EFFECTS OF REGRESSION OF LEFT VENTRICULAR HYPERTROPHY FOLLOWING ATENOLOL OR BUNAZOSIN THERAPY ON ISCHEMIC CARDIAC FUNCTION AND MYOCARDIAL METABOLISM IN SPONTANEOUSLY HYPERTENSIVE RATS

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The effects of regression of left ventricular hypertrophy following atenolol and bunazosin therapy on ischemic cardiac function and myocardial metabolism in spontaneously hypertensive rats (SHR) were studied. Atenolol (50 mg/kg/day) and bunazosin (5 mg/kg/day) were administered to SHR from 19 to 26 weeks of age, whereas tap water was given to control SHR and normotensive Wistar-Kyoto rats (WKY). Both atenolol and bunazosin significantly decreased arterial blood pressure and significantly decelerated the increase in left ventricular weight in SHR.

At the end of the long-term treatment, hearts were removed and perfused by the working heart technique for 15 min, and then global ischemia was induced for either 10 or 30 min. The ischemic heart was reperfused for 30 min. The pressure-rate product and the extent of recovery of the coronary flow after reperfusion following 30 min of ischemia in the bunazosin-treated SHR were significantly higher than those in the control SHR and the atenolol-treated SHR. The levels of adenosine triphosphate (ATP), creatine phosphate (CrP), and energy charge potential in the SHR heart reperfused after 30 min of ischemia were significantly lower than those in the reperfused WKY. Both atenolol and bunazosin improved the restoration of ATP and CrP in SHR after reperfusion following 30 min of ischemia. In conclusion, antihypertensive therapy with either atenolol or bunazosin was effective in preventing cardiac hypertrophy and ischemic damage caused by different mechanisms. Factors resulting from stimulation of the cardiac α_1 adrenoceptor may play an important role in the development of hypertensive cardiac hypertrophy, just as factors resulting from stimulation of the β_1 -adrenoceptor do.

CARDIAC hypertrophy in hypertension has been regarded as a secondary response to the increased pressure load^{1,2}

Key words:

Spontaneously hypertensive rats
Isolated perfused heart
Myocardial ischemia
Atenolol
Bunazosin

Studies in animal models and hypertensive patients suggest that the control of arterial blood pressure by antihypertensive agents does not always result in regression of left ventricular hypertrophy³⁻⁹. In spontaneously hypertensive rats (SHR), α -methyldopa reduces ventricular weight with moderate blood pressure control, whereas the vasodi-

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TABLE I EFFECTS OF LONG-TERM TREATMENT WITH ATENOLOL AND BUNAZOSIN ON BODY WEIGHT, SYSTOLIC BLOOD PRESSURE, AND VENTRICULAR WEIGHT

	WKY	SHR		
	Control (n=8)	Control (n=8)	Atenolol-treated (n=6)	Bunazosin-treated (n=6)
Body weight (g)	362 ± 4	348 ± 4 [#]	332 ± 5 [#]	336 ± 4 [#]
Blood pressure (mmHg)	120 ± 2	178 ± 6 [#]	153 ± 4 ^{*#}	151 ± 3 ^{*#}
Whole heart weight (mg)	1056 ± 24	1243 ± 27 [#]	1036 ± 13 [*]	1017 ± 18 [*]
LV weight (mg)	852 ± 16	1054 ± 16 [#]	897 ± 15 [*]	857 ± 16 [*]
RV weight (mg)	189 ± 10	202 ± 12	151 ± 17	168 ± 10
$\frac{\text{whole heart weight}}{\text{Body weight}} \times 10^3$	2.921 ± 0.064	3.598 ± 0.040 [#]	3.125 ± 0.022 [*]	3.027 ± 0.041 [*]
$\frac{\text{LV weight}}{\text{Body weight}} \times 10^3$	2.359 ± 0.050	3.010 ± 0.045 [#]	2.697 ± 0.029 ^{*#}	2.551 ± 0.023 ^{*#}
$\frac{\text{RV weight}}{\text{Body weight}} \times 10^3$	0.528 ± 0.025	0.574 ± 0.032	0.458 ± 0.089	0.527 ± 0.020

LV weight=left ventricular weight; RV weight=right ventricular weight
Values are means ± SE (n=number of animals)

* $p < 0.05$, compared with control SHR.

[#] $p < 0.05$, compared with control WKY.

lators, hydralazine and minoxidil, do not reduce ventricular hypertrophy or even accelerate it despite reducing blood pressure to normotensive levels^{3,4,8,9}. These discrepancies between reduction of high blood pressure and regression of cardiac hypertrophy by various antihypertensive agents suggest that the cardiac hypertrophy in hypertension is regulated by other factors in addition to the pressure overload.

Hypertension is one of the major risk factors in ischemic heart disease^{10,11}. When the pressure overload has continued for a long time, severe irreversible histological changes occur in the hypertrophied myocardium^{3,12} in which the energy demand increases, leading to great susceptibility to ischemia or hypoxia^{13,14}. In previous studies, we reported that the isolated perfused heart of SHR was more liable to irreversible ischemic damage than that of normotensive Wistar-Kyoto rats (WKY)¹⁵ and that long-term treatment with diltiazem reduced the left ventricular hypertrophy and improved the ischemic myocardial metabolism in SHR¹⁶. The present study was undertaken to investigate whether long-term treatment with atenolol, a β_1 adrenoceptor blocker, or bunazosin, a selective α_1 adrenoceptor

blocker¹⁷ would decrease left ventricular hypertrophy in SHR, and whether these drugs would improve the ischemic changes in the mechanical function and metabolism of the isolated perfused hearts of SHR.

METHODS

Animals

Thirty-six male normotensive Wistar-Kyoto rats aged 19 weeks (WKY/NCrj, Charles River Japan Inc.) and 103 male age-matched spontaneously hypertensive rats (SHR/NCrj, Charles River Japan Inc.) were divided into control (36 WKY and 38 SHR), atenolol-treated (33 SHR), and bunazosin-treated (32 SHR) groups. Either atenolol or bunazosin was added to drinking fluid (0.5 mg/ml or 0.05 mg/ml, respectively) and given ad libitum for 7 weeks. Tap water was given to the control animals. In the atenolol-treated SHR and the bunazosin-treated SHR, each rat received about 50 and 5 mg/kg daily, respectively. All rats were kept under the same conditions and fed rat chow (Nihon Clea, CE-2). Systolic blood pressure was measured at 19 weeks of age and 26 weeks of age by tail plethysmography (Narco, PE-300) after 20 min of prewarming at 37°C in

Fig.1. Effect of long-term treatment with atenolol or bunazosin on recovery of pressure-rate product during reperfusion after ischemia. After 15 min of working heart perfusion, ischemia was induced by lowering the afterload pressure from 60 to 0 mmHg. After either 10 or 30 min of ischemia, hearts were reperused for 30 min as a working heart preparation by raising the afterload pressure to 60 mmHg again. (□, control WKY; ○, control SHR; ▲, atenolol-treated SHR; ●, bunazosin-treated SHR) Data were obtained from the same hearts shown in Table II. Values are means $\pm$ SE

* $p < 0.05$, compared with control SHR.

$p < 0.05$, compared with control WKY.

conscious rats.

Heart perfusion

The 26-week-old rats were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). Hearts were rapidly excised and perfused by Langendorff's technique with Krebs-Henseleit bicarbonate buffer (37°C) containing 11 mM glucose equilibrated with a gas mixture of 95% O₂-5% CO₂. The pulmonary artery and the left atrium were cannulated respectively and both the caval veins were ligated. After 10 min of Langendorff perfusion, the heart was perfused by the working heart technique¹⁸ with a left atrial filling pressure of 9 mmHg and a hydrostatic aortic afterload pressure of 60 mmHg. After 15 min of working heart perfusion, global ischemia was induced for either 10 or 30 min by lowering the afterload pressure from 60 to 0 mmHg, resulting in almost zero coronary flow and cessation of heart beat. When the heart was reperused, afterload pressure was raised to 60 mmHg. The period of reperfusion was 30 min. Peak aortic pressure and

heart rate were recorded on a pressure recorder (Nihon Koden, RJG-4121) via a pressure transducer (Nihon Koden, MPU-0.5A) throughout the perfusion experiment. The coronary flow was determined by collecting the perfusate that dripped from the pulmonary arterial cannula. Treatment with atenolol or bunazosin was discontinued at least 20h before the perfusion experiment.

Biochemical assays

At the end of each perfusion, the heart was quickly frozen by clamping it between blocks of metal chilled in liquid nitrogen. The frozen heart tissue was pulverized in a mortar cooled with liquid nitrogen. A part of the pulverized myocardial tissue powder was weighed, and then dried in an oven overnight for measurement of its dry weight. The remainder of the tissue powder was used for determination of the tissue levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), creatine phosphate (CrP) and lactate. These metabolites were analyzed in

Fig.2. Effect of long term treatment with atenolol or bunazosin on coronary flow during reperfusion after ischemia. Data were obtained from the same hearts shown in Fig. 1. Values are means $\pm$ SE
 * $p < 0.05$, compared with control SHR.
 # $p < 0.05$, compared with control WKY.

neutralized 6% perchloric acid extract according to the enzymatic method of Bergmeyer.¹⁹ Total adenine nucleotide was the sum of the concentration of ATP, ADP and AMP. Energy charge potential (ECP)²⁰ was calculated according to the following equation,

$$\text{ECP} = \frac{[\text{ATP}] + 1/2[\text{ADP}]}{([\text{ATP}] + [\text{ADP}] + [\text{AMP}])}$$

Measurement of ventricular weight

To measure left ventricular (including the ventricular septum) and right ventricular weights, 6 to 8 hearts from each of the 4 groups were perfused for 10 min by Langendorff's technique. The ventricles were weighed after dissecting the atria and vessels and blotting on filter paper.

Statistics

All values are expressed as the mean $\pm$ SE. Analysis of variance was used for multiple group comparisons, using either Student's *t*-test or the Newman-Keuls multiple range test, as was appropriate. Statistical significance was defined as $p < 0.05$. Changes in mean pressure-rate product and coronary flow with or without drug therapy were statistically analyzed for each group by the 2-way analysis of variance.

RESULTS

Blood pressure and ventricular weight

The body weights of 19-week-old WKY and SHR were 352 ± 2 g ($n = 36$) and 327 ± 3 g ($n = 103$), respectively. Systolic blood pressures of these animals were 124 ± 3 mmHg (WKY) and 182 ± 1 mmHg (SHR), respectively. The body weight of SHR was significantly lower ($p < 0.01$) than that of WKY, and the systolic pressure was markedly higher ($p < 0.01$) than that of WKY. The SHR group was divided into 3 subgroups and treated for 7 weeks with atenolol (atenolol-treated SHR), with bunazosin (bunazosin-treated SHR) or without drugs (control SHR). Because the heart was frozen with liquid nitrogen at the end of perfusion study in order to determine the tissue levels of high-energy phosphates, it was impossible to measure the precise weight of the heart. Therefore, 8 rats from the control WKY, 8 rats from the control SHR, 6 rats from the atenolol-treated SHR and 6 rats from the bunazosin-treated SHR were randomly chosen from 26-week-old animals to determine the whole heart weight, the left ventricular weight (including the ventricular septum), and the right ventricular weight (Table I). The body weights of all SHR groups

TABLE II ATP LEVEL

	WKY	SHR		
	Control	Control	Atenolol-treated	Bunazosin-treated
		(μmoles/g dry weight)		
Preischemia	18.6±0.9 (n=6)	19.9±0.9 (n=7)	20.9±2.4 (n=5)	21.1±1.2 (n=5)
Ischemia (10 min)	9.9±0.4 (n=5)	10.4±0.3 (n=5)	9.0±0.4 (n=5)	12.6±1.0 (n=5)
Ischemia (30 min)	3.5±0.6 (n=6)	2.8±0.2 (n=5)	3.5±0.7 (n=5)	3.9±0.2 (n=6)
Ischemia (10 min) + Reperfusion (30 min)	12.9±1.0 (n=6)	12.3±1.2 (n=6)	13.9±1.4 (n=6)	14.7±0.8 (n=5)
Ischemia (30 min) + Reperfusion (30 min)	11.6±0.5 (n=5)	6.3±0.4*# (n=7)	8.2±0.8*# (n=6)	9.3±0.7*# (n=5)

Values are means ± SE; () = number of observations.

* $p < 0.05$, compared with control SHR.

$p < 0.05$, ## $p < 0.01$, compared with control WKY.

were slightly lower ($p < 0.01$) than those of the control WKY. Treatment with either atenolol or bunazosin for 7 weeks markedly decreased the systolic blood pressure in SHR ($p < 0.01$, respectively). Both the whole heart (left and right ventricle) and the left ventricular (LV) weights in the control SHR were significantly higher than those in the control WKY ($p < 0.05$, respectively). The ratio of whole heart weight to body weight and the ratio of LV weight to body weight in the control SHR were significantly higher than those in the control WKY ($p < 0.05$, respectively). No significant difference was observed in the right ventricular (RV) weight and the ratio of RV weight to body weight among the 4 groups. The treatment with either atenolol or bunazosin in SHR for 7 weeks decreased the whole heart weight, the LV weight, the ratio of whole heart weight to body weight, and the ratio of LV weight to body weight significantly ($p < 0.05$, respectively).

Perfusion experiments

Regardless of treatment with or without drugs, the pressure-rate product and the coronary flow before ischemia (preischemia) in SHR were not significantly different from those in WKY. The preischemic pressure-rate products of the control WKY, control

SHR, atenolol-treated SHR and bunazosin-treated SHR were 23.8 ± 1.2 , 22.4 ± 0.4 , 23.0 ± 0.6 , and 24.1 ± 0.4 mmHg· $10^3 \cdot \text{min}^{-1}$, respectively. The preischemic coronary flow of the control WKY, control SHR, atenolol-treated SHR and bunazosin-treated SHR were 17.7 ± 0.7 , 15.7 ± 0.4 , 15.3 ± 0.4 , and 15.6 ± 0.4 ml/min, respectively. The values of the preischemic coronary flow per unit of the whole heart weight in the control WKY, control SHR, atenolol-treated SHR and bunazosin-treated SHR, which were calculated by collecting coronary flow and the values in Table I, were 16.1 ± 0.5 , 12.1 ± 0.3 , 13.4 ± 0.5 , and 14.6 ± 0.4 ml/min·g $^{-1}$, respectively. The coronary flow per unit of the whole heart weight in the control SHR was significantly lower than that in the control WKY ($p < 0.05$), and was significantly improved by atenolol and bunazosin.

After the onset of ischemia, the coronary flow rapidly fell to near zero, and the pressure-rate product progressively decreased and became almost zero within 5 min in both WKY and SHR. The pressure-rate product (Fig. 1) and the coronary flow (Fig. 2) are plotted as a function of the period of reperfusion. In the control heart that was made ischemic for 10 min, the extent of recovery of the pressure-rate product during reperfusion in the control SHR was

TABLE III ADP LEVEL

	WKY	SHR		
	Control	Control	Atenolol-treated	Bunazosin-treated
		(μmoles/g dry weight)		
Preischemia	4.4±0.5 (n=6)	5.3±0.7 (n=7)	3.7±0.9 (n=5)	3.4±0.2 (n=5)
Ischemia (10 min)	5.1±0.2 (n=5)	5.0±0.1 (n=5)	4.7±0.3 (n=5)	5.2±0.2 (n=5)
Ischemia (30 min)	3.3±0.1 (n=6)	3.3±0.3 (n=5)	2.7±0.3 (n=5)	3.4±0.2 (n=6)
Ischemia (10 min) + Reperfusion (30 min)	3.5±0.5 (n=6)	3.5±0.5 (n=6)	3.5±0.4 (n=6)	4.0±0.4 (n=5)
Ischemia (30 min) + Reperfusion (30 min)	3.1±0.1 (n=5)	3.6±0.2 (n=7)	3.1±0.1 (n=6)	2.8±0.4 (n=5)

Values are means ± SE; () = number of observations.

TABLE IV AMP LEVEL

	WKY	SHR		
	Control	Control	Atenolol-treated	Bunazosin-treated
		(μmoles/g dry weight)		
Preischemia	1.6±0.1 (n=6)	1.9±0.1 (n=7)	2.4±0.9 (n=5)	1.3±0.1 (n=5)
Ischemia (10 min)	1.9±0.1 (n=5)	2.4±0.1 (n=5)	1.8±0.1 (n=5)	2.3±0.1 (n=5)
Ischemia (30 min)	4.8±0.1 (n=6)	5.2±0.3 (n=5)	4.8±0.2 (n=5)	5.4±0.1 (n=6)
Ischemia (10 min) + Reperfusion (30 min)	1.6±0.3 (n=6)	1.6±0.2 (n=6)	2.3±0.2 (n=6)	1.6±0.2 (n=5)
Ischemia (30 min) + Reperfusion (30 min)	1.2±0.1 (n=5)	1.7±0.1 (n=7)	1.6±0.2 (n=6)	1.2±0.1 (n=5)

Values are means ± SE; () = number of observations.

higher than that in the control WKY, although the extent of recovery of the coronary flow was similar. Both the extent of recovery of the pressure-rate product and the extent of percent recovery of the coronary flow during reperfusion in the bunazosin-treated SHR were higher than those in the control SHR. When the ischemic period was increased for 10 to 30 min, the pressure-rate product and the coronary flow in both SHR and WKY recovered very little during re-

perfusion. Both the extent of recovery of the pressure-rate product and the extent of percent recovery of the coronary flow during reperfusion in the control SHR were significantly lower than those in the control WKY ($p < 0.05$, respectively). Bunazosin significantly improved ($p < 0.05$) the extent of recovery of the pressure-rate product, but atenolol did not (62% vs. 18% of the preischemic values). Bunazosin markedly improved ($p < 0.05$) the extent of percent recovery of

Fig.3. Changes in tissue total adenine nucleotides during ischemia and the following reperfusion. Hearts were frozen with liquid nitrogen immediately before the onset of ischemia (preischemia), 10 or 30 min after ischemia, or 30 min of after reperfusion following 10 or 30 min of ischemia. Data were calculated from Table II, III and IV. Values are means $\pm$ SE.

* $p < 0.05$, compared with control SHR.

$p < 0.05$; ## $p < 0.01$, compared with control WKY.

Fig.4. Changes in ECP during ischemia and the following reperfusion. Data were calculated from Table II, III, and IV. Values are means $\pm$ SE.

** $p < 0.01$, compared with control SHR.

$p < 0.05$, ## $p < 0.01$, compared with control WKY.

the coronary flow during reperfusion, whereas atenolol did not (75% vs. 45% of the preischemic values).

At the end of each perfusion experiment,

the heart was frozen and prepared to determine the tissue levels of ATP, ADP, AMP, CrP, and lactate. The level of ATP is shown in Table II. There were no significant differ-

TABLE V CREATINE PHOSPHATE LEVEL

	WKY	SHR		
	Control	Control	Atenolol-treated	Bunazosin-treated
		(μmoles/g dry weight)		
Preischemia	17.7±0.9 (n=6)	18.9±0.6 (n=7)	21.2±3.2 (n=5)	21.0±2.9 (n=5)
Ischemia (10 min)	7.1±0.5 (n=5)	7.4±0.2 (n=5)	8.5±0.6 (n=5)	8.8±0.9 (n=5)
Ischemia (30 min)	5.5±0.5 (n=6)	4.8±0.3 (n=5)	6.1±2.9 (n=5)	5.4±0.2 (n=6)
Ischemia (10 min) + Reperfusion (30 min)	26.3±1.1 (n=6)	29.4±2.9 (n=6)	26.2±3.4 (n=6)	26.9±1.4 (n=5)
Ischemia (30 min) + Reperfusion (30 min)	25.7±1.0 (n=5)	11.1±1.0# # (n=7)	18.4±3.2** (n=6)	21.9±1.4** (n=5)

Values are means ± SE; () = number of observations.

***p* < 0.01, compared with control SHR.

#*p* < 0.01, compared with control WKY.

ences in ATP levels before ischemia among the 4 groups. In both WKY and SHR in either the absence or presence of atenolol or bunazosin, ischemia decreased the level of ATP depending on the period of ischemia. Reperfusion after 10 min of ischemia in the control WKY and the control SHR resulted in recovery of ATP levels to 70% and 60%, respectively, of the preischemic values. Treatment with atenolol or bunazosin improved the restoration of the ATP level to 67% or 70%, respectively, of the preischemic values. When the period of ischemia was prolonged to 30 min, the level of ATP after reperfusion became about 63% of the preischemic level in the control WKY. Although the level of ATP after reperfusion in the control SHR was only 31% of the preischemic level, the levels in the atenolol-treated SHR and the bunazosin-treated SHR were 40% and 44%, respectively. These values were significantly higher (*p* < 0.05) than that in the control SHR. The level of ADP is shown in Table III. The preischemic level of ADP was 3.4–5.3 μmoles/g in all 4 groups. The ADP level slightly increased after 10 min of ischemia, and then decreased after 30 min of ischemia. Reperfusion after 10 min of ischemia slightly decreased the ADP level in all 4 groups. Reperfusion after 30 min of ischemia slightly

decreased the ADP level in the control WKY and in the bunazosin-treated SHR, but slightly increased in the control SHR and in the atenolol-treated SHR. Table IV shows the level of AMP. The level of AMP in the preischemic heart was 1.3–2.4 μmoles/g in all 4 groups. Ischemia increased the AMP level, depending on the time period of ischemia. After 30 min of reperfusion, the AMP level that had been increased by ischemia decreased toward the preischemic level. However, treatment with atenolol or bunazosin in SHR did not affect the changes in both ADP and AMP levels due to ischemia and reperfusion. The total adenine nucleotide level calculated as the sum of the concentration of ATP, ADP and AMP is illustrated in Fig. 3. The levels of total adenine nucleotide in all 4 groups decreased during ischemia. Reperfusion after ischemia did not restore these values completely. In particular, after 30 min of reperfusion following 30 min of ischemia, the level of total adenine nucleotide in the control SHR was markedly lower (*p* < 0.01) than that in the control WKY (11.6±1.1 vs 15.9±1.1 μmoles/g dry weight). Treatment with bunazosin improved the restoration of the total adenine nucleotide significantly (*p* < 0.05), but treatment with atenolol did not. Fig. 4 shows changes in energy charge potential

TABLE VI LACTATE LEVEL

	WKY	SHR		
	Control	Control	Atenolol-treated	Bunazosin-treated
		(μmoles/g dry weight)		
Preischemia	1.0±0.4 (n=6)	2.1±0.4 (n=7)	1.9±0.3 (n=6)	2.6±1.2 (n=5)
Ischemia (10 min)	18.8±6.9 (n=5)	30.5±2.0 (n=5)	27.7±7.0 (n=5)	28.5±3.9 (n=5)
Ischemia (30 min)	32.9±3.3 (n=6)	30.5±4.8 (n=5)	39.8±3.7 (n=5)	40.2±3.9 (n=6)
Ischemia (10 min) + Reperfusion (30 min)	5.1±1.3 (n=6)	8.2±2.3 (n=6)	7.0±1.2 (n=6)	7.1±1.5 (n=5)
Ischemia (30 min) + Reperfusion (30 min)	8.3±3.3 (n=5)	11.9±1.9 (n=7)	9.9±1.8 (n=6)	6.9±2.7 (n=5)

Values are means ± S.E.; () = number of observations.

(ECP) caused by ischemia and reperfusion. Preischemic values of ECP were constant at around 0.86 in all 4 groups. ECP was decreased by ischemia, and then restored by reperfusion. In the heart reperfused after 30 min of ischemia, ECP in the control SHR was significantly lower ($p < 0.01$) than that in the control WKY (0.70 ± 0.02 vs. 0.83 ± 0.02). The value of ECP after reperfusion following 30 min of ischemia in the bunazosin-treated SHR was higher ($p < 0.01$) than that in the control SHR, but that in the atenolol-treated SHR was not. Table V shows the level of CrP. The preischemic levels of CrP were between 17.7 and 21.2 μmoles/g and there was no significant difference among 4 groups. Either 10 or 30 min of ischemia decreased the CrP levels to 25–42% of the preischemic levels. After 30 min of reperfusion following 10 min of ischemia, the CrP levels in 4 groups recovered beyond the preischemic level. In the heart reperfused after 30 min of ischemia, the CrP level in the control SHR, which recovered to only 58% of the preischemic level, was slightly lower ($p < 0.01$) than that in the control WKY. The CrP levels after 30 min of reperfusion in the atenolol-treated SHR and in the bunazosin-treated SHR were markedly higher ($p < 0.01$) than that in the control SHR. The level of lactate is listed in Table VI. The level of lactate that had accumu-

lated during ischemia was decreased by reperfusion. In the heart reperfused for 30 min after either 10 or 30 min of ischemia, the lactate levels in 4 groups were still higher than those in the preischemic hearts. However, there was no significant difference among 4 groups during preischemia, ischemia and reperfusion.

DISCUSSION

This study shows the differences between the effects of antihypertensive therapy with atenolol and bunazosin on lowering blood pressure, regression of left ventricular hypertrophy and ischemic myocardial damage in SHR. The extent of regression of LV hypertrophy with bunazosin therapy in SHR was slightly larger than with atenolol therapy, while these antihypertensive drugs reduced the blood pressure to the same level. Antihypertensive therapy with bunazosin in SHR improved myocardial energy charge potential and increased the extent of the recovery of cardiac mechanical function during reperfusion after 30 min of ischemia, but treatment with atenolol did not. The difference in ischemic myocardial energy metabolism between the atenolol-treated SHR and the bunazosin-treated SHR may be explained by different effects on myocardial structure. These results strongly suggest that both the

cardiac α_1 adrenoceptor and β_1 adrenoceptor blocking effects play important roles both in the regression of cardiac hypertrophy and in the reduction of blood pressure by different mechanisms.

In the present study, both atenolol (50 mg/kg/day) and bunazosin (5 mg/kg/day) therapy for 7 weeks reduced the blood pressure and the ratio of LV weight to body weight, and caused the regression of LV hypertrophy in SHR (Table I). Both drugs were administered in the drinking water, because this route and these doses of administration had been shown to lower the blood pressure without excessive stress on the animal.³ Igarashi et al²¹ have shown that treatment with bunazosin at a dose range of 0.1 to 10 mg/kg (p.o.) in SHR (40-week-old) moderately but dose-relatedly reduces systolic blood pressure. Lauva et al²² have reported that treatment with atenolol (20 mg/kg twice daily, subcutaneously injected) in SHR reduces the blood pressure and attenuates the increase in LV mass. Vogt et al²³ have shown that an oral dose of 50 mg/kg atenolol reduces left ventricular pressure and LV weight in SHR. Thus, it would be widely accepted that combinations of dosage, route applied, and age of animals influence the experimental results in this kind of trial, and the data from the present study are in agreement with earlier studies which also demonstrated the modification of the blood pressure and the ratio of LV weight to body weight in SHR treated with either atenolol or bunazosin.

The development of cardiac hypertrophy in hypertension has been understood to be an adaptation to chronic pressure overload. Lack of a parallel between blood pressure levels and the degree of cardiac hypertrophy in hypertension has been demonstrated both in other experimental animal models and in clinical studies.^{3,4,8,9} In a previous study, we reported that diltiazem therapy in SHR induced the regression of LV hypertrophy without lowering blood pressure.¹⁶ The mechanism of development of cardiac hypertrophy in hypertension is complicated, and many factors are involved in its development and regression.²⁴ The adrenergic and the renin-angiotensin systems participate in hypertensive cardiac hypertrophy. According to protein synthesis, thyroxine, growth

hormone, parathyroid hormone and insulin may influence the development and regression of cardiac hypertrophy. Sen et al²⁵ reported that in hypertrophied myocardium there was a soluble factor which stimulated protein synthesis and suggested that this factor might play a key role in the modulation of myocardial structure during development or regression of myocardial hypertrophy during hypertension.

Beta adrenoceptor blockers, such as acebutolol, timolol, atenolol, carteolol, nadolol and labetalol, do not always reduce cardiac hypertrophy in SHR and hypertensive patients.³²⁻³⁵ In the present study, atenolol, a β_1 adrenoceptor blocker, reduced blood pressure and induced regression of left ventricular hypertrophy in SHR. These results confirm that the cardiac β_1 adrenoceptor plays an important role in the development and regression of cardiac hypertrophy in SHR.

Simpson²⁶ recently reported that norepinephrine stimulated hypertrophy of cultured rat myocardial cells through an α_1 adrenergic receptor. α_1 adrenergic stimulation increased myocardial protein synthesis in myocardial cells, and regulated protein kinase C via phosphatidyl inositol turnover.^{27,28} Prazosin, a selective α_1 adrenoceptor blocker, inhibited norepinephrine-stimulated hypertrophy of cultured rat myocardial cells.²⁹ Ruskoaho³⁰ reported that long-term treatment with prazosin reduced arterial blood pressure and induced the regression of LV hypertrophy in SHR. In the previous study, treatment with diltiazem did not change the blood pressure, but reduced the LV hypertrophy in SHR.¹⁶ Nayler et al³¹ have shown that diltiazem has some α_1 adrenoceptor blocking activity. In the present study, long-term treatment with bunazosin, a selective α_1 adrenoceptor blocker, reduced blood pressure and decreased the ratio of LV weight to body weight in SHR. These findings suggest that the blocking effect of a cardiac α_1 adrenoceptor plays an important role in the regression of cardiac hypertrophy.

Wicker et al³⁶ reported that the coronary flow per unit of LV mass decreased with the development of cardiac hypertrophy in hypertension. The coronary flow per unit of the whole heart weight in the control SHR

was significantly lower ($p < 0.05$) than that in the control WKY (12.1 ± 0.3 vs. 16.1 ± 0.5 ml/min·g⁻¹). Either atenolol or bunazosin significantly improved ($p < 0.05$) it to 13.4 ± 0.5 or 14.6 ± 0.4 ml/min·g⁻¹, respectively. After reperfusion following 30 min of ischemia, the extent of percent recovery of the coronary flow in the bunazosin-treated SHR was greater than those in the control SHR and the atenolol-treated SHR (Fig. 2). These results suggest that the regression of cardiac hypertrophy improves the coronary flow reserve, and that the treatment of the hypertensive cardiac hypertrophy with atenolol or bunazosin may protect the myocardium from ischemic damage.

As shown in Fig. 1, the extent of recovery of pressure-rate product during reperfusion in the control SHR, atenolol-treated SHR and bunazosin-treated SHR was slightly larger than that in the control WKY when the period of ischemia was 10 min. When the period of ischemia was prolonged to 30 min, the extent of recovery of the pressure-rate product in the control SHR was significantly lower than that in the control WKY. Bunazosin improved the recovery of the pressure-rate product significantly, but atenolol did not. In the present study, there was no difference in the myocardial high-energy phosphates before ischemia among the control WKY, control SHR, atenolol-treated SHR and bunazosin-treated SHR. The levels of ATP after reperfusion following 30 min of ischemia in the atenolol-treated SHR and bunazosin-treated SHR were significantly higher than that in the control SHR (Table II). The restoration of total adenine nucleotides and ECP during reperfusion in the atenolol-treated SHR or bunazosin-treated SHR was greater than that in the control SHR, but there was a significant difference only in the bunazosin-treated SHR (Figs. 3 and 4). These results strongly suggest that the regression of cardiac hypertrophy improves the ischemic changes in the mechanical function and metabolism.

In the present study, the extent of recovery of the pressure-rate product in the bunazosin-treated SHR after reperfusion following 30 min of ischemia was significantly higher than in the control SHR (Fig. 1). Tubau et al³⁷ have reported that pressure overload may shift a type of isomyosin from

V1 to V3 in the rat myocardium. Vogt et al²³ have reported that the isomyosin pattern in WKY or SHR is V1 or V3 predominant, respectively, and that chronic therapy with atenolol in SHR does not change it. Bunazosin might reduce the cardiac hypertrophy while changing the isomyosin pattern to be V1 isomyosin predominant. Not only cardiac mass, but also the myocardial structure may be modified by treatment with atenolol or bunazosin. It would be necessary to study the effects of antihypertensive drugs on myocardial isomyosin and mechanical function.

In conclusion, long-term treatment with either atenolol or bunazosin in SHR reduced the blood pressure and induced regression of cardiac hypertrophy and improvement of coronary flow reserve. Both atenolol and bunazosin were effective in the prevention of ischemic myocardial damage in perfused rat hearts. Some factors resulting from stimulation of the cardiac α_1 adrenoceptor may play an important role in the development of the hypertensive cardiac hypertrophy, just as factors resulting from stimulation of the cardiac β_1 adrenoceptor do.

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