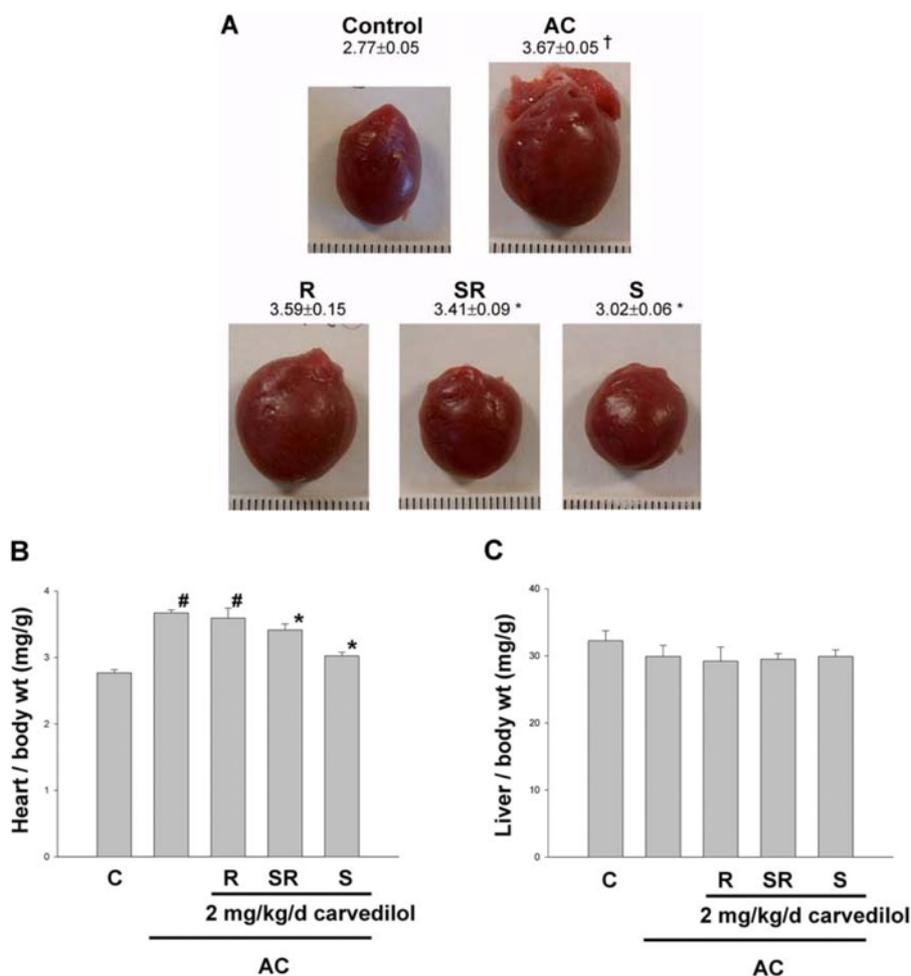


Figure 2. Regression of pressure overload induced cardiac hypertrophy *in vivo* by carvedilol. A. Representative hearts of rats treated with 18 weeks aortic constriction (AC) or 15 weeks AC+carvedilol for 3 weeks. bar=1 mm. B. Heart wet weight was normalized to body weight in each rat as an index of cardiac hypertrophy. Heart weight to body weight ratio was reversed by 2 mg/kg/d carvedilol in hypertrophied heart induced by aortic constriction (AC). C. Liver weight to body weight ratio. R, R-carvedilol; SR, SR-carvedilol; S, S-carvedilol. [†]#P<0.001 compared with sham; *P<0.001 compared with AC, n≥6.

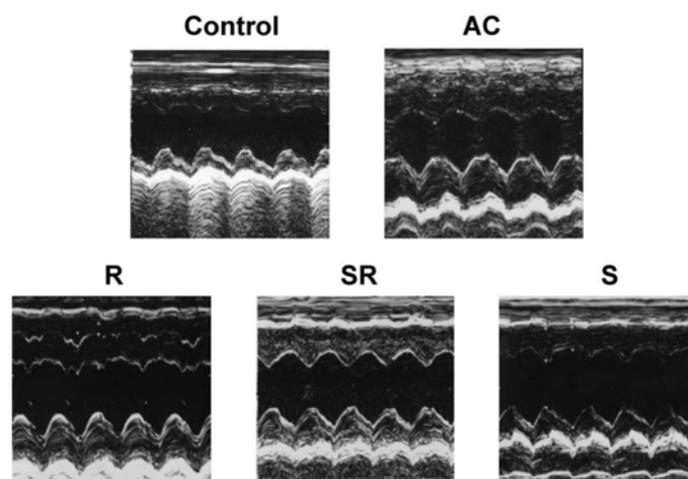


Figure 3. Representative M-mode echocardiograms after 3 weeks of carvedilol administration in established cardiac hypertrophy induced by 15 weeks of aortic constriction (AC). Quantitative data are shown in Table 1. Concentric cardiac remodeling was observed in the AC group. The increased wall thickness was reversed by *S*-carvedilol. R, *R*-carvedilol; SR, *SR*-carvedilol; S, *S*-carvedilol.

Results

Regression of preestablished cardiac hypertrophy by carvedilol

We examined whether carvedilol can reverse preexisting cardiac hypertrophy, which might be of greater clinical significance. The amount of water intake was measured every day and administration of carvedilol did not alter water intake in either the sham-operated or aortic constricted rats. Sham group did not show any difference in heart weight comparing with control. As expected, the left ventricular wall thickness increased after 15 weeks of AC (Table 1). Maintenance of AC group with vehicle treatment for the subsequent 3 weeks results in a further increase in the ventricular wall thickness and HW/BW ratio, suggesting that cardiac hypertrophy is progressive. However, carvedilol administration for a 3-week period after 15 weeks of AC relieved the preexisting cardiac hypertrophy and prevented further progression. HW/BW ratio was significantly reduced by *SR*- and *S*-carvedilol compared to AC group, although heart weight was not significantly changed by *R*-carvedilol administration. Each carvedilol enantiomer did not significantly affect either body weight or liver weight (Figure 2). Reversal of preestablished cardiac hypertrophy was also confirmed by echocardiography and revealed that the regression of the heart weight paralleled the reduction of left ventricular wall thickness (Figure 3).

Effect of carvedilol enantiomers on cardiac function of preexisting cardiac hypertrophy

Compared with sham-operated rats, aortic-banded rats displayed a substantial increase in interventricular septum

thickness in diastole (IVSd) and LV posterior wall thickness in diastole (PWTd). Relative wall thickness (RWT) was also markedly increased from 0.62 ± 0.05 at 15 weeks to 0.84 ± 0.09 at 18 weeks in the AC group, which reveals evidence of progression of concentric hypertrophy. Importantly, carvedilol administration for a 3-week period after 15 weeks of AC significantly decreased PWTd and RWT, most significantly in *S*-carvedilol group. *S*-carvedilol treated aortic-banded rats also had an increase in cardiac contractility, assessed by fractional shortening, compared to the AC group revealed that *S*-carvedilol prevents progression of heart failure (Table 1).

Serum levels of enzyme activities

Serum AST and ALT levels, indices of acute liver failure, showed significant increase in AC group when compared to normal control. Interestingly, serum AST and ALT levels were reduced only by *S*-carvedilol treatment. On the contrary, *R*-carvedilol showed rather a significant risk of hepatotoxicity (Table 2). Serum levels of CK and LDH are diagnostic indicators of myocardial injury. Serum CK and LDH levels were found to be significantly increased in preexisting cardiac hypertrophy. These were significantly reduced in *S*-carvedilol groups, while *SR*-carvedilol and *R*-carvedilol showed less effects. These results revealed that *S*-carvedilol is more cardioprotective and less hepatotoxic than racemic or *R*-carvedilol.

Effect of carvedilol enantiomers on ECG of cardiac hypertrophy

We examined the effect of carvedilol on ECGs on preexisting cardiac hypertrophy (Figure 5). Abnormal ECGs were observed in the AC group and these wave were

Table 2. The effect of carvedilol on the release of intracellular enzymes from hypertrophic heart

	AST (U/L)	ALT (U/L)	CK (U/L)	LDH (μ mole/L)
Control	96.3 \pm 12.7	51.3 \pm 2.4	219.6 \pm 72.5	94.3 \pm 22.0
AC	134.0 \pm 28.0	60.0 \pm 5.0	524.3 \pm 177.7 [†]	132.7 \pm 22.6 [†]
Treatment (2 mg/kg/day)				
R-Carvedilol	445.3 \pm 312.1	122.0 \pm 59.5	652.2 \pm 177.1	209.0 \pm 68.2
SR-Carvedilol	144.7 \pm 23.5	61.3 \pm 82.1	775.7 \pm 256.3	178.3 \pm 32.1
S-Carvedilol	97.0 \pm 12.5*	50.0 \pm 2.5*	285.0 \pm 135.7*	83.3 \pm 21.1*

AST, aspartate transaminase; ALT, alanine transaminase; CK, creatine kinase; LDH, lactate dehydrogenase. Results are expressed as mean \pm SE. Control, treated with vehicle; AC, aortic constriction. [†] P <0.05 compared with normal control group; * P <0.05 compared to the AC group.

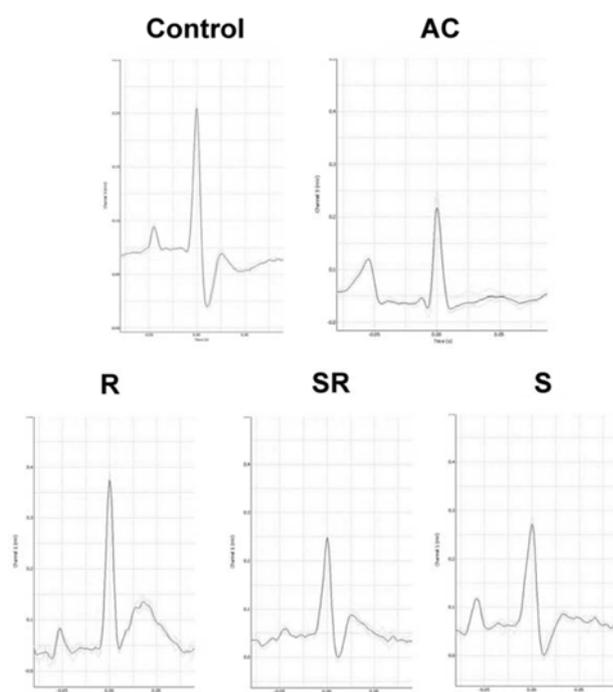


Figure 4. Representative electrocardiograms after 3 weeks of carvedilol administration in established cardiac hypertrophy induced by 15 weeks of aortic constriction (AC). Quantitative data are shown in Table 3. Abnormal ECGs were observed in the AC group and these wave were significantly reversed by S-carvedilol. R, R-carvedilol; SR, SR-carvedilol; S, S-carvedilol.

significantly reversed by S-carvedilol. Values of the voltage-duration product and of its individual components, RR interval, PR interval, P duration and QTc are presented in Table 3. RR interval significantly increased and heart rate decreased in AC group compared to normal control. These parameters were reversed by carvedilol treatment and did not differ among enantiomers. P duration and T amplitude tended to be higher in AC group and significantly decreased to normal range by S-carvedilol.

Discussion

Carvedilol is a nonselective, vasodilating β -blocker that

blocks β_1 -, β_2 -, and α_1 -receptors and has potent antioxidant and free radical-scavenging properties that is used in the treatment of hypertension, angina, and congestive heart failure. In the present study, we showed that a daily low dose carvedilol can reverse the cardiac hypertrophic changes induced by pressure overload and improve cardiac performance mostly by reducing LV end-diastolic and end-systolic dimensions. In addition, we found that S-carvedilol had a more favorable effect than SR- and R-carvedilol on inhibiting myocardial hypertrophy.

It is known that developing hypertrophy occurred within the first 2 weeks in overloaded rat heart and was characterized by a rapid increase of cardiac mass in both left and right ventricles. Compensated hypertrophy occurred between 2 and 8 weeks where normal or mild depression in hemodynamic function was observed, and decompensated hypertrophy (or heart failure) occurred between 8 and 16 weeks and was characterized by circulatory congestion, decreased *in vivo* and *in vitro* cardiac function, and a shift in myosin heavy chain isozyme expression. Therefore, we investigated the regression effects of carvedilol on established cardiac hypertrophy after 15 weeks of aortic constriction and 3-week period of carvedilol administration. In this study, maintenance of AC group with vehicle treatment results in a further increase in the ventricular wall thickness and decrease of cardiac function, suggesting that decompensated hypertrophy is occurred. However, carvedilol administration for a 3-week period relieved the preexisting cardiac hypertrophy and prevented heart failure progression.

Carvedilol is a nonselective β -antagonist with additional antagonist activity at α_1 -adrenergic receptor without producing an intrinsic sympathomimetic effect, such as increasing cardiac noradrenaline, or causing an upregulation of β -receptors (Bril *et al.*, 1992; Gilbert *et al.*, 1993). Hence, the use of this drug is associated with a more complete antagonism of the sympathetic nervous system than is associated with other β -blockers. In humans, 25 \pm 50 mg of carvedilol is used to treat heart failure (Bohm *et al.*, 1992; Bristow *et al.*, 1996). The

Table 3. The effect of carvedilol on ECG parameters of hypertrophic heart

	RR interval (sec)	Heart rate (bpm)	PR interval (sec)	P duration (sec)	QTc (sec)	T amplitude (mV)
Control	0.19±0.01	319±16	0.045±0.001	0.015±0.002	0.150±0.023	94.3±22.0
AC	0.26±0.02 [†]	236±18 [†]	0.047±0.003	0.019±0.001 [†]	0.134±0.010	132.7±22.6 [†]
Treatment (2 mg/kg/day)						
R-Carvedilol	0.20±0.01*	302±17*	0.047±0.004	0.018±0.002	0.177±0.006	209.0±68.2
SR-Carvedilol	0.21±0.035*	310±27*	0.040±0.003	0.016±0.002*	0.147±0.003	178.3±32.1
S-Carvedilol	0.20±0.02*	318±24*	0.050±0.002	0.017±0.001*	0.175±0.010	83.3±21.1*

AC, 18 weeks of aortic constriction; RR interval, interval from the onset of one QRS complex to the onset of the next QRS complex; PR interval, From the beginning of the P wave to the beginning of the QRS complex; QTc, QT interval corrected for rate; T wave, represents the repolarization of the ventricles. [†] $P < 0.05$ compared with normal control group; * $P < 0.05$ compared to the AC group.

reason why we used 2 mg/kg for one group was that this dose is equivalent to 25 mg in humans when one compares the dosage of carvedilol corrected by using body surface area.

Carvedilol has been used as a racemic mixture clinically. Therefore, we compared the effects of racemic carvedilol and carvedilol enantiomers on preexisting cardiac hypertrophy. In the present study, we showed that *S*-carvedilol that has greater affinity for β - and α_1 -adrenergic receptors is superior in reversal of myocardial hypertrophy than *R*-carvedilol that has affinity only for α_1 -adrenergic receptor. Sustained high blood pressure is one of the strongest causes of the development of cardiac hypertrophy. Alpha 1-adrenergic receptors on peripheral vessels and coronary arteries have been found to mediate vasoconstrictor response postsynaptically and combined adrenergic blockade with carvedilol was found to be superior to selective β_1 -blockade in the COMET (Poole-Wilson *et al.*, 2003). This result has led many to speculate of a more impacting role on α_1 -adrenergic receptor in the progression of cardiac hypertrophy and heart failure. Therefore, blockage of pressure overload induced cardiac hypertrophy by carvedilol raised the possibility that carvedilol might ameliorate the hypertension induced by AC and that the blockage of hypertrophy might have been secondary to afterload reduction by α_1 -adrenergic blockade rather than a direct cardiac effect. However, carvedilol, at doses that do not reduce systemic blood pressure, has been reported to prevent cardiac growth and remodeling in stroke prone spontaneously hypertensive rats. In addition, recent large clinical studies have failed to show a benefit of α_1 -blockade using specific α_1 -adrenergic blocker, prazosin and doxazosin, in the pathogenesis of heart failure (Gregorini *et al.*, 1998). Moreover, treatment of α_1 -adrenergic blocker develops tachyphylaxis within days of continued therapy (Packer, 1998). Although the beneficial effect of carvedilol on cardiovascular structure seems to be related to its blood pressure lowering effect, it is unlikely that the reduction in cardiac hypertrophy seen with this lower dose of carvedilol was mainly caused

by relief of pressure overload.

A different location of the AC may differently activate the signal transduction pathway. When the aortic arch was constricted, mechanical force may have been the major cause of cardiac hypertrophy. In contrast, the renin-angiotensin system (RAS) may be involved predominantly in suprarenal abdominal AC and contribute to the initial development of cardiac hypertrophy and sympathetic activation in the compensated heart. It has been shown that losartan, an angiotensin II AT1 receptor antagonist, attenuates cardiac hypertrophy in suprarenal abdominal aorta constricted rat (Li *et al.*, 2003), but has no effect on the weight gain of the ventricle during aortic arch constriction (Baba *et al.*, 1999). It has been reported that plasma renin activity was elevated with α_1 -adrenergic blocker, indicating an increased activation of the renin-angiotensin-aldosterone system (Colucci *et al.*, 1980). Because renin release can be mediated by stimulation of the β_1 -receptor, one can speculate that unopposed α_1 -antagonism can lead to the noted plasma renin activity levels, and an increase in sodium retention due to increased renin-angiotensin-aldosterone system activation would lead to edema that can contribute negatively to a compromised cardiovascular state. However, chronic administration of carvedilol on renal function showed significant differences in plasma renin activity and aldosterone activity compared with results seen in trials using α_1 -antagonists and demonstrated a preservation of renal blood flow and decreased in renal vascular resistance, along with no change in plasma renin activity and aldosterone levels (Dupont, 1990). Given that carvedilol can inhibit renin release mediated by stimulation of the β_1 -receptor, the antihypertrophic effect of *S*-carvedilol in the present study could have been mediated by RAS blockage and these suggest that inhibition of RAS by *S*-carvedilol does play a major role in the superior antihypertrophic effect than *R*-carvedilol possessed only α_1 -adrenergic blockage.

Pressure overload induces LV hypertrophy as a compensatory

response to increased wall stress. This has been considered the central mechanism by which cardiac function is maintained within normal ranges in chronically overloaded hearts. Accordingly, suppression of myocardial hypertrophy is expected to cause heart failure. However, it has been suggested that under conditions of pressure overload, the development of cardiac hypertrophy and normalization of wall stress may not be a required compensatory response to pressure overload and may not be necessary to preserve cardiac function (Hill *et al.*, 2000). Recently, it has been demonstrated that using genetically engineered mice that have markedly blunted growth responses to pressure overload, cardiac function was well maintained after loading (using a partial aortic constriction), despite the failure to correct wall stress. Indeed, function was in fact better maintained than in wild-type mice, in which hypertrophy ensued (Esposito *et al.*, 2002). Moreover, Hill and his coworkers (2000) reported preserved cardiac output without hypertrophic compensation in the setting of pressure overload in thoracic aortic banding mice treated with cyclosporine A.

In this study, we examined the effect of carvedilol on cardiac function using echocardiogram and electrocardiogram. Treatment with carvedilol attenuated cardiac hypertrophy and improved cardiac function in pressure overloaded heart and normalized ECG waves, most greatly in *S*-carvedilol group. These results suggest that treatment with *S*-carvedilol allowed the heart to adapt to pressure overload, even in the absence of LV hypertrophy.

An alternative hypothesis that may explain why less cardiovascular outcomes have been shown with *R*-carvedilol use but not with the combined α_1 - and β -blocker, *S*-carvedilol may be a result of its stereopharmacokinetic properties. Tissue distribution of carvedilol enantiomers determined under steady-state conditions in rats demonstrated that *S*-carvedilol was predominant in all tissues (heart, liver, lung, and kidney). This preferential tissue partitioning of *S*-carvedilol was in accordance with its higher unbound fraction in plasma (Stahl *et al.*, 1993). Free fraction of the *S*-carvedilol in blood is 1.65-fold greater than that of the *R*-carvedilol. Tissue-to-blood partition coefficient values for the *S*-carvedilol were 1.6 to 2.1-fold greater than those for the *R*-carvedilol in all tissues, showing that the *S*-carvedilol accumulates more extensively in the tissue including the heart (Fujimaki, 1992).

Calcineurin inhibitors, such as cyclosporine A and FK506 have been well known to inhibit cardiac hypertrophy. However, nephrotoxicity and the immunosuppressive effect of calcineurin inhibitors limit their therapeutic benefit (Ventura *et al.*, 1997). Carvedilol has been used in the treatment of hypertension, angina, and congestive heart failure in safety

for a longtime. In present experiment, *S*-carvedilol significantly regressed cardiac hypertrophy induced by pressure overload without significant effects on normal heart and liver. There was no evidence of nonspecific toxicity since no effects on normal growth, weight gain, or physical activity were found. Therefore, *S*-carvedilol would be a useful modality with more potent and low toxicity to regress preexisting cardiac hypertrophy which might be of greater clinical significance because the patient would most likely already have hypertrophy at the initiation of treatment.

In conclusion, this study demonstrates that low dose carvedilol, most significantly with *S*-carvedilol, regressed cardiac hypertrophy and improved cardiac performance in pressure overloaded hearts. These findings may have important clinical implications in developing new therapeutic strategies to prevent the transition from cardiac hypertrophy to heart failure.

Acknowledgments

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